

## Cohort to Genome

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The prospective cohort study is one of the epidemiological methods with little measurement bias but requires enormous time and effort and cost to conduct research. The Japan Environment and Children's Study (Ecochil) is a nationwide prospective cohort study, which aims primarily to clarify environmental factors and genetic factors that influence neurological development etc. by recruiting 100,000 pregnant women. Their infants will be followed for 13 years after birth. Parts of the data are now analyzed and released. In addition, in the Tohoku Medical Mega Bank project that began after the Great East Ja-

pan Earthquake, a cohort of 150 thousand inhabitants of the disaster areas was formed in combination with their health survey. New findings and information as the basis of genome-omics medicine have been published one after another. The 70,000 people of the cohort are three generations cohort, which include 20,000 pregnant women in Miyagi prefecture and their family. It draws worldwide attention as the first three generation birth cohort. The lecture will outline the prospective cohort studies of the field of obstetrics and gynecology and will mention the impact on future genome research.

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Special Lecture **ST**

## The Dawn of a New Era in Fetal Behavioral Science

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*Kagawa University***1. Our previous activities in OB/GYN ultrasound study**

In 1992, we reported the use of ophthalmic artery velocimetry in pregnant women for the first time in the world (Lancet 1992 ; 340 : 182-3). In this work, we demonstrated that the vascular resistance of the ophthalmic artery is significantly reduced in women with pregnancy-induced hypertension (PIH). Subsequently, we demonstrated that there is a difference in the circulation of the maternal ophthalmic artery between mild and severe PIH cases (Am J Obstet Gynecol 1997 ; 177 : 174-8). Furthermore, we reported that vascular resistance is reduced in pregnancies associated with small-for-gestational-age fetuses (Ultrasound Obstet Gynecol 1998 ; 11 : 328-31), as well as in pregnant women with diabetes (Hum Reprod 2000 ; 15 : 222-3).

We performed intrauterine sonography with a 20-MHz high-frequency miniature (2.4-mm diameter) ultrasound transducer to observe embryos in the early stages of pregnancy (Am J Obstet Gynecol 1995 ; 173 : 1770-4 ; Hum Reprod 1996 ; 11 : 2758-61, 1997 ; 12 : 1873-6, 1997 ; 12 : 2286-91). We also demonstrated that intrauterine sonography can be used effectively to observe the development of the embryonic brain and central nervous system (Hum Reprod 2000 ; 15 : 1407-12 ; Ultrasound Obstet Gynecol 2009 ; 34 : 47-51).

3D/4D ultrasound can be used to monitor fetal growth and diagnose fetal abnormalities (Hum Reprod 1997 ; 12 : 1800-4, 1998 ; 13 : 740-3,

2000 ; 15 : 2438-42 ; Obstet Gynecol 1998 ; 91 : 218-23 ; Ultrasound Obstet Gynecol 1998 ; 12 : 235-9, 2002 ; 19 : 471-4 ; Arch Gynecol Obstet 2012 ; 286 : 1431-5 ; Ultrasound Med Biol 2012 ; 38 : 396-401), as well as in the evaluation of the normal and abnormal placenta (Placenta 2009 ; 30 : 391-7, 2010 ; 32 : 105-15, 2016 ; 45 : 32-6 ; Ultrasound Obstet Gynecol doi : 10.1002 / uog.18837).

**2. The dawn of a new era in fetal behavior research**

The development and abnormalities of the brain and central nervous system of a fetus can be assessed directly by observing the fetal movement and behavior in womb. A major limitation of conventional 2D ultrasound is the inability to detect the movement and behavior of a fetus that occur outside of the imaging plane. 4D ultrasound has overcome this limitation and opened new doors to advance the field of research (Inf Child Dev 2010 ; 19 : 99-118 ; J Obstet Gynecol Res 2016 ; 45 : 32-6 ; J Perinat Med 2017 ; 45 : 729-36), thus contributing to the dawn of a new era in fetal behavior research that includes “fetal neurology” and “fetal psychology”.

**3. Fetal behavior in the first half of pregnancy**

By observing fetal movements at 10-13 weeks of gestation, we demonstrated that there is a difference in fetal behaviors between 10-11 and 12-13 weeks of gestation (Int J Gynecol Obstet 2010 ; 109 : 190-3). Furthermore, we monitored fetal movements for 60 minutes at 14-18 weeks of gestation and demonstrated that fetuses were in

the active and resting phases for 59.4 and 40.6% of the time, respectively (J Ultrasound Med 2001 ; 20 : 1271-5). Movement of the arms was observed the most frequently at 14-16 weeks, and that of the arms and legs was observed the most frequently at 17-19 weeks (J Perinat Med 2017 ; 45 : 737-43).

#### 4. Fetal behavior in the last half of pregnancy

We examined the frequencies of various fetal facial expressions (mouthing, yawning, smiling, tongue expulsion, scowling, sucking, and blinking) after 20 weeks of gestation, and found that mouthing was the most frequent up to 9 months, and both mouthing and blinking were the most frequent after 9 months (Int J Gynecol Obstet 2006 ; 94 : 108-13, 2013 ; 121 : 257-60, 2014 ; 126 : 275-9 ; J Matern Fetal Neonatal Med doi : 10.1080/14767058.2017.1330880).

#### 5. KANET test

The Kurjak Antenatal Neurodevelopmental test (KANET) is used in 4D ultrasound to assess fetal neurobehavior. Using the KANET test, we demonstrated for the first time that for the assessment of fetal behaviors, particularly facial expressions, we must consider differences in race and ethnicity (J Perinat Med 2016 ; 44 : 217-21). In addition, we demonstrated that there is no sex difference in the fetal neurobehavioral function or its development, or in the developmental processes of the brain and central nervous system (J Perinat Med 2016 ; 44 : 585-8).

Since June 2013, we have performed the KANET test in 433 cases, and identified 22 cases

of borderline fetal behavior (5.08%), of which 13.6% (n=3) had developmental disorders after birth.

#### 6. Inter-twin contact and fetal behavior in twin pregnancies

We used 4D ultrasound to observe twin pregnancies in the early stages of pregnancy (10-13 weeks of gestation) for the first time, and reported the characteristics of inter-twin contact and frequencies of reactions towards such interaction (Int J Gynecol Obstet 2010 ; 108 : 104-7 ; J Matern Fetal Neonatal Med 2012 ; 25 : 226-30 ; Ultrasound Med Biol 2011 ; 37 : 1948-51). Furthermore, we demonstrated that at less than 20 weeks of gestation, the movement of twin fetuses is significantly restricted compared with that of singleton fetuses due to the limited space in the uterus and mutual interference (J Perinat Med doi : 10.1515/jpm-2017-0158).

#### 7. Future perspectives in fetal behavior research

- 1) Elucidate the mechanisms of fetal brain and central nervous system functions
- 2) Develop novel neurological diagnostic test applicable during the fetal period
- 3) Discover novel fetal behaviors
- 4) Elucidate the neurological development and personality formation in twin fetuses

As listed above, we anticipate that future research in fetal behavior will help uncover the function and development of the fetal brain and central nervous system, heralding a new era of knowledge.

The Best of the best : Symposium 1 (Oncology) **ST**  
 Recent Development of Precision Medicine for Gynecologic Cancers; Bench to Bedside

## 1) Analysis of Genomic Alterations and Drug Sensitivity of Gynecologic Tumor Toward Genomic-based Medicine

Akira HIRASAWA

*Keio University*

### 【Objective】

Ovarian cancer (OC) is difficult to detect early and has a poor prognosis. Therefore, appropriate cancer preventive measures are necessary for those with high risk of ovarian cancer onset, and personalized treatment strategies should be chosen for unaffected patients. About 10-20% of ovarian cancer is inherited due to pathogenic germline variants of the cancer-related genes ; however, this frequency in Japanese patients is largely unknown. Considering that pathologic variants of somatic cells could predict the molecular mechanisms and therapeutic targets, and the data from drug sensitivity and resistance testing (DSRT) of the tumor cells could help to select the candidate drugs, we aimed to establish individualized therapeutic strategy from genomic analysis and DSRT data.

### 【Method】

#### 1. Prevalence of germline variants

Samples from 230 individuals, having ovarian, fallopian tube, or peritoneal cancer, were recruited in this study. Germ-line DNA was enriched, followed by sequencing.

#### 2. Detection of ovarian cancer cell mutation

Target capture sequencing was performed on DNA taken from the same cancer tissues as those analyzed for germline variants, using the same method.

#### 3. High-throughput DSRT of ovarian cancer cell

lines

We applied DSRT technology to determine detailed dose-response curves from 306 drugs in 29 established OC cell lines. The panel included 137 approved as well as emerging, investigational, and pre-clinical oncology drugs, all of which were tested at five different concentrations, over a 10,000-fold concentration range. The area under the dose-response curve estimated the drug-sensitivity score.

### 【Result】

#### 1. Prevalence of pathogenic germline variants and the clinicopathological characteristics

Out of 230 patients, 41 women with OC had pathogenic germline variants in OC-associated genes. Nineteen (8.3%) and eight cases (3.5%) carried germ line *BRCA1* and *BRCA2* pathogenic variants, respectively, and only one case had gross deletion covering more than one exon of *BRCA1*. Six cases (2.6%) carried pathogenic germ line variants of MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).

#### 2. Profiling of somatic variants

Profile of the somatic pathogenic variants importantly include : *TP53*, *KMT2C*, *BRCA1*, *BRCA2*, *NF1*, *FAT3*, *ERBB2* genes in high-grade serous carcinoma, *ARID1A* and *KMT2C* in clear cell carcinoma, *ARID1A*, *PTEN*, *KMT2C*, and *PIK3CA* in endometrial carcinoma, and *KMT2C*, *TP53*, *ERBB2*, *PTEN*, and *KRAS* in mucinous

carcinoma.

### 3. DSRT profiling

Bioinformatic processing of the drug-response data from OC cell lines indicated that the clusters were according to drug categories, rather than the histological origin. Many emerging or non-approved drugs were found sensitive in sub-

groups of OC cell lines.

### **【Conclusion】**

Using the integrated data with genomic analysis and DSRT, personalized cancer prevention and treatment may be established for gynecological cancer.

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The Best of the best : Symposium 1 (Oncology) **ST**  
Recent Development of Precision Medicine for Gynecologic Cancers; Bench to Bedside

## 2) Large-scale Exploration of Novel Therapeutic Targets Using Clinical Features of Ovarian Cancer as Biomarkers

Masafumi TOYOSHIMA

*Tohoku University*

### **[Objectives]**

Ovarian cancer is the most challenging gynecologic malignancy despite current comprehensive treatments. The development of individualized medicine specific for each tumor and patient is gaining recognition as a next-generation ovarian cancer treatment strategy. We conducted research aimed at developing novel therapeutic methods using the clinical features of ovarian cancer as biomarkers. We focused on the following two features : (1) c-Myc gene amplification or overexpression (which is observed in 30-60% of ovarian cancers), (2) acquisition of cisplatin resistance. One current example of individualized treatment is the treatment of BRCA-deficient ovarian cancers with a PARP (poly ADP ribose polymerase) inhibitor. The combined loss of BRCA and PARP activity results in synthetic lethality. Synthetic lethal action can potentially be utilized for novel cancer therapeutics to decrease side effects. However, it is difficult to determine suitable synthetic lethal molecules for therapeutic targets. Therefore, we focused on High Throughput Screening (HTS), which allows many compounds to be screened using an automated robot. Considering the characteristics of the above (1) (2) biomarkers, we used HTS to search for new therapeutic targets with synthetic lethal action.

### **[Methods]**

Research (1) Functional genomics HTS using RNA interference (RNAi) was performed in the Quellos HTS core, at the University of Washington, USA. Two ovarian cancer cell lines, TOV 112 D (c-Myc dependent growth) and CaOV 3 (c-Myc independent growth), were used. An RNAi library covering 6,550 genes (three independent siRNAs for each gene) was applied via HTS and 94 genes showed synthetic lethal action with c-Myc overexpression in the primary screen. These genes were subjected to network analysis and pathway analysis. Thirty genes were further selected and subjected to secondary screening with siRNA independent of the library. Finally, the synthetic lethal mechanism with c-Myc alteration was further analyzed on the extracted gene.

Research (2) Functional genomics HTS was performed using A2780CP70, a cisplatin resistant ovarian cancer cell line, in the same way as Research (1). A group of genes that cancels cisplatin resistance by functional inhibition was explored, from the same RNAi library as above, comparing IC<sub>20</sub> concentration of the cisplatin-added and non-added groups. A secondary screening with siRNA independent of the library was conducted for the 30 genes selected in the primary screening. The mechanism of overcoming cisplatin resistance of target candidate mole-

cules was analyzed in detail.

### [Results]

Research (1) From the HTS and validation assays, Furin, a proprotein convertase, was selected as a target molecule which shows synthetic lethal action with c-Myc overexpression. Expression vectors for c-Myc and Furin were constructed and transfected into OSE2 cells, an established cell line from normal ovarian surface epithelium. We found that cell proliferation was significantly increased only when Furin and c-Myc were simultaneously overexpressed. Immunohistochemical staining analysis of ovarian cancers showed no correlation between the expression level of Furin and c-Myc and overall patient prognosis. However, in sub-group analysis, high Furin expression in the c-Myc high expression group was significantly correlated with poor prognosis. We identified Furin as a potential therapeutic target molecule, which shows a synthetic lethal effect with c-Myc overexpression in ovarian cancer.

Research (2) Of the leads from HTS and validation assays, we focused on a tyrosine kinase receptor, TIE-1, which increased cisplatin sensitivity in the A2780CP70 ovarian cancer cell line. Overexpression of TIE-1 significantly reduced cisplatin sensitivity in three types of ovarian cancer cell lines. In addition, TIE-1 expression levels were significantly increased in each cisplatin resistance-acquiring strain compared to their three parent lines. Emission spectroscopic analysis showed that TIE-1 expression does not change intracellular cisplatin concentrations, indicating that TIE-1 does not alter cisplatin uptake or export. Cisplatin-treated TIE-1 knockdown cells showed significantly increased expression of  $\gamma$ H2AX, a marker for DNA double strand breaks. By examining the DNA damage

reaction pathway, we found that TIE-1 regulates nucleotide excision repair (NER). Furthermore, we found that TIE-1 regulates the expression level of the XPC complex, which recognizes DNA distortion due to crosslinking. We administered 7 anticancer drugs with different cell killing mechanisms to the TIE-1 knockdown ovarian cancer cell line. The IC<sub>50</sub>s of cisplatin and carboplatin were markedly decreased compared to other drugs. Nine samples of ovarian cancers from patients who underwent surgery at our institute, were collected during a secondary debulking surgery and evaluated with anti-TIE-1 IHC. The expression level of TIE-1 protein was significantly increased in samples from tumors resistant to paclitaxel and carboplatin (TC) therapy (n=6) than those that responded to TC therapy (n=3). These results indicate that TIE-1 is involved in cisplatin resistance of ovarian cancer by enhancing NER through the regulation of XPC, and that TIE-1 inhibition is effective for overcoming drug resistance in DNA cross-linking anti-cancer drugs.

### [Conclusions]

We consistently search for novel therapeutic targets using clinical features of ovarian cancer as biomarkers. The targets of cancer therapy are becoming more specific with the progress of cancer genomics research. It is creative that we adopted unbiased, large-scale screening of novel therapeutic targets, using two different biomarkers. In this study, we used HTS and secondary verification to identify two novel ovarian cancer mechanisms : high co-expression of Furin and c-Myc in ovarian cancer with poor prognosis and TIE-1 inhibition of cisplatin resistance. Further research will be needed to develop the target molecules identified in this study for clinical practice.

The Best of the best : Symposium 1 (Oncology) **ST**  
Recent Development of Precision Medicine for Gynecologic Cancers; Bench to Bedside

### 3) Individualized Therapeutic Approach for Conquering Refractory Serous Endometrial Cancer (SEC)

Tsukasa BABA

*Kyoto University*

#### **[Introduction]**

Endometrial cancer (EC) is one of the leading causes of gynecologic malignancy, and the incidence of EC in Japan has nearly doubled in the past decade. Most patients present with low grade and early stage disease with favorable prognosis, but cases of high-grade tumors are aggressive and frequently diagnosed with tumor spread beyond the uterus. Serous endometrial cancer (SEC) is a histological subtype which represents highly progressive properties with poor prognosis, and its oncogenic profile is known different from endometrioid endometrial cancers. Although SEC is known to harbor several genetic alterations, it still remains unclear which molecular pathway is responsible for its unfavorable features, especially therapy-refractory and metastatic natures. Recent studies exhibited anti-tumor immunity evasion (ATIE) is also known to play crucial roles in refractory cancers, but ATIE in SEC has not been clarified so far due to lacking immunocompetent assessment models. In this study, we aimed to figure out SEC-specific pathways to reveal the mechanism promoting tumor growth and progression, and we also provide biological evidence that SEC-driver gene is associated with its clinical malicious roles such as chemo-resistance and ATIE.

#### **[Methods]**

Gene expression microarray and immunohisto-

chemical (IHC) staining were conducted using 2 cohorts of endometrial cancers, 91 samples of Kyoto University cohort and 462 samples of British Columbia University cohort, under protocols approved by the Institutional Review Board to investigate SEC-specific pathways. Tumor infiltrating CD8+T cells (TILs) and CD33+cells (MDSC) were counted and MDSC-TIL ratio was calculated to assess tumor micro-environmental immunity.

For in vitro assay, four human SEC cell lines, SPAC-1L, SPEC2, ARK1, and ARK2, were used. Cellular proliferation, migration, and invasion were assessed with or without siRNAs for target genes. In vivo tumorigenesis was also assessed with NOD-SCID mice. Furthermore, proliferation assay and apoptosis assay were performed in STAT1 suppressed SPAC-1L cells treated by cisplatin. In addition, cleaved-Casp3 protein expression, DNA repair, DNA damage status, and STAT1 phosphorylation was also assessed in these manner. For assessing the cellular functional impact of STAT1 pathway activity, dominant-negative STAT1 on sites of serine-727 or tyrosine-701 were introduced in SPAC-1L cells, respectively.

A mouse endometrial cancer cell line, ppp268, was established by conditional uterine deletion of Pten and Trp53 using the Cre/loxP approach, and murine cMyc was further introduced to de-



velop ppp268-cMyc cells for assessing immunocompetent tumorigenicity on C57BL6 mice.

#### **[Results]**

Genome-wide analysis revealed STAT1 pathway was significantly highly activated in SEC, and its expression was confirmed significantly higher in SECs tissue by IHC staining in both cohorts. Furthermore, high STAT1 status in SEC emerged a poor prognosis. In SECs, colocalization of ICAM-1 & PD-L1 was observed at tumor frontier with TILs, and TILs were more frequently observed in the center of tumors without recurrence resulting in that overall survival was significantly better in cases with low MDSC-TIL ratio.

It was confirmed that IFN $\gamma$  induced STAT1 expression not only to promote cellular proliferation, adhesion, and invasion, but to induce expression of cMyc, ICAM-1 and PD-L1 in SPAC-IL cells. In contrast, suppression of STAT1 by shRNA or dominant negative plasmid inhibited xenograft tumor growth on NOD-SCID mice.

In silico analysis using cBioPortal addressed amplification of MYC and up-regulated of MYC mRNA in 42% SPECS. A hundred and eight of the 227 up-regulated genes in the SEC signature harbored the MYC binding site motif by GATHER analysis, and the predictive MYC activity signature score was statistically higher in SECs than in other subtypes of endometrial cancers, while that in SPAC-IL cells was diminished with STAT1 knockdown.

Among four SEC cell lines, highly STAT1 expressing cells, ARK2 and SPAC-IL, were more resistant to cisplatin than other 2 cell lines, and suppressing STAT1 expression sensitized SPAC-IL to cisplatin. Cisplatin treatment inhibited proliferation of STAT1 knockdown SPAC-IL significantly, and Cisplatin IC<sub>50</sub> value was remarkably decreased compared to wild type counterpart. Furthermore, down regulation

of STAT1 significantly increased DNA damage resulting in higher apoptosis activity and prominent cleaved-Casp3 protein expression. In STAT1 suppressed cells treated with cisplatin, DNA repair pathways were not affected but only cellular uptake of cisplatin was prominently increased. This blockade of cisplatin uptake was induced through STAT1 phosphorylation on serine-727 in nucleus (nSer-pSTAT1), but a CK2 inhibitor (CK2I) as a regulator of phosphorylation reduced nSer-pSTAT1 to enhance DNA damage induced by cisplatin, and xenograft tumor was almost diminished by cisplatin and CK2I.

Immunocompetent tumorigenicity got superior by transduction of cMyc, and cMyc tumor exhibited highly nuclear atypia and glandular structure mimicking SEC. In cMyc tumors, MDSCs were more frequently observed, and MDSC-TIL ratio was also high.

#### **[Discussion]**

Previous studies showed that STAT1 activates anti-proliferative and pro-apoptotic genes as a tumor suppressor ; in contrast, STAT1 in SEC appears to function as a tumor pro-survival gene. The highly-progressive features of SEC might be partially due to constitutively high STAT1 expression and consequent up-regulation of downstream STAT1 target genes under a highly orchestrated series of tumor microenvironment components, and we propose that constitutively high STAT1 expression in SEC has a tumor promoting role rather than tumor suppressing role through nSer-pSTAT1.

These results indicate that STAT1 pathway including Myc activity is associated with SEC aggressive features and may confer SEC refractory phenotypes by enhancing cisplatin resistance and ATIE. Therefore, targeting STAT1 pathway might be a promising intervention for SEC management.

## 4) Individualization of Cancer Stem Cells and Development of Personalized Medicine in Cervical Cancer

Katsuyuki ADACHI

*Saitama Cancer Center / The University of Tokyo*

### 【Introduction】

Cancerous tissues consist of polyclonal cells with wide variety of metabolic status and proliferation activities. In general, so-called cancer stem cell (CSC) hypothesis suggests that CSCs have an ability to acquire heterogenic cell properties and lose self-renewal ability in the process of tumor formation. This heterogeneity can lead to therapeutic resistance and a novel approach to target CSCs instead of already differentiated clones is required. *In-vitro* models to investigate the biology of CSCs is highly important for the development of future cancer treatment. It is known that human papillomavirus (HPV) oncoprotein E6 inhibits p53-dependent apoptosis. Therefore, the acquisition of mechanisms to escape apoptosis may be a critical step to generate CSCs in cervical cancer.

### 【Objective】

In this study, our challenge is directed to gain knowledge contributing to future personalized medicine targeting CSCs. We conducted several experiments, aiming [1] to clarify the association of CSCs-related molecules with cancer recurrence and prognosis in clinical cases, [2] to elucidate the mechanism for apoptosis tolerance in CSCs, [3] to analyze amino acid metabolic pathway activities to reveal the differences in the metabolic properties between CSCs and cancer cells, and [4] to examine HPV-type specificities

among the CSC clones induced from HPV infected iPS cells.

### 【Method】

[1] The expression profiles of the molecules involved in self-renewal ability of CSCs were investigated in clinical samples of cervical cancer tissues. It is known that BMP (Bone Morphogenetic Protein), one of the TGF- $\beta$  superfamily, is involved in the differentiation of stem cells. Gremlin 1, a molecule that has an antagonistic effect on BMP, was evaluated for its applicability as a prognostic marker and as an individualization marker for treatment choice. Under approval of the institutional ethical committee, Gremlin 1 expression was assessed in the cervical cancer tissues of 104 patients (stage I to stage II) who underwent surgery at the University of Tokyo Hospital from 2005 to 2014. By stimulating CaSKi cells, a cervical cancer cell line with Gremlin 1, the changes in CSC marker expression patterns and CSC-like cell properties were evaluated. [2] Using three-dimensional culture technology, CSCs were induced on a non-adherent plate from HPV 16, 18 positive cervical cancer cell lines (SiHa, CaSki, HeLa). The CSCs derived from those different cell lines were given a stress with an anticancer agent and an apoptosis inducer and evaluated for the incidence of apoptosis. [3] To identify distinctive properties between CSCs and functionally-

differentiated cancer cells, metabolome analysis covering total amino acid metabolites was carried out. [4] We established a method to induce reserve cells (iRCs) from iPS cells. The iPS-derived iRCs were transfected with HPV 16 and HPV 18. The acquisition of CSC-like properties was evaluated in the transfectants. The HPV-type specific characteristics of the infected iRC clones was analyzed.

#### **【Results】**

[1] High Gremlin 1 expression in the cervical cancer specimens was associated with shorter progression-free survival ( $P=0.0004$ ). The stimulation with Gremlin 1 facilitated dedifferentiation of CaSKi cells into CSCs, with enhanced expression of stem cell markers. This finding proposes that inhibition of Gremlin 1 signaling could be a new therapeutic strategy to increase the response to anti-cancer drugs. [2] CSCs derived from SiHa were resistant to the apoptosis induction by ER stress inducers, whereas the apoptosis was efficiently induced in CC. This resistance to ER stress inducer in CSCs were abrogated by the addition of blockers for the ER stress clearance pathway. The CSCs derived from SiHa, CaSKi, and HeLa showed distinctive morphology. The ability to form spheres which is paralleled with the capacity of dedifferentiation into CSCs was highest in CaSKi. [3] In metabolome analy-

sis, we found the elevation of serine and glutamine levels accompanied with TCA circuit activation in CSCs but not in CC. [4] Induction of iRCs with comparable characteristics to the reserve cells present in SCJ from human iPS cells was established. This iRCs expressed SCJ marker such as CK7, AGR2, CD63, and MMP7. Furthermore, the iRC with HPV 16, 18 gene transductions demonstrated CSC-like cell properties.

#### **【Summary】**

Cervical cancers with high expression of Gremlin 1 had poor prognosis, supporting the importance of therapeutic approach targeting CSCs in those patients. CSCs showed altered amino acid metabolism compared to CC, with activation of the enzymes involved in TCA cycle. The difference of acid metabolism might be a future target for CSC treatment. Our *in-vitro* data suggest that IRE pathway inhibitor would be a promising strategy to solve CSCs resistance to Cisplatin which rely on ER stress-induced apoptosis as its anticancer efficacy, and demonstrate possibility of overcoming Cisplatin tolerance by using IRE pathway inhibitor in combination. Our *in-vitro* technology to generate CSCs from iPS cells of the patient's cervical tissue contribute to the development of novel therapy targeting CSCs.

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The Best of the best : Symposium 2 (Reproduction/Endocrinology, Perinatology and Women's Healthcare) **ST**  
The Latest Knowledge Obtained from the Prospective Study in the Reproduction/  
Perinatology and the Prospect of Preemptive Medicine

1) Efficacy of a Prospective Multifaceted Community-based Intervention  
to Prevent Preterm Birth

Takashi OHBA

*Kumamoto University*

To prevent early preterm birth and reduce the low birth weight infants, we conducted Kumamoto RAINBOW Project, a multifaceted implementation focused on the reduction of chorioamnionitis and periodontal disease, as well as instruction regarding lifestyle factors that can reduce the likelihood of premature labor. Following model studies conducted in two areas, we have implemented the project in Kumamoto Prefecture from Aug. 2012 to Jan. 2014 and 20,701 pregnant women were enrolled. The incidence of bacterial vaginosis and periodontitis were 12.0%

and 32.2%, respectively. The mean gestational age at birth, birth rate of low birth weight (LBW) infants, very LBW infants, and preterm birth of the subjects were 38.9 weeks, 8.10%, 0.65%, and 4.58%, respectively. The subjects who were enrolled in this project primarily gave birth in 2013 and 2014. The community-based birth rate of LBW infants in Kumamoto prefecture was 9.19% in these two years, which was significantly reduced from the mean birth rate (10.02%) in the preceding 6 years.

The Best of the best : Symposium 2 (Reproduction/Endocrinology, Perinatology and Women's Healthcare) **ST**  
 The Latest Knowledge Obtained from the Prospective Study in the Reproduction/  
 Perinatology and the Prospect of Preemptive Medicine

2) Prospective Cohort Studies of Maternal and Neonatal Screening  
 Methods for Developing Preemptive Medicine for Congenital Infection

Kenji TANIMURA

Kobe University

**【Objective】**

Recently, it has been demonstrated that early intervention with antiviral drugs may improve neurological outcome in infants with symptomatic congenital CMV infection (CCI).

It is known that maternal acetylsalicylic acid (AcSPM) therapy can reduce the incidence of congenital *T.gondii* infection (CTI).

Therefore, detection of mothers and newborns at high risk for congenital infection (CI) is important.

We conducted four prospective cohort studies to establish the useful maternal and neonatal screening methods for CTI or CCI.

**【Methods】**

These studies were approved by the institutional review boards, and informed consent was obtained.

**A) A prospective study to evaluate the efficacy of maternal screening for CTI**

From 2005 to 2017, pregnant women with positive or equivocal *T. gondii* IgM underwent serum IgG avidity measurements. They were divided into 3 groups based on avidity index (AI) : acute infection (AI<30%), borderline (30%≤AI≤35%), and chronic infection (AI>35%). Pregnant women with an AI<30% and those who desired medication underwent AcSPM therapy. Amniocentesis followed by multiplex nested PCR for *T.gondii*-DNA in the amniotic fluid (AF) was performed when the women with an AI≤35% desired it. At birth, PCR for the AF and/or umbilical cord blood (UCB) was performed when informed consent

was obtained. The presence of CTI was assessed by blood PCR, IgM, and imaging examinations of infants.

**B. A prospective study to evaluate the efficacy of maternal and neonatal screening for CCI**

**1) Neonatal universal urine screening and antiviral therapy for symptomatic CCI**

Neonates born at Kobe University Hospital and affiliated hospitals were prospectively screened for urinary CMV-DNA by PCR from 2009 to 2017, and CMV-positive newborns were further examined. Newborns diagnosed as symptomatic CCI were treated with valganciclovir (VGCV) for 6 weeks. Clinical neurological outcomes were evaluated at age of 12 months.

**2) Predictive factors of CCI in high-risk pregnant women.**

From 2009 to 2016, 300 CMV IgM-positive pregnant women were enrolled. The maternal clinical and laboratory findings, including serum CMV IgM and IgG ; AI ; C7-HRP ; PCR for the maternal serum, urine, and uterine cervical secretion ; and fetal ultrasound findings, were evaluated. To determine predictive factors for CCI, logistic regression analyses were performed.

**3) Maternal serological screening for CCI in low-risk pregnant women.**

From 2010 to 2016, 2,193 pregnant women at low-risk for CCI underwent screening of IgG and AI. IgG-negative women underwent educational intervention and remeasurement of IgG at 34-35

GW. Women with an  $AI \leq 45\%$  received further examinations, including IgM. CCI was diagnosed by the detection of CMV-DNA in the newborn urine. Primary infection was defined as an  $AI < 35\%$  and/or positive IgM ( $> 1.2$  index). Serum samples from women with an  $AI > 45\%$  were stored, and the IgM levels were measured later. The efficacy of AI and IgM for CCI screening was compared.

In addition, risk factors for CCI in pregnant women with non-primary infection were determined by logistic regression analyses.

### [Results]

#### A. A prospective study to evaluate the efficacy of maternal screening for CTI

- Ninety (22%) of the 402 pregnant women with positive or equivocal IgM had an  $AI < 30\%$ .
- Seven newborns with CTI were detected. They had an  $AI < 30\%$  and positive PCR results in the AF or UCB.
- All six live births, including one infant who underwent medication for 1 year, had no sequelae. None of women with an  $AI \geq 30\%$  had CTI.

#### B. A prospective study to evaluate the efficacy of maternal and neonatal screening for CCI

##### 1) Neonatal universal urine screening and antiviral therapy for symptomatic CCI.

- In the urine screening of 10,356 newborns, 48 (0.46%) tested positive for CMV-DNA.
- Twenty-two were diagnosed as symptomatic CCI and 18 received antiviral therapy.
- Six infants developed severe sequelae (43%), 2 developed mild sequelae (14%), and 6 developed normally (43%) at age of 12 months.

##### 2) Predictive factors of CCI in high-risk pregnant women.

- Twenty-two (7.3%) of the 300 IgM-positive women had CCI.
- Multivariable analysis revealed that the presence of ultrasound fetal abnormalities (OR, 32 ; 95% CI, 8.5-120) and positive PCR results in the uterine cervical secretion (OR, 16 ; 95% CI, 5.0-54) were independent predictive factors of CCI in IgM-positive women.

##### 3) Maternal serological screening for CCI in low-

##### risk pregnant women.

- A total of 1,562 women of the 2,193 (71%) tested positive for IgG, and 631 (29%) were negative.
- Five (0.8%) of the 631 IgG-negative women had seroconversion, and 1 of them had asymptomatic CCI.
- Eighty-eight of the 183 women with an  $AI \leq 45\%$  had an  $AI < 35\%$  and/or  $IgM > 1.2$ , and 2 had CCI (1 asymptomatic, 1 symptomatic).
- Seven (0.5%) of the 1,287 women with an  $AI > 45\%$  together with  $IgM \leq 1.2$  had newborns with CCI, including 3 symptomatic and 4 asymptomatic CCI.
- The application of an  $AI < 35\%$  for CCI screening yielded 22% sensitivity, 95% specificity, 2.5% PPV, 99.5% NPV, and 95% accuracy and was similar to that of IgM (93% accuracy).
- Multivariable logistic regression analyses demonstrated that threatened premature labor (OR 8.4, 95%CI 1.5-48) was a single risk factor for CCI in women with non-primary infection.

### [Conclusions]

- Maternal screening using *T. gondii* IgG, IgM, AI measurements and PCR test is useful for detecting a high risk pregnancy and useful for diagnosing and treating CTI.
- The present studies for the first time demonstrate that the presence of CMV-DNA in the maternal uterine cervical secretion and ultrasound fetal abnormalities are predictive factors for CCI in high-risk pregnant women and that threatened premature labor is a risk factor for CCI in pregnant women with non-primary CMV infection.
- Maternal serological CMV screening can identify pregnancies with CCI from primary infection, but overlooks a number of those from non-primary infection.
- The combination of early diagnosis through screening newborn urine samples and antiviral treatment may improve neurological outcome in symptomatic CCI infants.

In conclusion, preemptive strategies using maternal or neonatal universal screening and drug therapy for mothers or newborns at high-risk can reduce the occurrence of CI and sequela associated with it.

The Best of the best : Symposium 2 (Reproduction/Endocrinology, Perinatology and Women's Healthcare) **ST**  
 The Latest Knowledge Obtained from the Prospective Study in the Reproduction/  
 Perinatology and the Prospect of Preemptive Medicine

3) Elucidation of Environmental Factors and Pathological Conditions  
 Affecting Fetal Development—Focus on Perinatal Mental Health—

Hidekazu NISHIGORI

*Tohoku University*

**[Objective]**

It is well known that the fetal environment affects the development of children, and perinatal mental health is also important as an environmental factor. The present study focused on areas related to perinatal mental health with the principal aim of clarifying risk factors. Moreover, the present study aimed to clarify the pathology of fetal brain function developmental abnormalities in using the “fertile hen’s egg-embryo-chick” system as an experimental animal model and to develop an early detection method of fetal brain function developmental abnormalities applying fetal electrocardiogram as basic research for clarification of pathology and preemptive medical treatment.

**[Method 1]**

We used the data of the Japan Environment and Children’s Study (JECS), a large-scale prospective birth cohort study in Japan. JECS is a project of the Ministry of the Environment and is a survey aimed at clarifying the relationship between environmental factors and pediatric diseases from the gestation period. From January 2011, pregnant women were recruited and approximately 100,000 mother and child pairs are participating ; the survey will continue until the child becomes 13 years old. Tohoku University is participating in the survey as the Miyagi Re-

gional Center, which is one of the 15 regional centers located throughout Japan. Although the investigation was temporarily suspended due to the Great East Japan Earthquake in March 2011, it was quickly resumed and 9,217 sets are participating in Miyagi. Primary fixed data at birth (approximately 10,000 pairs) and complete fixed data at birth (approximately 100,000 pairs) could be analyzed. Psychotropic drug use and risk of congenital anomalies in pregnant women were set as complete fixed data, and the other tasks were analyzed using primary fixed data. Psychological distress was assessed using the Kessler Psychological Distress Scale (K6) for screening ; a score of 13 points or higher was defined as “psychological distress symptoms (PDs)”. SAS version 9.3 and 9.4 were used for statistical analyses.

**[Result 1]**

We conducted a survey on PDs and intimate partner violence (IPV) in the areas affected by the Great East Japan Earthquake as well as “social capital (SC),” which has received much attention after the disaster. SC is defined as “characteristics of social organizations such as bonds (kizuna in Japanese), trust and networks. The subjects comprised approximately 7,500 pregnant women who responded to the questionnaire from June 2011 and gave birth by December 2011 ; a comparison with subjects nationwide.



The frequency of PDs was significantly higher (5.5% vs. 3.0%), physical IPV was higher (5.9% vs. 1.5%), feeling that “most people were trustworthy” was lower (24% vs. 33%), while feeling that “they had helpful neighbors” was conversely high (69% vs. 57%) in the north coastal area of Miyagi. Risk factors of psychological IPV in Miyagi, were “disease or injury of someone close” and “changes in the family structure” that might be attributed to the disaster. Risk factors for PDs were IPV and “being unable to contact close trustworthy people as desired.”

Previous study showed the possibility of prevention of PDs in pregnant women by diet such as fermented foods, but the present study indicates that the intake of yogurt, lactic acid beverages, cheese, Japanese pickles, miso soup, or fermented soybeans was not significantly associated with PDs.

The use of psychotropic drugs by pregnant women and risk of congenital anomalies have been reported in Europe and the United States, but there have been no large-scale prospective studies in Japan. The present study indicates that the use of selective serotonin reuptake inhibitors until the 12th gestational week was associated with urogenital abnormality in children (odds ratio 3.23).

Moreover, there were no previous studies on SC and the risk of complications of pregnancy. It was revealed that the emotional support and neighborhood trust associated with the lower prevalence of gestational diabetes.

#### **[Method 2]**

It has been reported that abnormal secretion of hormones such as glucocorticoid occurs due to perinatal mental health problems, and that the use of psychotropic drugs, affects the fetus and adversely affects the behavioral development of the child. Therefore, as an animal experimental model of behavioral development from the fetal

period, we developed a “fertile hen’s egg-embryo-chick” system. Chick embryos hatch on egg age day 21, and chick embryonic brain development at egg age 14 days is equivalent to the third trimester in humans. Glucocorticoid receptor antagonist (mifepristone), inhibitor of thyroid hormone biosynthesis (methimazole), and sodium valproate, and caffeine were administered to eggs (day 14 or 15) under conditions in which the timing and dose did not increase the congenital anomaly rate and the hatching rate was 80% or higher. All groups were compared with the control group.

#### **[Result 2]**

Mifepristone and methimazole were shown to delay hatching, imprinting, aggregation, belongingness, and vocalization ability. Sodium valproate was shown to delay aggregation, belongingness, and vocalization ability. Caffeine promoted hatching behaviors. Behavioral development was not correlated with brain weight.

#### **[Method 3]**

We attempted clinical application to fetal development using a fetal electrocardiographic device, which we were the first to develop in the world, with the aim of preemptive treatment for fetal developmental abnormalities. We used this device in a “fertile hen’s egg-embryo-chick” system to attempt new detection of embryonic brain function development abnormalities.

#### **[Result 3]**

Methimazole was administered under the same conditions as in Method 2, and results of examination of electrocardiography of the chick embryo performed on egg age day 19 reduced the spectral power in the low frequency area. The effects of glucocorticoid administration are currently under analysis.



## 4) Effects of Various Environments on the Perinatal Prognosis of Mothers and Infants

Seiichi MOROKUMA

*Kyushu University*

### **【Background】**

Recently, there has been an increased interest in environmental influences during pregnancy. Although “the environment” encompasses a wide variety of aspects, these can be broadly divided into many chemical substances including those found in food and the atmosphere. Maternal life-style factors such as diet and sleep also play an important role.

### **【Objective】**

In this study, we investigated the association between air pollutant exposure as an external environmental factor, and pregnancy-induced hypertension, placenta previa, placenta accreta, placental abruption, small for gestational age (SGA) occurrence, and fetal heart rate abnormalities. It was assumed that hyperemesis of pregnancy included exposure to malnutrition early in pregnancy, and SGA was regarded as the outcome. We investigated the association between these factors.

### **【Methods】**

Patient records were obtained on 47,835 mothers and their infants delivered in the Kyushu and Okinawa regions. All charts included were registered in the Japan Society of Obstetrics and Gynecology Perinatal Database between 2005 and 2010. The air pollutant molecules investigated included photochemical oxidants (Ox), suspended

particulate matter (SPM), nitrous oxide (NO<sub>2</sub>), and sulfur dioxide (SO<sub>2</sub>).

To assess environmental effects on pregnancy-induced hypertension, air pollution data including the mean concentration of air pollutants during the 0-12 week gestation period was analyzed. To assess pollutant exposure effects on placenta previa or placenta accrete occurrence, air pollution data including mean concentration of air pollutants during the 0-4 week gestation period (implantation period), and during the 5-12 week gestation period were analyzed. There were 821 mothers (1.7%) who suffered from placental abruption. To assess the effects of air pollutants on placental abruption occurrence, the mean concentration of air pollutants from 5 days before delivery was analyzed. To evaluate the correlation between SGA and pollutant exposure, the mean concentration of air pollutants during the 0-12 week gestation period was analyzed. SGA was defined as a birthweight below the 10th percentile for the gestational age-specific standard. Cases of false-positive fetal heart rate abnormalities were defined as those diagnosed with abnormal fetal heart rate at  $\geq 32$  weeks gestation with an umbilical cord blood pH  $\geq 7.2$  and an Apgar score  $\geq 7$  at 1 and 5 minutes. Air pollution data for early, mid, and late pregnancy were used for this group.

The association between hyperemesis gravida and SGA was investigated by using primary fixed data from the Japan Environment and Children's Study (JECS) carried out by the Environment Ministry. The fixed data included 10,228 deliveries. The required information was available on a cohort of 8,631 mothers who had full-term singleton deliveries. The extent of hyperemesis gravida was assessed using patient questionnaires. Pregnant women were asked the following question: "Did you have morning sickness from conception until about week 12 of the pregnancy?" The answers were interpreted as the following: 1=no, 2=just nausea, 3=vomiting but able to eat, 4=vomiting and unable to eat. It was assumed that those who answered 1, 2, or 3 were able to eat, and for those who answered 4, it was assumed that they were unable to eat because of severe morning sickness. The body weight of patients was also taken in consideration. It was assumed that those who lost 5% of body weight during early pregnancy suffered from hyperemesis gravida. The association between air pollution and hyperemesis gravida was investigated using various types of regression analysis.

#### **【Results】**

Our study demonstrated that a high-level of exposure to Ox during the 0-12 week gestation period was associated with pregnancy-induced hypertension [odds ratio (OR) =1.20, 95% confidence interval (CI) =1.01-1.42]. There was no association with exposure to other pollutants (Environ Res. 2015). Exposure to SPM and Ox during the 0-4 week gestation period was associated with placenta previa (SPM : OR=1.12, 95% CI=

1.01-1.23 ; Ox : OR=1.08, 95% CI=1.00-1.16). Exposure to SPM was also associated with placenta accreta (excluding placenta previa) (OR=1.33, 95% CI=1.07-1.66). There was no association with exposure to SPM, Ox, and other pollutants during the 5-12 week gestation period (Environ Int. 2016). Exposure to SO<sub>2</sub> 2 days before birth was associated with placental abruption (OR=1.4, 95% CI=1.1-1.8). There was no association with exposure on other days or to other pollutants (Epidemiology. 2016). Exposure to Ox during the 0-12 week gestation period was associated with SGA (OR=1.07, 95% CI=1.01-1.12), but there was no association with exposure to Ox at 13 weeks gestation or with exposure to other pollutants (Environ Pollut. 2017). Exposure to SPM during early pregnancy was associated with a false-positive fetal heart rate abnormality (OR=1.20 ; 95% CI =1.05-1.37) (Sci Rep. 2017). Hyperemesis gravida was not associated with SGA (OR=0.81, 95% CI=0.39-1.66).

#### **【Discussion】**

Our study showed how air pollution affects the uterus and placenta. Because the air pollution extended across a wide area, the number of pregnant women exposed was large. However, preventive measures are available, and education may help to decrease exposure. Learning more about the effects of pollutants on pregnancy will have significant clinical implications within the field of obstetrics. By learning more, appropriate preventative measure can be developed and implemented. Therefore, further research is warranted in this area to help improve our current understanding of the effects of air pollution on pregnant women and their newborns.

## Precision Medicine : New Frontier in Women's Health

Linda Giudice

*University of California, USA*

Precision medicine is an emerging approach for disease prevention, novel diagnostics, and individualized treatments based on a person's genes, environment, and lifestyle. Big science and big data, new technologies, and clinical cohorts with deep phenotyping and bio-specimens for analyses comprise the basis of precision medicine, which is inextricably linked to social and environmental determinants of health. It is envisioned that Women's Precision Medicine, integrating women's health and precision medi-

cine, will involve new clinical and scientific knowledge and paradigms, transdisciplinary healthcare teams, novel research collaborations and workflows, and innovative opportunities for educators and the next generation of healthcare providers and investigators. Women's Precision Medicine has the promise of individualized therapies, diagnostics and prognostics to improve the health and well-being of women world-wide.

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## Linda Giudice

Linda C. Giudice, MD, PhD is Distinguished Professor, Chair Emerita, and the Robert B. Jaffe MD Endowed Professor in the Reproductive Sciences in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco (UCSF). She is a biochemist and reproductive endocrinologist specializing in endometriosis and infertility. Her research focuses on human endometrial function and regeneration, genetics and epigenetics of endometriosis, placental-uterine interactions relevant to pregnancy outcomes, and evaluating the evidence of environmental impacts on reproductive health and human development. She has mentored over 250 students, fellows and faculty, authored > 300 peer-reviewed publications, and is co-editor of 7 textbooks on women's health, reproductive environmental health, endocrinology, endometrium and endometriosis. She is Past-President of the American Society for Reproductive Medicine, the Society for Gynecologic Investigation, and the World Endometriosis Society, and is President-elect of the International Federation of Fertility Societies, and Chair of the International Federation of Gynecology and Obstetrics (FIGO) Reproductive and Developmental Environmental Health Working Group. Dr. Giudice is on the UCSF Steering Committee on Women's Precision Medicine, the March of Dimes Scientific Advisory Council, and is an elected member of the U.S. National Academy of Medicine and the U.S. National Academy of Inventors.

## Genetics of Pre-eclampsia

Hannele Laivuori<sup>1,2,3,4</sup>

*Tampere University Hospital, Finland<sup>1</sup>,*

*University of Tampere, Finland<sup>2</sup>,*

*University of Helsinki, Finland<sup>3</sup>,*

*University of Helsinki and Helsinki University Hospital, Finland<sup>4</sup>*

Pre-eclampsia has its origins in early pregnancy long before the onset of its signs and symptoms. The genetic basis of pre-eclampsia and its link with increased lifetime risk of cardiovascular diseases are incompletely understood. According to the epidemiological studies maternal and paternal genes affect the risk. The Inter-PregGen consortium funded by the EU 7<sup>th</sup> Framework Programme has studied many thousands of women affected by pre-eclampsia from Western Europe and Central Asia, together with their partners and offspring, using genome-wide association screening (GWAS). The consortium has reported the first GWAS of offspring from pre-eclamptic pregnancies and discovery of the first genome-wide significant susceptibility locus near the *fms*-related tyrosine kinase gene (*FLT1*) encoding *fms*-like tyrosine kinase 1 implicated in pre-eclampsia. Using targeted exome sequencing we have found maternal low-fre-

quency variants in *FLT1* that may protect from pre-eclampsia. These variants are enriched in a Finnish population and may also protect from heart failure in later life. Identification of rare/low frequency variants associated with pre-eclampsia in both previously identified loci and novel loci may be easier in founder populations. Centrally collected medical, prescription and many other national registries may disclose new genotype-phenotype relationships. Any new gene discovery will highlight a known pathway or reveal a new biochemical pathway in the pathogenic process leading to pre-eclampsia and may also help identifying individuals with higher risk for later cardiovascular disease. A successful strategy of combining genetic factors and non-genetic factors in early pregnancy for risk prediction of pre-eclampsia would be a major advance in healthcare.

## Hannele Laivuori

Hannele Laivuori M.D., Ph.D. is an associate professor at the Faculty of Medicine and Life Sciences, University of Tampere and an assistant chief physician at the Department of Obstetrics and Gynecology, Tampere University Hospital, Finland. She is board certified in Obstetrics and gynecology and in Clinical genetics. Professor Laivuori serves also as a clinical team leader at the Institute for Molecular Medicine Finland (FIMM), HiLIFE Unit, University of Helsinki in the FinnGen project. It is an international large-scale genomics public-private partnership research project, which brings together Finnish bio-banks, universities, hospital districts and international pharmaceutical companies. Professor Laivuori is scientifically recognized for her work on genetics of pre-eclampsia. She has led the clinical translation arm of the InterPregGen project funded by the EU 7<sup>th</sup> Framework programme, a largest Genetics of pre-eclampsia study to date. She currently lists over 100 papers published in the peer-reviewed literature. She is regularly invited to lecture at international meetings. Professor Laivuori is an active mentor having supervised several graduate students and postdoctoral fellows. She has also been active in improving careers of clinical medical researchers.

## Reducing the Rate of Preterm Birth – Results of a State-wide Implementation Program

John Newnham

*The University of Western Australia, Australia*

Preterm birth (PTB) is the single greatest cause of death in the newborn period and a major contributor to long-term disability. Discovering how to safely prevent early birth needs to be one of our highest priorities. In 2014, Western Australia introduced a state-wide whole-of-population multi-faceted PTB prevention program based on seven interventions. These included avoidance of non-medically indicated late preterm/early term birth; routine measurement of cervix length at mid-pregnancy ultrasound scans; vaginal progesterone for shortened cervix or prior history of early birth; appropriate use of cerclage; smoking avoidance; and a dedicated new clinic. The new clinical guidelines were promoted by a state-wide outreach program for all health care practitioners and a public health campaign was introduced for

women and their families based on print and social media (known as “thewholeninemonths”). In the first full calendar year (2015) the rate of singleton PTB state-wide fell by 7.6% and the effect continued down to the 28–31 week gestational age group. In the state’s major tertiary level centre the PTB rate fell by 20% and was accompanied by a significant increase in births in the 39 week age group. There was no change in the stillbirth rate. These findings have shown that a comprehensive and multifaceted prevention program aimed at both health care practitioners and the general public and using existing knowledge can significantly lower the rate of preterm birth. Further research is required to expand the effect and to determine how the program can be adopted into other health care environments.

## John Newnham

John Newnham is Professor of Obstetrics at The University of Western Australia (UWA) and is a sub-specialist in Maternal Fetal Medicine. He is Head of the UWA Division of Obstetrics and Gynaecology based at King Edward Memorial Hospital in Perth and Chief Scientific Director of the Women and Infants Research Foundation.

His research interests focus on prevention of preterm birth and the early life origins of health and disease. He has initiated many clinical and laboratory research studies, including The Raine Study and the Western Australian Preterm Birth Prevention Initiative.



## Overseas Invited Lecture 4

## Personalized Cancer Models for Discovery and Development of Novel Therapeutic Targets

Christopher Kemp

*Fred Hutchinson Cancer Research Center, USA*

A major goal of precision oncology is to utilize genomic information to inform patient care. While there are spectacular examples of success, for the great majority of cancer patients, genomic information is insufficient to guide patient care or select effective therapeutic options. We have developed an approach that employs high throughput functional testing with both

siRNA and drugs using patient tumor samples. This functional data combined with genomic analysis is used to distinguish driver from passenger mutations and identify novel drug targets and potentially effective drugs specific to a given patient. We will describe applications of this approach to identify novel targets for cisplatin resistant ovarian cancer.

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## Christopher Kemp

Christopher Kemp received an MS in Toxicology from Oregon State University and a PhD in Oncology from the University of Wisconsin. He did postdoctoral research at the Beatson Institute, University of Glasgow and has been a faculty at the Fred Hutchinson Cancer Research Center for 23 years. He has made major discoveries in cancer genetics, including identifying p27/Kip1 and CTCF as haploinsufficient tumor suppressor genes. He has studied the interaction between Ras, p53 and Arf during tumor progression using mouse models. More recently his work is focused on identifying new cancer drug targets using siRNA screening and patient relevant cancer models. This work has led to a successful clinical trial targeting the WEE1 kinase in head and neck cancer patients.

## How Has Our Understanding of Abnormal Uterine Bleeding (AUB) Changed during the Last Decade?

Rohana Haththotuwa<sup>1,2,3</sup>

*Ninewells Care Mother and Baby Hospital, Sri Lanka<sup>1</sup>,*

*AOFOG<sup>2</sup>,*

*FIGO, Committee for Menstrual Disorders<sup>3</sup>*

Abnormal uterine bleeding (AUB) has been a neglected area till recently. But during the last decade many changes have taken place regarding, the cultural issues, terminology, classification of causes & the investigations & treatment of AUB.

Culturally menstruation has been a taboo subject, been plagued with myths, fears, misunderstandings which prevented women particularly in the developing countries from attending to house hold activities, social functions and religious places during menstruation. This resulted in a delay in women seeking treatment for AUB. There has been a reduction of these myths and cultural issues over the years with the improvement in education.

With regards to the nomenclature the terms used were ill-defined and there was no uniformity around the world sometimes within the same institution there was no clear definition all-around making it difficult to communicate. Understand research publications, design clinical trials and to teach & educate. So the confusing terms like menorrhagia, metrorrhagia, dysfunctional bleeding has been discarded and simple English terms using the frequency, regularity, duration and volume to describe various forms of AUB.

The classification of causes has been done under the PALM (with structural abnormality), COEIN (without structural abnormality) classification. Further the structural abnormalities like polyps, adenomyoses and leiomyoma are been sub-classified.

Major changes have taken in the investigations with the development of trans vaginal & 3 D ultra sound scans, CT Scanning, MRI & Hysteroscopy.

In the medical management choice of treatment agents have increased during the recent past. These include anti fibrinolytics, COX inhibitors, newer oral contraceptives, Levonorgestrel intra uterine system, GnRH agonists & antagonists, and Progesterone receptor modulators.

In the surgical side the need for hysterectomy due to AUB has markedly reduced due to the improved medical therapy and the development of uterus sparing surgical procedures which include hysteroscopic polypectomy, endometrial ablation & resection, adenomyomectomy and uterine artery embolisation.

These changes during the last decade has resulted in a marked improvement in the understanding and management of AUB.

## Rohana Haththotuwa

Consultant Obstetrician & Gynaecologist

Chairman, Ninewells CARE Mother & Baby Hospital

Secretary General, Asia Oceania Federation of Obstetrics & Gynaecology (AOFOG)

Chairman, Menstrual Disorders Committee, FIGO

Vice President, South Asian Federation of Obstetrics & Gynaecology

Past President, Sri Lanka College of Obstetricians & Gynaecologists

Past President, Menopause Society of Sri Lanka

Vice President, South Asian Federation of Menopause Societies

Treasurer, Asia Pacific Society for Infections in Gynaecology & Obstetrics from 2010

Country Representative *Aspire* (*Asia Pacific Initiative in Reproductive Endocrinology*)

## Optimisation of Antenatal Steroid Therapy

Matthew Kemp

*The University of Western Australia, Australia*

Antenatal steroids are routinely given to women in anticipation of preterm delivery. The most common agents in clinical use today are betamethasone (as a combined preparation of acetate and phosphate), betamethasone or dexamethasone phosphate. Antenatal steroids act via the glucocorticoid receptor to drive precocious maturation of the preterm lung, resulting in improved outcomes (chiefly reduced lung and brain injury) for preterm infants. Although antenatal steroids convey clear benefit when administered appropriately, their use remains un-optimised ; as such, a 50 kg woman in preterm labour at 26 weeks' gestation receives the exact

same dose of potent steroids as a 120 kg woman in preterm labour at 34 weeks' gestation. There is significant variation in the efficacy of antenatal steroid therapy, and on-going debate remains around the use of repeat (aka "rescue") courses of steroids, and the use of steroids in late preterm birth.

Drawing on evidence from clinical and basic science studies, this paper will advance the argument that antenatal steroids can and should undergo further, patient-specific optimisation in an effort to improve the efficacy and safety of this important therapy for preterm infants and their mothers.

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## Matthew Kemp

Matt completed his undergraduate studies in New Zealand at Otago University. He holds PhDs in Medicine (University of New South Wales) and Education (University of Western Australia), and completed postdoctoral training at Oxford University with the support of an MRC Career Development Fellowship. He is presently employed as an Associate Professor (Research) in the Division of Obstetrics and Gynecology at the University of Western Australia.

His research interests in perinatology are focused on improving outcomes for preterm infants, and include anti-inflammatory and antibiotic therapies, antenatal steroid treatment optimisation, and the development of an artificial uterine life support platform for extremely preterm infants.

Matt's work has been supported by a range of national and international agencies including the National Health and Medical Research Council, the National Institutes of Health, the Bill and Melinda Gates Foundation, the Royal Society, the Ramaciotti Foundations and the Financial Markets Foundation for Children. He maintains an active research interest in evidence-based graduate education and is presently completing the Program for Leadership Development at Harvard Business School.

## Overseas Invited Lecture 7

## A Search Engine of Personalized Treatments for Ovarian Cancer

Carla Grandori<sup>1,2</sup>, Franz X. Schaub<sup>1</sup>, Rachele Rosati<sup>2</sup>, Reid C. I. Shaw<sup>2</sup>, Hallie A. Swan<sup>1</sup>,  
 Michael J. Churchill<sup>1</sup>, Roland M. Watt<sup>1</sup>, Caroline Bridgwater<sup>1</sup>,  
 Stephanie A. T. Murphy<sup>1</sup>, Robert L. Diaz<sup>1</sup>, Vijayakrishna Gadi<sup>3</sup>, Chris J. Kemp<sup>3</sup>,  
 Shalini C. Pereira<sup>1</sup>

*SEngine Precision Medicine, USA<sup>1</sup>,*

*Cure First, USA<sup>2</sup>,*

*Fred Hutchinson Cancer Research Center, USA<sup>3</sup>*

**【Background】**

Ovarian cancer exhibits a distinct and unique mosaic of genomic alterations, which rarely indicating therapeutic choices. To advance a functional approach to precision medicine we have developed a high-throughput assay that employs organoid cultures derived from patient specimens to directly determine drug responses to a comprehensive set of 131 oncology drugs. Here we present the results obtained with this novel test, named P.A.R.I.S. in analogy with Paris who defeated Achilles, by aiming precisely at its weakness, to aid oncologists select personalized treatments.

**【Experimental Procedures】**

Organoids are derived from surgical resections, biopsies or ascites and exposed to a library of clinically relevant drugs. The assay measures cell viability and multi-dose response curves are evaluated and drug are ranked using a proprie-

tary set of metrics, resulting in a SPM™ score, which weights both the sensitivity and uniqueness of each tumor response. The results are integrated with genomic data and reported to the clinician to highlight treatment options.

**【Results】**

Thus far, SEngine has performed drug screen studies with >150 cancer organoids from >20 tumor types and established high reproducibility. Results from several ovarian cancer specimens will be presented. To facilitate communication of the test results, SEngine has developed an in-house application suite (SEngine Medicine APP), consisting of interactive charts, statistical analysis, and reactive reports which can be shared with oncologists and investigators. We will discuss applications of the P.A.R.I.S. test to accelerate development of novel targeted drugs and overcome drug resistance in ovarian cancer.

## Carla Grandori

**Dr. Carla Grandori, MD, PhD. CEO of SEngine Precision Medicine and Scientific Director, Cure First.**

I am a cancer researcher of >30 years, aiming to contribute to the discovery of less-toxic treatments for cancer. I received an MD degree in 1982 from the University of Rome, La Sapienza, followed by a PhD at the Rockefeller University in New York under the guidance of Dr. Hanafusa, a pioneer of oncogenes. My research career continued at the Fred Hutchinson Cancer Center, focused on the MYC oncogene and was complemented by industry experience at Rosetta Inpharmatics (a subsidiary of Merck). Adopting the technology of high-throughput RNAi screens my laboratory identified MYC synthetic lethal genes as candidates for therapeutics. In 2009, I joined as director the Quellos High Throughput Screening (HTS) facility at the University of Washington, and awarded a Presidential Entrepreneurial Award from the UW. Our technology was recognized in 2013 with a prestigious grant from the Cancer Target Discovery and Development Network (CTD<sup>2</sup>, NCI) to continue the discovery of novel drug targets. In 2012, I co-founded Cure First, a not for profit organization dedicated to accelerate research and delivery of personalized treatments for cancer. In 2015, I co-founded and since led SEngine Precision Medicine, advancing novel drugs and personalized treatments to the clinic.



## Overseas Invited Lecture 8 (Web Lecture)

## Screening and Prevention of Preeclampsia

Kypros Nicolaides

*King's College London, UK*

[CV]

**Qualifications :**

1974 Biochemistry and Physiology BSc (1st class honours), King's College, London University.

1978 Medicine, MBBS, King's College Hospital, London University.

1984 Obstetrics and Gynaecology, MRCOG.

2014 Obstetrics and Gynaecology, FRCOG.

**Present post from 1992 :**

Professor of Fetal Medicine, King's College, London,

**Awards :**

1. Ian Donald Gold Award of the International Society Ultrasound in Obstetrics & Gynecology, for Highest Contribution in Ultrasound, 1999

2. Eric Saling Award of the World Association of Perinatal Medicine, for highest scientific contribution in Perinatal Medicine, 2001

3. Excellence in Letters, Culture and Science, Government of Cyprus, 2004

4. Honorary Fellowship of the American Institute of Ultrasound in Medicine, USA 2004.

5. Maternity Prize of the European Association of Perinatal Medicine, 2014.

6. Eardley Holland Gold Medal of the Royal College of Obstetricians and Gynaecologists, 2015.

7. Honorary Doctorate in Medicine : University of Athens in Greece (2005), University of Warsaw in Poland (2009), University of Bucharest in Romania (2009), University of Jinan in China (2010), Spinoza Chair, University of Amsterdam, in the Netherlands (2010), University of Olomouc in Czechia 2011, University of Ioannina in Greece 2012, European University of Cyprus in Cyprus (2013), University of Thessaly in Greece (2016), Aristotelion University of Thessaloniki in Greece (2017).

**Scientific Activities :**

• Published 1,378 peer-review papers in Scientific Journals. He ranks 237<sup>th</sup> in the list of the most highly cited researchers, both living and deceased. He ranks 1<sup>st</sup> amongst all Obstetricians

and Gynaecologists. His h-index is 142 and his work has been cited 86,732 times.

• Edited several books and introduced internet based courses for health care professionals and patients in 20 languages.

• Supervised 52 research fellows who obtained PhDs and MDs.

• Provided training in Fetal Medicine to more than 500 doctors from 50 countries.

• Introduced new methods of fetal therapy, including intrauterine blood transfusions for fetal anemia, thoraco-amniotic shunting for drainage of pleural effusions, endoscopic laser surgery for severe twin-to-twin transfusion syndrome and endoscopic tracheal occlusion for diaphragmatic hernia.

• Described new methods of screening for fetal abnormalities, including the lemon and banana signs for spina bifida and nuchal translucency for Down's syndrome which are now the accepted methods of screening throughout the world.

• Introduced new approach for early screening for pregnancy complications, including preeclampsia, preterm birth, gestational diabetes, miscarriage and stillbirth, macrosomia and fetal growth restriction.

• Demonstrated the benefit of progesterone in prevention of preterm birth and aspirin in prevention of preeclampsia.

**Founder and Chairman of the Fetal Medicine Foundation**

This charity was set up in 1995. The main source of income is a private clinic which donates all its profits to the charity. The aims are to promote research and training in Fetal Medicine throughout the World. More than £22,000,000 have been donated to finance the training of many doctors from all over the world and to carry out major multicentre studies on screening and prevention of preterm delivery and preeclampsia, which are the leading causes of perinatal mortality.

MEMO

## Overseas Invited Lecture 9

## Management of Preterm Labor, Delivery and Newborn at National Hospitals in Cambodia

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Im Sethika<sup>3</sup>, Soeung Sophornmony<sup>4</sup>, Siek Meng<sup>4</sup>, Chhea Chhorvann<sup>5</sup>,  
Chau Darapheak<sup>5</sup>, Noriko Fujita<sup>6</sup>

*Cambodian Society of Gynecology and Obstetrics, Cambodia<sup>1</sup>,*

*National Maternal and Child Health Center, Cambodia<sup>2</sup>,*

*Calmette Hospital, Cambodia<sup>3</sup>,*

*Khmer Soviet Friendship Hospital, Cambodia<sup>4</sup>,*

*National Institute of Public Health, Cambodia<sup>5</sup>,*

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### 【Objectives】

The study aims to review the current clinical management of preterm labor delivery and newborn outcomes at three national hospitals in Cambodia, the referral centers in the domain of gynecology and obstetrics.

### 【Methods】

Patient records on preterm delivery were reviewed by hospital staffs for three months period from August to October 2016. Maternal background information, clinical symptoms of mother, laboratory test results, clinical management, mode of delivery, postpartum, and newborn outcome were collected for statistical analysis at the National Institute of Public Health Cambodia in December 2016.

### 【Results】

The total number of preterm delivery in three national hospitals was 605 representing 11% of total number of deliveries. The percentage of

women who received corticosteroid before delivery was 43.6%. Among all preterm newborns 6.3% of them died. The proportion of newborn death was more likely found among women who did not received corticosteroid (33.3% vs 83.3% for <1,000g, 14.5% vs 55.6% for 1,000–1,499g and 1.9% vs 9.5% for 1,500–1,999g). Percentage of newborn death was higher among women who came from the provinces than women living in the capital Phnom Penh (3.9% vs 8.3%). Women who had induced labor newborn death have higher than spontaneous vaginal delivery (4.6% vs 15.6%).

### 【Conclusion】

Our data showed low percentage of corticosteroid use but proved efficiency to improve the newborn outcomes among the referral hospital in the capital Phnom Penh. Protocol for preterm labor delivery should be standardized and promoted urgently in Cambodia.

## Sann Chan Soeung

PROFESSION : Medical Doctor  
: Professor of University of Medical Science in Phnom Penh, Cambodia

### WORK EXPERIENCES :

- 1982 : OB-GY Ward at Kossamak Hospital
- 1999 : Chief of Technical Bureau of the National Maternal and Child Health Center (NMCHC)
- 2000 : Deputy Director of the NMCHC and Manager of National Immunization Program, Ministry of Health
- 2015 : Head of Scientific Committee of the Cambodian Society of Gynecology and Obstetrics

### STUDIES :

- Management of Preterm Labor Delivery and Newborn at the National Hospitals in Cambodia (2016)
- Evaluation of Maternal Neonatal Tetanus in Cambodia in collaboration with WHO and UNICEF (2013)
- Evaluation of Measles in Cambodia in collaboration with WHO and UNICEF (2012)
- Prevalence of chronic hepatitis B virus infection after implementation of a hepatitis B vaccination program among children in three province in Cambodia (2012)
- The social determinants of health and health service access : an in depth study in four communities in Phnom Penh (2012)
- Hepatitis B survey in Cambodia using rapid test (2009)

## Overseas Invited Lecture 10

## Prenatal Programming, Epigenetics and Transgenerational Outcomes

Stephen Matthews

*University of Toronto and The Lunenfeld–Tanenbaum Research Institute, Sinai Health Systems, Canada*

The developing fetal brain is highly responsive to endocrine, nutritional and chemical cues. Glucocorticoids (GC) are critical for normal brain development and are tightly regulated at low levels in the fetus for the majority of pregnancy. Levels increase rapidly in late gestation. This surge is critical for fetal lung development and maturation of other organ systems including the brain. Fetal GC levels can be elevated earlier in gestation as a result of maternal or fetal stress or maternal treatment with synthetic GCs. The latter occurs in cases of threatened preterm birth (>10% of all pregnancies). Using an animal model, we have shown that premature exposure of the fetal brain to GC can lead to profound changes in the epigenetic (DNA methylation, acetylation) and transcriptional landscapes in the

prefrontal cortex (PFC), hippocampus and hypothalamic paraventricular nucleus (PVN). Effects are associated with altered function of the hypothalamic–pituitary–adrenal (HPA) and stress-related behaviours in offspring, and these effects are maintained in to adulthood. Most recently, we have shown that the effects of GCs on epigenetic/transcriptional landscapes, HPA function and behaviours can extend across multiple generations, and that this can occur via maternal and paternal transmission. Our findings have significant implications for clinical practice, but also our fundamental understanding of the mechanisms by which the fetal endocrine environment impacts the developing brain leading to life-long modification of endocrine function and behaviours.

## Stephen Matthews

Stephen G. Matthews is Professor of Physiology, Obstetrics and Medicine at the University of Toronto and Director of Research at the Alliance for Human Development. Professor Matthews received his PhD from the University of Cambridge, UK, was appointed to the University of Toronto in 1996 and served as Chair of the Department of Physiology from 2007–2014. He has secured over \$25M in research funding and has published over 200 full papers. He has won a number of prestigious research prizes including The 2006 Mortyn Jones Memorial Medal, and The 2012 President's Achievement Award from the SRI (formerly SGI). Professor Matthews has served on Editorial Boards of several Journals including *Endocrinology* and *Journal of Neuroendocrinology*. He is a member of Council for SRI and DOHaD and has served as Scientific Program Chair for both Societies. In 2015, he co-founded DOHaD Canada. His research is focused towards understanding how the fetal environment affects developmental trajectories leading to modified neurologic and endocrine function. He has established that these effects can extend across multiple generations. With a focus on epigenetics, his research team is determining the molecular mechanisms by which such 'programming' can occur. In parallel, he is investigating drug and hormone transport mechanisms in the placenta and fetal brain, with a focus on protection of the fetus. Professor Matthews is committed to translating fundamental research. He is currently co-leading large pregnancy intervention studies in India and Africa focused towards improving maternal, infant and child health.

## Gene Correction in Human Embryos

Shoukhrat Mitalipov

*Center for Embryonic Cell and Gene Therapy, Oregon Health & Science University, USA*

*In vitro* fertilization (IVF) represents a successful cell therapy approach for treatment of infertility. However, IVF is increasingly utilized for preimplantation genetic diagnosis (PGD) followed by embryo selection to prevent the transmission of heritable human diseases. We recently sought to complement PGD by attempting to rescue mutant embryos by correcting the heterozygous deletion in *MYBPC3* gene causing hypertrophic cardiomyopathy (HCM). Our study demonstrated that in a substantial portion of heterozygous human embryos, CRISPR-Cas9-induced double-strand breaks (DSBs) at the mu-

tant paternal *MYBPC3* locus, were efficiently repaired by homology-directed repair (HDR) mechanisms using the wild type maternal allele as a template. By modulating the cell cycle stage at which CRISPR-Cas9 was introduced, we were able to avoid mosaicism in embryos and achieve a high yield of homozygous embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos.

## Shoukhrat Mitalipov

Shoukhrat Mitalipov, Ph.D., directs the OHSU Center for Embryonic and Gene Therapy, where he is focused on developing treatments to prevent the transmission of genetic disease from parent to child. Mitalipov is also a professor of biomedical engineering and obstetrics, gynecology and pediatrics in the OHSU School of Medicine with appointments in the Oregon National Primate Research Center and Knight Cardiovascular Institute. Mitalipov earned his Ph.D. in 1994 from the Research Center for Medical Genetics in Moscow. He arrived at OHSU in 1998 after conducting postdoctoral research in stem cell and developmental biology at Utah State University.

In August 2017, Dr. Mitalipov and his colleagues published groundbreaking research in *Nature* demonstrating that the gene-editing tool CRISPR can be effectively used to repair a disease-causing mutation in a human embryo and prevent the disease from being passed down to future generations. The focus of the study was the gene mutation that causes hypertrophic cardiomyopathy, a common inherited condition that can cause sudden cardiac death and heart failure. This is the first time scientists have successfully tested the gene repair method on donated clinical-quality human eggs. Results of this landmark research were reported in thousands of media outlets worldwide.



## Overseas Invited Lecture 12

## Evidence and Eminence in Secondary Prevention of Preterm Birth –An Overview Comparing Vaginal Progesterone, Cerclage and Cervical Pessary in Singleton and Twin Pregnancies–

Birgit Arabin

*Philipps University/Clara Angela Foundation, Germany*

Transvaginal sonography (TVS) is used for secondary prevention of preterm birth (PTB), but the sensitivity is still low. Trials based on TVS show controversial results — by addressing the controversies we try to optimize transparency for clinicians who need to make decisions on a daily basis.

**Vaginal progesterone** may reduce PTB < 34 weeks in screened singleton pregnancies. Up to now, no positive long-term effect could be demonstrated. It has no benefit to prolong pregnancies after preterm contractions and in risk patients without cervical shortening. Randomized controlled trials (RCTs) apart one non-registered and non-placebo-controlled trial showed no benefit in unselected or selected twin pregnancies. Meta-analyses for singleton and twin pregnancies still demonstrate conflicting results dependent on selection criteria.

**A cerclage** is (only) indicated in singleton preg-

nancies with previous PTB and combined cervical shortening in the current pregnancy. The short- and long-term outcome could not be improved, whereas maternal complications seem increased. A cervical cerclage should not be indicated in twin pregnancies even not when they have a short CL.

**A cervical pessary** in singleton pregnancies seems to be effective in hands of experienced clinicians. Then it has been shown to prolong pregnancies and to reduce poor neonatal outcome. Mainly in twin pregnancies, pessary treatment seems to be promising compared to other options when the therapy is started at early stages of precocious cervical ripening. Studies have proven cost-effectiveness and improved long-term outcome.

Comparative trials and a prospective meta-analysis are in progress to better compare treatment options in specific subgroups.

## Birgit Arabin

|                           |   |
|---------------------------|---|
| <b>Medical University</b> | 1971–1975 Albert Ludwig University Freiburg (Germany)<br>1975–1978 Free University Berlin   |
| <b>Medical Curriculum</b> | 1978–1979 Research Fellow University Hospital Brussels and at the Institute for Perinatal Medicine Berlin<br>1979–1985 Residency OBGYN Ruprecht Karl University Heidelberg<br>1985–1988 Assistant Professor Institute for Perinatal Medicine Berlin<br>1988–1993 Assistant Professor Free University Berlin<br>1992–1993 Lecturer/Studies School of Public Health Hannover<br>1993–2008 Consultant Perinatal Centre Zwolle – NL<br>Subspecialist Maternal Fetal Medicine in Germany & The Netherlands<br>Level III DEGUM Ultrasound/Germany<br>Lecturer Private University Witten–Herdecke & Humboldt University Berlin<br>2008–now Head of Prenatal/High risk pregnancy Academic Perinatal Board Philipps University Marburg–Germany |
| <b>Sabbatical</b>         | 1988 Harris Birthright Center London/ Prof. Nicolaides<br>1991 Dep. of Prenatal Medicine Bonn/ Prof. Hansmann<br>2008 Centre for Prenatal Therapy Poissy–Paris/ Prof. Ville   |
| <b>Organizations</b>      | Member/Board of Societies of Perinatal Medicine such as WAPM, SMFM, ISUOG, IAPM, NVOG, DGGG, DGPM, DGPPM<br>Reviewer German Research Funding BMBF/several international journals  |
| <b>References</b>         | Appr. 50 books/ book chapters, >100 peer reviewed papers, >500 international lectures preferably on topics of Perinatal Medicine  |
| <b>Medical Interests</b>  | Prevention of preterm birth, fetal growth, prenatal diagnosis, fetal programming, twin pregnancy, public health concepts, national and international education and postgraduate training, partnerships in the field of perinatal medicine   |
| <b>Awards</b>             | Staupe Pfannestiel Price 1988,<br>Ambroise Pare Medal Int. Academy Perinatal Medicine 2005,<br>Award World Association Perinatal Medicine 2008,<br>Hackert Price Prenatal Medicine 2009,<br>Pschyrembel Medal 2013<br>Dexeus Medal 2015<br>Dr. honoris causa Sorbonne–Paris 2016  |
| <b>Varia</b>              | 1997 Founder Clara Angela Foundation Witten/Berlin <a href="http://clara-angela.info">http://clara-angela.info</a><br>based on Dr. Arabin GmbH <a href="http://www.dr-arabin.de">www.dr-arabin.de</a>   |
| <b>Other Interests</b>    | Music, literature and poetry, implication of humanity into political concepts, to live a balanced life, to organize original meetings, to create an angel museum.   |

## Ultrasound Grading of Cesarean Scar Pregnancies and Its Implication for the Strategy of Management : Experience at a Single Medical Center

Chien-Nan Lee<sup>1,2</sup>

*National Taiwan University Hospital, Taiwan<sup>1</sup>,*

*President elect. the Federation of Asia and Oceania Perinatal Societies<sup>2</sup>*

### **【Objectives】**

A cesarean section pregnancy (CSP) is a pregnancy in which the gestational sac is implanted in the previous cesarean section scar. The clinical manifestations of CSP present a wide range of differences, and optimal management is yet to be defined. We propose an ultrasound grading system and discuss its implications for the management of CSP.

### **【Methods】**

This was an observational, retrospective cohort study. We enrolled 109 patients with the diagnosis of CSP from our department and classified these cases into four grades according to the implantation depth and the ultrasound morphology. A gestational sac (GS) embedded in less than one-half thickness of the myometrium was categorized as grade I, and a GS embedded in more than one-half thickness was considered grade II. In grade III CSP, the GS bulged out of the cesarean scar, and grade IV was defined as cases in which the GS became an amorphous tumor with rich vascularity at the site of a previous cesarean scar.

### **【Results】**

Seventy-eight women received surgery, and the complication rate was 12.8% (10/78). Linear regression analysis demonstrated a significant association between the invasiveness of the operation and the ultrasound grading. The main-stream operation for grade I CSP was transcervical resection, while the majority of grade III and IV patients required hysterotomy or hysterectomy. Another 31 women received chemotherapy with methotrexate as their initial treatment. The success rate for chemotherapy was only 61.3% ; the remaining patients had to receive further surgery due to persistent CSP or heavy bleeding during or after chemotherapy. Fifteen patients (48.3%) receiving chemotherapy suffered from complications (mostly bleeding). Among them, 7 (22.6%) patients experienced bleeding of more than 1,000 mL, while 10 (32.3%) of these 31 patients required blood transfusions to stabilize.

### **【Conclusions】**

Our new ultrasonographic grading system may help determine the optimal surgical strategy for CSP. Chemotherapy with methotrexate for CSP is not satisfactory and is associated with a high rate of complications.

## Chien-Nan Lee

Prof. Chien-Nan Lee is the Professor and Attending Physician of Obstetrics, Department of Obstetrics and Gynecology, National Taiwan University Hospital. He is the Federation of Asia and Oceania Perinatal Societies of President. His special interests are ultrasound of fetal anomaly, high risk pregnancy and prenatal genetic diagnosis. He is one of the top experts on those therapeutic area internationally.

Prof. Lee, as a professional obstetricians and a senior researcher, he published lots of clinical papers and train many young obstetricians to make them become not only clinicians but also scholars in clinical researches.

Prof. Lee is continuously appointed as a medical consultant or advisor for ultrasound of fetal anomaly, high risk pregnancy and prenatal genetic diagnosis. Also, he is frequently invited as an international speaker to share his valuable experiences and expertise in many countries, recently, he was just invited to give lectures in Vietnam, Japan and China etc.

## Prevention of Preterm Birth : Progesterone vs Cerclage

Keun-Young Lee

*Hallym University, Korea*

There are 15 million babies delivered prematurely every year, and the incidence of preterm birth is rising. Each year 1.1 million babies die of complications from preterm birth (PTB), making PTB one of the important issues in the obstetrics field worldwide. Several studies have proven that the use of either progesterone or cervical cerclage is effective in the prevention of preterm delivery. Regarding progesterone, the exact mechanism of its action in preventing PTB is unknown, although several mechanisms are proposed. In general, the evidence seems to favor two mechanisms : an anti-inflammatory effect that counteracts the inflammatory process leading to PTB, and a local increase in progesterone in gestational tissues that counteracts the functional decrease in progesterone leading to PTB. Regarding cervical cerclage, meanwhile, compared to the case of no intervention it is associated with reductions in the rate of PTB at 37 weeks of gestations and in perinatal mortality. There are many different guidelines for preventing PTB recommended by the ACOG, SMFM, SOGC, and NICE. Most of their regimens mix the measurement of CL by transvaginal ultrasound

followed by either progesterone or cervical cerclage. However, there is controversy about the issue of progesterone vs cerclage for prevention of PTB. We don't have sufficient data to determine what the best treatment for PTB prevention is, among progesterone vs cerclage vs cerclage with progesterone. Several studies have investigated the use of vaginal progesterone after cerclage and pessary. Among the various routes of progesterone delivery, including intramuscular, vaginal and oral, vaginal progesterone has the advantages of easy access and satisfactory patient compliance. Although expectant management is an alternative to using vaginal progesterone after cerclage for short cervical length, randomized studies and long-term safety data are needed to establish consensus guidelines. Adjuvant vaginal progesterone therapy with PEICC has been associated with reductions in SPTB, low birthweight and neonatal intensive care unit admission. I would also like to introduce my algorithm, based on my clinical experiences including ultrasound-indicated cerclage by Lee's cerclage balloon and my published papers.

## Keun-Young Lee

### Contact details :

Department of Obstetrics and Gynecology  
Kangnam Sacred Heart Hospital  
College of Medicine, Hallym University  
Seoul  
Korea

**Current position :** Professor in the Department of Obstetrics and Gynecology, Vice President, Hallym University Medical Center

**Primary speciality :** Obstetrics and gynecology, and maternal-fetal medicine

**Clinical interest :** Preterm Labour, cervical insufficiency

**Biography :** Keun-Young Lee is a Professor in the Department of Obstetrics and Gynecology at the Hallym University College of Medicine, Seoul, Korea. He trained in medicine at Chung-Ang University, Seoul, Korea, and obtained his PhD at same institute. He has current position since 1997, and appointed Vice President of the Hallym University Medical Center in 2010. He has previously been chairman of the department (2006-2014) and Director of the Kangnam Sacred Heart Hospital, (2006-2010) and was past President of the Korean Society for Maternal-Fetal Medicine (2008-2010).

Professor Lee is expert at performing rescue, transabdominal and ultrasound-indicated cerclage procedures, and has developed a new method of emergency cerclage, as well as new diagnosis and treatment methods for cervical incompetence. He made Lee's (uniconcave) cerclage balloon and have patented with the Korean, USA, Japanese government and EU. He has a special interest in clinical and translational research for cervical insufficiency, particularly the pathophysiology of cervical insufficiency and preterm labour, and has built up a large bank of biological samples, including cervical mucus, amniotic fluid, maternal serum and neonatal secretion.

Professor Lee has published more than 130 papers and received several awards, including awards from the Korean Society of Ultrasound (2000) and "Best Paper of the Year" prize from the Korean Society of Obstetrics and Gynecology (2005). He is influential in Korea and internationally, and has been invited to speak at several international congress. Professor Lee has authored many articles and several text book chapters in the field of cervical insufficiency. He has been worked as an editorial board at several international journal of Obstetrics such as Maternal-Fetal Neonatal Medicine.

**Patent :** Lee's Cercalge Balloon

**Published "Use of a uniconcave balloon in emergency cerclage"**

**American Journal of Obstetrics and Gynecology, 2015, 212 : 111-114**

Korean Patent 10-117085

USA Patent 9,028,506 B

Japan Patent 5863717

## 1) Current Status and Issues of Cervical Cancer Screening in Japan

Kiyoshi Ito

*Tohoku University / JSOG*

In Japan, cervical cancer screening is conducted as a national project, and early discovery had contributed to reduction of morbidity and mortality rates for cervical cancer. Miyagi prefecture is one of the first areas in Japan to be involved in mass screening for cervical cancer since the 1960's. However, incidence rates for cervical cancer has recently been increasing especially among young women such as 20s and 30s in Japan. In the national screening guideline, cervical cancer screening is performed by cervical cytology (Pap smears) in women aged 20 years and over every two years, although there is no upper age limitation. At this present, there are several problems existed in cervical cancer screening and prevention program in Japan. First of all, the rate of cervical cancer screening is extremely low especially among young gen-

eration. The effects of a free-coupon program under financial support from the national government was limited. Secondly, no surveillance data exist at the national level. Third, cervical cancer screening using either human papillomavirus (HPV) testing alone or HPV testing combined with cytology is still not recommended for population-based screening, although screening using conventional and liquid-based cytology is recommended. Finally, the proactive recommendation for HPV vaccinations by the government has been suspended since June 2013, following repeated media reports of adverse events after the vaccination. Thereafter, the rate of HPV vaccination decreased dramatically. I will overview the current status on cervical cancer screening and prevention in Japan.

# MEMO



## 2) Paradigm Change in Cervical Cancer Screening with HPV Testing

Young-Tak Kim

*University of Ulsan, Asan Medical Center, Korea / AOFOG*

In 2015, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated interim clinical guidance for use of primary hrHPV testing for cervical cancer screening. That is based on grown evidence for screening with primary hrHPV testing. Previously approved US FDA labeling for hrHPV testing included triage of equivocal cytology (i.e., ASC-US) and as an adjunct to cytology when screening women 30 years and older (cotesting). However, a large prospectively-conducted FDA registration trial of primary hrHPV screening demonstrated improved sensitivity against CIN2 and CIN3 over cytology alone. In April 2014, the FDA approved modified labeling of a hrHPV assay to include primary hrHPV screening for women 25 years and older. Data from ATHENA and other studies support the use of genotyping for HPV 16 and 18 as a way to triage hrHPV positive women.

Primary hrHPV screening has made an important scientific and clinical advance in cervical cancer screening since it offers better reassurance of low cancer risk compared to cytology-only screening conducted at the same interval. Primary hrHPV screening can be considered as an alternative to current cytology-based screening approaches including cytology alone and cotesting. Until now, there is lack of firm consensus about a well-defined and evaluated strategy to manage hrHPV-positive women, inadequate information to define appropriate screening intervals for hrHPV-negative women, and lack of data on testing errors due to specimen inadequacy and cost-effectiveness. While there continue to be numerous practical and research questions, primary hrHPV testing has a potential to further reduce morbidity and mortality of cervical cancer.

## Young-Tak Kim

### Present Title and Affiliation :

Professor of Department of Obstetrics and Gynecology  
 Director, Asan Medical International  
 University of Ulsan, Asan Medical Center, Seoul, Korea

### Education and Certification :

1981 M.D. College of Medicine, Yonsei University, Seoul, Korea  
 1991 Ph.D. Graduate School, Yonsei University, Seoul, Korea

### Postgraduate Training :

1994–1995 Fellowship at the Dept. of Pathology, Johns Hopkins University Hospital, USA.  
 2003–2004 Visiting Professor, Ohio State University Hospital, USA

### Academic and Administrative Appointments :

2002 : Secretary General, IXth Biennial Meeting of IGCS 2002  
 2002–2003 : Member of Educational Committee of IGCS  
 2003–2004 : Member of Developmental Committee of IGCS  
 2004–2005 : Representative of Asia–Oceania in Nominating Committee of IGCS  
 2005–2006 : Secretary General of AOGIN  
 2007–2015 : Council of Asia Oceania Federation of Obstetricians and gynecologists (AOFOG)  
 2007–2008 : Cervix Committee Member of GOG  
 2009–2012 : Chairman of Scientific Committee of KSOG  
 2014– Executive Board Member of Korean Society of Cancer  
 2015– Executive Council of FIGO  
 2015– Chairman of Oncology Committee of AOFOG  
 2016– Chairman of Educational Committee of AOGIN  
 2016– Member of Educational Committee of IGCS  
 2016– President of Korean Society of Gynecologic Oncology

### 3) Paradigm Change in Cervical Cancer Screening with HPV Testing

Yin-Ling Woo

*University Malaya Medical Centre, Malaysia / AOFOG*

Organized cervical screening in high-resourced countries have led to significant reductions in new cases of cervical cancer. However, it is acknowledged that the implementation of Pap smear programs in many countries have not been successful for the lack of highly skilled human resources, infrastructure and other barriers to screening. In the meantime, many countries are now adopting HPV vaccination as primary prevention. This does not negate the need for cervical cancer screening but calls for a paradigm change. The 2013 WHO guidelines along

with many professional bodies clearly recommend HPV testing for cervical screening. In fact, many high income countries are now in the process of changing their well-established cytology based programs into HPV testing based programs. The entire landscape of cervical cancer prevention is now changing and stakeholders need to review the necessary steps and options that will be appropriate for their setting. The application of design thinking principles to cervical screening should serve as a starting point in addressing the unmet needs.

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## Yin-Ling Woo

Professor Woo Yin Ling is a Consultant Gynaecological Oncologist in University Malaya Medical Centre, Kuala Lumpur. She is a clinician scientist, having completed her specialist and subspecialty training in gynaecological oncology in the UK. Professor Woo was a Royal College of O and G Gold medallist for the MRCOG. She was also awarded the Gordon Hamilton-Fairley Fellowship by Cancer Research UK to undertake her research in the area of human papillomavirus immunology and was conferred her PhD by the University of Cambridge.

Professor Woo is now part of a multidisciplinary team in University Malaya Medical Centre involved in cancer service provision/ development and collaborative research. Her most recent undertaking involves applying the principles of design thinking to cervical screening in Malaysia.

#### 4) AOFOG Initiatives for Cervical Cancer Control in Low Resource Countries

Pisake Lumbiganon<sup>1,2</sup>

*The Royal Thai College of Obstetricians and Gynaecologists, Thailand / AOFOG<sup>1</sup>,*

*Vice President, Asia Oceania Federation of Obstetrics and Gynecology<sup>2</sup>*

Cervical cancer is one of the leading causes of cancer death in women most of which occur in low- to middle income countries. Unfortunately, about half of cervical cancer cases in the world occur in Asian countries. Asian countries with high incidence of cervical cancer include Bangladesh, Cambodia, Indonesia, India, Myanmar, Philippines and Thailand.

HPV is the most common infection usually occur early in sexual life. A minority of HPV infections persist and may lead to cervical pre-cancer in women. These pre-cancer lesions if not treated properly, may progress to cancer 10 to 20 years later. HPV vaccine has been recently launched in many countries but it will take more than 10 to 20 years before it can have significant effect in cervical cancer control. Cervical cancer is a treatable disease if detected in pre-cancer or early invasive stage. The main reason for is usu-

ally the lack of effective secondary prevention that include adequate screening coverage and effective treatment of those women with positive tests.

Asia and Oceania Federation of Obstetrics and Gynecology (AOFOG) is a regional professional organization responsible for improving reproductive health in the region. At its recent executive board and action plan meeting in Penang, Malaysia AOFOG decided to initiate pilot project for cervical cancer control in Asia. Philippines and Thailand were selected to be the first two countries to start comprehensive cervical cancer control. International organizations such as JHPIEGO and WHO were approached for possible technical supports. Appropriate strategies for each country will be planned, implemented and evaluated.

## Pisake Lumbiganon

Pisake Lumbiganon is a Professor of Obstetrics and Gynecology, Convenor of Cochrane Thailand and Director of the WHO Collaborating Centre on Research Synthesis in Reproductive Health based at Faculty of Medicine, Khon Kaen University, Thailand. He is also the President of the Royal Thai College of Obstetricians and Gynaecologists and the Vice President of Asia Oceania Federation of Obstetrics and Gynecology. He got his MD and Obstetrics and Gynaecology training from Ramathibodi Hospital, Mahidol University in Thailand and Master of Sciences in Clinical Epidemiology from the University of Pennsylvania in the US. He has been involved with various WHO Reproductive Health Research projects including many multicentre randomized controlled trials. He has been convening the Thai Cochrane Network since its inception in 2002. He has published more than 150 papers including many Cochrane reviews in various international journals. He was awarded as the distinguished researcher in medical science by the National Research Council of Thailand in 2010. He was a dean of the Faculty of Medicine at Khon Kaen University from 2009 to 2013. His main areas of interest includes maternal and perinatal health, evidence based practices, systematic review and meta-analysis.

## AOFOG Program : Cervical Cancer Screening in Asian Countries

### 5) Cervical Cancer in Cambodia and Its Challenges

Koum Kanal<sup>1</sup>, Chhun Luon<sup>2</sup>, Sann Chan Soeung<sup>1</sup>

*Cambodian Society of Gynecology and Obstetrics, Cambodia / AOFOG<sup>1</sup>,*

*NCD Bureau, MoH, Cambodia<sup>2</sup>*

Uterine cervical cancer is the most common type of cancer among women and becomes a major public health concern in Cambodia. It is estimated that 1,500 women are newly diagnosed cervical cancer cases and at least 900 women die of cervical cancer each year.

Cambodian Ministry of Health (MOH) is increasingly giving priority to cervical cancer from 2005. The MOH Non-Communicable Disease strategy (2012–2015) also emphasizes the high need to address cervical cancer prevention and control. For its implementation, since 2012, two screen and treat projects has been started to find out the most effective strategy for the Cambodian context. One pilot project is using (VIA+ Cryotherapy) in several provinces under the collaboration with MOH and NGOs, and results to be determined.

Another pilot has been conducted with the different implementation strategy (HPV test + LEEP) by SCGO with the collaboration of JSOG. Targeting female factory workers, this project uses a comprehensive approach, starting from health education to increase awareness for cervical cancer, primary screening with HPV test, and secondary check at national hospitals with colposcopy and early treatment with LEEP. First screening was conducted and 31 female factory workers participated in June 2017, with 4 cases of HPV test positive (positive rate of 12%). Registered female workers were about 20% of targeted people in the factory (older than 25 years old, ever married), but no one came for secondary check till September 2017. HPV test costs 5

US\$ per test, and it took only one month for laboratory technicians to handle HPV test properly under the quality control with JSOG support. Main challenges are to promote cervical cancer screening and to connect first screening and secondary check.

HPV vaccine demonstration program was also started since 2017. Core strategy of school vaccination is used with a target of 9-year old girls in 2 provinces and monitored by the MON National Immunization Program.

MOH plans to update Standards Operational Procedure on cervical cancer screen and treat into National Standard Operating Procedures for cervical cancer screening in Cambodia and finalize National Action Plan for Prevention & Control of Cervical Cancer.

Challenges we need to overcome are Leadership and governance, Health care financing Health Work Force, Medical products and technologies, information and research and service delivery.

Conclusion : Aging population of Cambodia start to increase. The incidence of cancer is indeed increasing and becoming a public health issue and an economic burden to society. It is necessary to have a comprehensive intervention including appropriate strategy, appropriate human resources and adequate system in the Cambodian context and need more investment to boost more coverage of vaccination, screening and to open more accessibility to cancer treatment in the whole country.

## Koum Kanal

President of CAMBODIAN Society of Gynecology and Obstetrics

Nationality: CAMBODIAN living in Phnom Penh, CAMBODIA as President of Cambodian Society of Gynecology and Obstetrics

Graduate as Medical Doctor in 1981 from Faculty of Medicine, University of Health Science in Phnom Penh, CAMBODIA and Professor Hospitalo Practitioner University from University of Health Science, Phnom Penh, Cambodia in 2000.

Working as Director of National Maternal and Child Center from 2000 to 2011 (till retired).

Now Still as Vice Chair of the Gynecology and Obstetrics Department of the University of Health Science and The President of The Cambodian Society of Gynecology and Obstetrics, CAMBODIA.



# 1) Acute Myometritis in Refractory Postpartum Hemorrhage : The Underlying Pathology and the Development of Novel Treatment for Uterine-type Amniotic Fluid Embolism

Naoaki Tamura

*Hamamatsu University School of Medicine / JSOG*

Postpartum hemorrhage is the main cause of maternal postpartum death over the world. It may occur in various pathologies, such as abnormal placental attachment, birth canal laceration, uterine atony, and abnormal blood coagulation, but uterine atony is the most frequent cause accounting for 70% of cases. Although excess uterine extension and fatigue of the uterine muscle during pregnancy and delivery are known as the main inducers of uterine atony, it cannot be explained by these conditions alone, and many cases of postpartum hemorrhage are resistant to treatment with compression of the uterus, such as circle massage and oxytocin administration. Why does this pathology of uterine contractile dysfunction develop? In the project on serodiagnosis of amniotic fluid embolism performed by our department in our country, patients who developed cardiopulmonary lethargy, massive bleeding, disseminated intravascular coagulation

of unknown cause during pregnancy or soon after delivery and required differentiation of amniotic fluid embolism were registered following the entry criteria, and development of uterine atony-induced treatment-resistant postpartum hemorrhage was identified in many cases accounting for about 80%. For this condition, we proposed a concept of uterine-type amniotic fluid embolism. Since complement activation, increase in IL-8, and uterine edematous changes are observed in uterine-type amniotic fluid embolism, we hypothesized that immune reactions in the maternal body cause local inflammation in the uterine muscle and induce treatment-resistant postpartum hemorrhage. We would like to present our study based on uterine pathology and introduce clinical application of C1 esterase inhibitor for uterine edema due to anaphylactoid reaction.

MEMO

## 2) Comparison of Various Markers for Intrauterine Growth Restriction/ Small-for-gestational Age Fetuses in the First Trimester

Chen-Yu Chen

*MacKay Memorial Hospital / TAOG*

Intrauterine growth restriction (IUGR) and small-for-gestational age (SGA) fetuses are at increased risk of perinatal mortality and morbidity worldwide. Prophylaxis with aspirin during the first or second trimesters and/or combined with heparin before conception, may reduce the incidence of IUGR/SGA in high risk groups.

Despite improvement in the understanding of the pathophysiology, abilities in the first trimester to precisely predict pregnant women who will develop IUGR/SGA are limited. While different measures of placental dysfunction are associated with increased risk for adverse pregnancy

outcomes, the abilities of various markers to accurately predict IUGR/SGA have been studied, such as biochemical serum markers, ultrasound and Doppler study of uterine and spiral arteries, and placental volume and vascularization.

Risk factors for IUGR/SGA are easy to assess but have poor predictive value. The use of first trimester biochemical markers in combination with ultrasound markers is promising as a potential screening tool. Modern assessments suggest combined algorithms using these strategies, all with the goal of a better prediction of IUGR/SGA.

## Chen-Yu Chen

Department : Obstetrics and Gynecology

Affiliation : MacKay Memorial Hospital

Nationality : Taiwan

\*Education :

1. M.D., College of Medicine, National Cheng Kung University, Taiwan
2. Ph.D., Institute of Biomedical Engineering and College of Medicine, National Taiwan University, Taiwan

\*Current positions :

1. Attending Physician & Director of Division of High Risk Pregnancy, Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taiwan
2. Associate Professor, Department of Medicine, MacKay Medical College, Taiwan

\*Honors and Awards :

1. New Talent Award (Taiwan Society of Perinatology, 2012)
2. Distinguished Paper Award (Taiwan Society of Perinatology, 2013, 2014, 2015, and 2016)
3. Distinguished Paper Award (Association of Chemical Sensors in Taiwan, 2015, 2016 and 2017)

\*Research Interests :

1. High risk pregnancy
2. Fetal therapy
3. Biomedical engineering
4. Nanomedicine

### 3) Maternal Anti-Fetal Rejection As a New Mechanism of Spontaneous Preterm Birth

JoonHo Lee

*Yonsei University / KSOG*

Preterm birth is defined as birth before 37 complete weeks of gestation, which is one of the most important causes of neonatal mortality and morbidity. It is classified into three groups (extremely preterm birth, moderately preterm birth, and late preterm birth) according to the gestational age at birth. As late preterm birth (birth between 34 and 36 weeks of gestation), accounting for more than 70% of preterm birth, is associated with long-term complications including neonatal respiratory distress syndrome, hy-

poglycemia, infantile death, cerebral palsy, mental retardation, behavioral disorders in childhood, management of late preterm birth is required. However, mechanism of late preterm birth is not yet established well, while intrauterine infection/inflammation is a well-known etiology of extremely preterm birth. Recently, maternal anti-fetal rejection has been proposed as a new mechanism of spontaneous preterm birth, especially late preterm birth, which will be discussed this time.

## JoonHo Lee

Assistant Professor  
 Division of Maternal-Fetal Medicine  
 Department of Obstetrics and Gynecology  
 Yonsei University College of Medicine

### Education

1999 M.D. in Seoul National University College of Medicine  
 2007 M.S. in Seoul National University College of Medicine  
 2013 Ph.D. in Seoul National University College of Medicine

### Postgraduate Training

2000-2004 Residency training in the Dept. of OBGY, Seoul National University Hospital (SNUH)  
 2007-2008 Clinical & Research Fellow in the Dept. of OBGY, SNUH  
 2009-2011 Research Associate in Perinatology Research Branch/NICHD/NIH/DHHS,  
 Hutzel Women's Hospital/Wayne State University  
 2011-2011 Visiting Scholar in the Dept. of Periodontitis and Oral Medicine,  
 University of Michigan School of Dentistry  
 2012-2015 Assistant professor in the Dept. of OBGY, SNUH  
 2016- Present position

### Representative Bibliography

Lee J, Romero R, Lee KA, et al. Meconium aspiration syndrome : a role for fetal systemic inflammation. *American Journal of Obstetrics and Gynecology*. 2016 ; 214 (3) : 366.e1-9.

Lee J, Romero R, Dong Z, et al. Glycogen phosphorylase isoenzyme BB plasma concentration is elevated in pregnancy and preterm preeclampsia. *Hypertension*. 2012 ; 59 (2) : 274-282.

Lee J, Romero R, Xu Y, et al. A Signature of Maternal Anti-fetal Rejection in Spontaneous Preterm Birth : Chronic Chorioamnionitis, Anti-Human Leukocyte Antigen Antibodies, and C4d. *PLoS One*. 2011 ; 6 (2) : e16806.

## 1) Current Status of Uterus Transplantation Research in Japan : Towards Clinical Application

Iori Kisu, Kouij Banno, Yusuke Matoba, Masataka Adachi, Daisuke Aoki

*Keio University / JSOG*

Uterus transplantation (UTx) has become an alternative to gestational surrogacy and adoption for women with uterine factor infertility. Brännström et al. achieved the first human delivery after UTx in 2014 and to date a total of 8 babies have been born after UTx from living donors. This outcome attracted much attention worldwide and many countries have recently prepared for UTx followed by Swedish team.

We launched UTx research in 2009 considering that UTx may provide new hope to these Japanese women. The guidelines of the International Federation of Gynecology and Obstetrics (FIGO) indicate that adequate studies in large animals, including primates, should be conducted before clinical application. Therefore, we have performed UTx research using cynomolgus macaque for this purpose, with the first successful

delivery after autologous UTx in non-human primates in 2012. We have examined many issues including immunological response and rejection in UTx and we believe UTx is possible from a technical viewpoint with our experimental experience and clinical data overseas.

However, this procedure has many medical, ethical and social issues that require discussion prior to clinical application. Moreover, UTx is still in the experimental stage overseas and the safety and efficacy remain unclear despite several clinical applications. Despite the many issues to be resolved, this new organ transplantation technology will provide new hope for women with uterine factor infertility and further development of the technology is important for future reproductive and gynecological medicine.

MEMO



## 2) Roles of Exosome-Associated Glycosphingolipids in Immune Tolerance of Embryo Implantation and Pregnancy

Hsien-Ming Wu

*Chang Gung Memorial Hospital Linkou Medical Center / TAOG*

Establishment of pregnancy requires synchronized growth between the endometrium and the blastocyst. Functional interaction between these occurs both during the pre-implantation phase of embryo implantation and during placentation. Pregnancy is a unique event in which a fetus, despite being genetically and immunologically different from the mother, develops in the uterus. Successful pregnancy implies avoidance of rejection by the maternal immune system. Exosomes released from the endometrium and the embryo are present in uterine fluid. These can transfer miRNA, mRNAs, proteins and lipids between cells, thus providing endometrial-embryo communication in the peri-implantation period. Exosomes have been considered of critical importance for embryo implantation and programming of human pregnancy. We examined that the action of glycosphingolipids (GSLs) in exosomes, and their role as preventing the embryo from being attacked by the maternal immune system. Human villus trophoblast cells were isolated from the abortus tissue from

healthy women undergoing pregnancy termination of a pregnancy at 6- to 12-wk gestation, after informed consent. Pretreatment with exosomes significantly induced macrophage M2 polarization. Moreover, isolated exosomes from villus trophoblast cells were confirmed by transmission electron microscopy images. Pretreatment with exosomes derived from villus trophoblast cells of a normal pregnancy significantly induced macrophage M2 polarization compared with anembryonic pregnancy through M1 macrophage marker expression by qRT-PCR. We demonstrate that GSLs were significant expressed in exosomes derived from villus trophoblast cells, indicating the GSLs have potential modulatory role on embryo implantation and decidual programming of human pregnancy. These represent a new concept regarding the immunomodulatory capacity of exosomes from embryos and villi, suggesting that exosomes have potential modulatory role on embryo implantation and decidual programming of human pregnancy.

## Hsien-Ming Wu

Hsien-Ming Wu received M.D. degree from Taipei Medical University in 1996. He received his PhD from the Graduate Institute of Clinical Medical Science, Chang Gung University, Taiwan in 2009 for his thesis on Gonadotrophin-releasing hormone (GnRH) signalings in intrauterine tissues. He trained as a postdoctoral research fellow in the University of British Columbia, Canada. He is presently working as an associate professor, clinician, teaching faculty, researcher and chief of Reproductive Endocrinology and Infertility in the Department of the Obstetrics and Gynecology of the Chang Gung Memorial Hospital, Linkou Medical Center, Taiwan.

His research interests include reproductive endocrinology, GnRH system, infertility, and artificial reproductive treatment. With over a hundred academic publications and presentations, Dr. Wu is a noted expert in the clinical management of infertility, IVF and other disorders of the reproductive system. Dr. Wu is the principal investigator for Ministry of Science and Technology-funded grants that have impacted infertility therapy in Taiwan.

Dr. Wu received a lot of awards, including the awards from Taiwan Society for Reproductive Medicine (TSRM), Chien-Tien Hsu Cancer Research Foundation, the Infertility Foundation of the Taiwan, and FertiLink reproduction meeting.

### 3) Fertility Preservation in Gynecologic Cancer Patients

Chan Woo Park

*Cheil General Hospital & Women's Healthcare Center, Dankook University College of Medicine / KSOG*

Despite predominantly occurring in postmenopausal women, approximately 20% of gynecologic malignancies take place in women of reproductive age who have yet to complete family planning. When broken down by subtype, 8% of endometrial cancers, 12% of ovarian cancers, and 40% of cervical cancers occur in patients during their childbearing years.

Improvements in cancer diagnosis and treatment have resulted in an improved survival rate, allowing these patients to focus on their quality of life. Fertility preservation (FP) has become an important issue for cancer patients of reproductive age.

In gynecologic malignancies, fertility-sparing surgery is a viable option for certain early-stage cancer patients, including those with early cervical carcinoma, early endometrial adenocarci-

noma, ovarian tumors of low malignancy, and some selected cases of unilateral ovarian carcinoma (stage IA). A conservative approach to fertility involves sparing the uterus and a unilateral ovary during surgery. However, in cases of advanced gynecologic malignancies, reproductive organs such as the uterus and ovaries must be removed by radical surgery. The removal of reproductive organs through radical surgery makes it difficult to consider future pregnancies. A few reports have discussed *ex vivo* retrieval in advanced-stage gynecologic cancer patients.

Herein, we report a case series of FP using *in vitro* matured oocytes retrieved from macroscopically normal ovarian tissue harvested during radical surgery, and live birth from *in vitro* fertilization after fertility-sparing surgery for early-stage gynecologic cancer patients.

## Chan Woo Park

Associate Professor  
Department of Obstetrics & Gynecology  
Cheil General Hospital & Women's Healthcare Center  
Dankook University College of Medicine

Chanwoo Park, MD, PhD received his doctorate of medicine and PhD in medical science at Hallym University, Chuncheon, Korea. He then went on to complete his internship and residency at the Kangdong Sacred Heart Hospital, Hallym University, Seoul, Korea. Dr. Park's clinical fellowship was in reproductive endocrinology and infertility at Samsung Cheil Hospital, Seoul, Korea. During his career he spent a year as a research fellow at the Division of REI, Dept. of Ob/Gyn at the Southwestern Medical Center, University of Texas, Dallas, TX, USA.

## The Most Important Discoveries of the Past Fifty Years in Gynecologic Pathology

Steven Silverberg

*Professor Emeritus of Pathology, University of Maryland, USA*

In commemoration of my 50th year as an academic pathologist, I have compiled two lists of important discoveries/publications in gynecologic pathology during those years. Both will be discussed in more detail in this lecture. The list based on responses from ten distinguished gynecologic pathologists is as follows : (1) role of HPV in lower female genital cancers and precancers ; (1) (tie) diagnostic immunohistochemistry ; (3) frequency of metastases to ovary/role of STIC ; (4) uterine serous carcinoma ; (5) AIS and gastric-type cervical adenocarcinomas ; (5) (tie) aspects of molecular pathology/genomics. My own list : (1) development of diagnostic im-

munohistochemistry in formalin-fixed, paraffin-embedded tissue specimens ; (1) (tie) WHO Classification of 1973 and The Bethesda System of 1988 ; (3) HPV as a causative agent in development of cervical, vaginal, and vulvar preinvasive and invasive carcinomas ; (4) endometrial atypical hyperplasia/intraepithelial carcinoma/EIN as type I carcinoma precursor ; (5) discoveries concerning ovarian and extraovarian serous carcinomas, and (tie) vaginal clear cell adenocarcinoma and its relation to intrauterine diethylstilbestrol (DES) administration. I hope that similar lists will emerge for gynecologic oncology, endocrinology, and other subspecialties.

## Steven Silverberg

Clinical Professor of Pathology

### Education

|      |   |      |
|------|---|------|
| A.B. | Brooklyn College, Brooklyn, New York          | 1958 |
| M.D. | Johns Hopkins University, Baltimore, Maryland | 1962 |

### Internship (medical)

|  |             |
|--|-------------|
| Cornell Division Bellevue and Memorial Hospitals, New York | 1962 – 1963 |
|--|-------------|

### Residency (anatomic pathology)

|                                |             |
|--------------------------------|-------------|
| Yale University, New Haven, CT | 1963 – 1965 |
|--------------------------------|-------------|

### Fellowship (pathology)

|  |             |
|--|-------------|
| Memorial Hospital for Cancer and Allied Diseases, New York, N.Y. | 1965 – 1966 |
|--|-------------|

### Certification

|   |      |
|---|------|
| Diplomate, American Board of Pathology<br>(certified in Anatomic Pathology) | 1969 |
|---|------|

Medical Licensures District of Columbia ; Maryland, #D0051037 (expires 9/30/13)

### Major Research

Interests Differential diagnosis, epidemiology, natural history and prognostic markers of cancers and precancers of female genital tract, breast, and prostate ; development and standardization of diagnostic and prognostic algorithms ; investigation of cytopathologic/histopathologic correlations ; study of variability in pathologic interpretations.

### Military Service

|   |             |
|---|-------------|
| Captain, USAF (MC), Staff Pathologist, Tachikawa Air Base Hospital, Japan | 1966 – 1968 |
|---|-------------|

### Employment History

|   |              |
|---|--------------|
| Assistant Professor of Surgical Pathology, Medical College of Virginia, Richmond, VA                  | 1968 – 1971  |
| Associate Professor   | 1971 – 1972  |
| Associate Professor of Pathology, University of Colorado Health Sciences Center, Denver, Colorado     | 1972 – 1978  |
| Professor of Pathology  | 1978 – 1981  |
| Professor of Pathology, George Washington University Medical Center, Washington, D.C.                 | 1981 – 1996  |
| Professor of Pathology, University of Maryland School of Medicine, Baltimore, MD                      | 1996 – 2003  |
| Clinical Professor, Department of Pathology, University of Maryland School of Medicine, Baltimore, MD | 1/04–6/30/08 |
| Professor Emeritus, University of Maryland School of Medicine   | 7/2010       |

### Major Academic Tasks

|  |             |
|--|-------------|
| Director of Pathology Residency Program, University of Maryland Medical System, Baltimore, MD                    | 1997 – 2004 |
| Medical Director of Pathologist Assistant Training Program, University of Maryland Medical System, Baltimore, MD | 1999 – 2004 |
| Director of Anatomic Pathology, University of Maryland Medical System, Baltimore, MD                             | 1996 – 2004 |
| Director of Anatomic Pathology, George Washington University, Washington DC                                      | 1981 – 1996 |
| Director of Surgical Pathology, University of Colorado, Denver, Colorado   | 1972 – 1981 |
| Executive Director, Colorado Regional Cancer Center, Denver, Colorado  | 1976 – 1980 |

### Professional Memberships

American Society for Clinical Pathology (Fellow) ;  
 International Academy of Pathology ; American Society of Cytopathology ; Japanese-American Society of Pathologists ;  
 Washington Society of Pathologists ; Arthur Purdy Stout Society of Surgical Pathologists ; Phi Beta Kappa ; Sigma Xi ; In-  
 ternational Society of Gynecological Pathologists ; Society of Gynecologic Oncologists (Associate Member) ;  
 International Gynecologic Cancer Society ; Papanicolaou Society ; Mid-Atlantic Gynecologic Oncology Society ; Interna-  
 tional Society of Breast Pathology ; Association of Directors of Anatomic and Surgical Pathology ; Maryland Society of Pa-  
 thology

## 1) Integrated Analysis of Genomic and Transcriptomic Data in Ovarian Clear Cell Carcinoma

Kosuke Yoshihara

*Niigata University / JSOG*

Clear cell carcinoma (CCC) is the second most common subtype of ovarian carcinomas (OCs) in Japan accounting for about 25% of OCs. CCC shows resistance to platinum-based chemotherapy and hence development of new therapeutic strategies based on molecular characteristics of CCC is urgently required. The aim of this study is to identify therapeutic molecular targets in CCC. We performed targeted sequencing of 25 homologous recombination (HR) associated genes including OC associated genes and RNA sequencing for 74 and 61 CCC samples, respectively. According to previous results, 74% of CCC harbored *ARID1A* somatic mutations, and coexistent *ARID1A* and *PIK3CA* mutations were de-

tected in 57% of CCC. In addition, 12 CCC samples (16%) had somatic mutations of HR associated genes that might be biomarkers of PARP inhibitor sensitivity. Next, we ran Pipeline for RNA sequencing Data Analysis (PRADA) to detect therapeutic targetable fusion transcripts with high confidence. In total, 151 fusion transcripts with high confidence were detected in 61 CCC samples. Especially, 10 CCC samples had a kinase in-frame fusion transcript which could be considered as therapeutic targets. This integrated molecular characterization provides a comprehensive foundation for developing CCC precision medicine.

MEMO



## 2) Discovery and Translation of Epigenetic Biomarker in Women's Cancers

Hung-Cheng Lai<sup>1,2</sup>

*Shuang Ho Hospital / TAOG<sup>1</sup>,*

*Taipei Medical University, Taiwan<sup>2</sup>*

Epigenetics is pervasive in almost every aspect of cancers. The pursuit of new diagnostics and therapeutics has been in high hopes since the burgeoning of epigenetic phenomenon in early 21st century. We have been exploring DNA methylation in gynecological cancers as an effort to improve cancer screening and develop new therapies.

The unsatisfactory cytology-based Pap smear and virus-based HPV testing leaves the unmet need for cervical cancer screening. By methylomic analysis, we discovered PAX1/ZNF582/POU4F3 methylated in cervical cancer with clinical applicability. In 2016, Taiwan FDA approved PAX1 (Cervi-M) as an adjunct testing for cervical cancer screening. In addition, combined

testing of POU4F3/HPV (CONFENDENCE) has completed a multi-center trial in Europe.

The incidence of endometrial cancer is increasing worldwide. There are no screening methods so far. We identified a panel of methylation biomarkers, and verified the feasibility of using the methylation profile of cervical scrapings to detect endometrial cancer. By a panel of DNA methylation from cervical scrapings, we can detect endometrial cancer with the sensitivity and specificity >90%. These molecular biomarkers expand the scope of Pap smear, which has been used for more than half a century and is used widely in developed countries with a high prevalence of uterine cancer. The transition to *in vitro* diagnostics and a prospective trial is ongoing.

## Hung-Cheng Lai

Professor  
Chair, Department of OB/ GYN  
School of Medicine, Taipei Medical University

Vice Superintendent, Chairman, Department of OB/ GYN, Shuang Ho Hospital, Taipei Medical University

### ◎Education

- PhD, Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, R.O.C. 2000.08-2003.02
- MD, National Defense Medical Center, Taipei, Taiwan, R.O.C. 1986.08-1993.07

### ◎Professional Experiences

- Visiting Scholar, Human Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, Columbus, Ohio, U.S.A., 2005.08-2005.12
- Visiting Scholar, German Cancer Research Center (DKFZ), Heidelberg, Germany, 2002.07-2002.08

### ◎Expertise

- Epigenetics and Biomarker · Cancer Stem Cells · Robotic Surgery

### ◎International Grant Reviewer

- Italian Ministry of Health (MOH), Italy
- United Arab Emirates University (UAEU), United Arab Emirates
- Health and Medical Research Fund (HMRF), Hong Kong
- Israel Science Foundation (ISF), Israel
- Dutch Cancer Society – KWF Kankerbestrijding, Netherlands

### ◎Editorial Board

- Editorial Board of the journal “Gynecologic Oncology”  
(official J. of Am. Society of Gynecology Oncology)
- Editorial Board of the journal “Journal of Gynecologic Oncology”  
(official J. of Asian Society of Gynecology Oncology)
- Associate editor of “Taiwanese Journal of Obstetrics and Gynecology”  
(official J. of Taiwan Association of Obstetrics and Gynecology)

### 3) HOXB9 as a Potential Target Gene for Overcoming Platinum Resistance in Mucinous Ovarian Cancer

Dong Hoon Suh

*Seoul National University / KSOG*

Although ovarian cancer is heterogeneous with various histologic types, current treatment guidelines are generally the same for all histologic types. Expression of HOX genes in epithelial ovarian cancer (EOC) was known to be histology-specific. We performed a series of in vitro and in vivo studies to find out a tailored strategy of inhibiting HOXB9 expression for overcoming platinum resistance in mucinous EOC. HOXA10 and HOXB9 showed exclusively high expression in SKOV-3 and RMUG-S, respectively. HOXA10 siRNA treatment made a significant decrease in cell viability of SKOV-3, but not RMUG-S. By contrast, HOXB9 siRNA treatment made a significant decrease in cell viability of RMUG-S, but not SKOV-3. HOXA10 siRNA and HOXB9 siRNA treatments : increased the expression level of cleaved PARP and caspase-3 in SKOV-3 and RMUG-S, respec-

tively ; expression of vimentin was decreased while expression of E-cadherin was increased ; SOX-2, Nanog, and Oct-4 also decreased in both cell lines after specific siRNA treatment. When injected with RMUG-S<sup>ko HOXB9</sup> and SKOV-3<sup>oe HOXB9</sup> in mouse models, we clearly showed that the tumors from RMUG-S<sup>ko HOXB9</sup> grew significantly slower than those from control. By contrast, the tumors from SKOV-3<sup>oe HOXB9</sup> grew significantly faster than those from control. After harvesting, the cells from the SKOV-3<sup>oe HOXB9</sup> were characterized with resistance to cisplatin and higher expression of vimentin than those from the control.

Our findings suggest that platinum-resistance of mucinous ovarian cancer might be defeated by inhibiting HOXB9, which could be a target of tailored strategy for overcoming the resistance to platinum in mucinous EOC.

## Dong Hoon Suh

Dong Hoon Suh is a clinical professor of the department of obstetrics and gynecology in Seoul National University Hospital. He is a gynecologic oncology specialist.

He is one of the acting members of the Asian Society of Gynecologic Oncology, ASGO, particularly taking an active part in its official journal, 'Journal of Gynecologic Oncology' as an associated editor. He has been also deeply involved in other medical journal activities as a committee member for Planning and Evaluation of Korean Association of Medical Journal Editors, KAMJE.

International Workshop for Junior Fellows (IWJF) :

1. Cross-country Differences in Routine Prenatal Examinations

1) Cross Country Differences in Routine Prenatal Examinations :  
The US and Japan

Supraja Rajagopalan

*Medical University of South California, USA*

*ACOG*

The tenants of prenatal care are universal, they are rooted in protecting mothers and their infants with the goal of reducing maternal and infant morbidity and mortality. The US and Japan are both strongly invested in this goal. While the two share many practices in prenatal care, there are also many differences. The goal of this presentation is to highlight an understanding of the differences in prenatal care between the two

countries. I aim to do this by exploring the historical, cultural, and economic contexts of health-care in each country. I will then apply each of these lenses to each prenatal care delivery system and to the specific components of prenatal examinations in practice. I will also discuss pregnancy outcomes in both countries as they relate to these systems of practice.

## International Workshop for Junior Fellows (IWJF) :

### 1. Cross-country Differences in Routine Prenatal Examinations

#### 2) Routine Prenatal Examinations in Taiwan

Cleo Tsai

*Cathay General Hospital, Taiwan*

*TAOG*

Prenatal routines around the world generally follow a set guideline, but may vary a bit from place to place due to prevalent diseases particular to a location or population group. The National Health Insurance system is unique to Taiwan. This system offers 10 prenatal visits including lab tests, urinalysis, and one mid-trimester ultrasound scan to assess for fetal anomalies. Another aspect particular to Taiwan is the increased prevalence of HBV and thalassemia carriers, and general screening for these two diseases is done upon the first prenatal lab testing. Amniocentesis is provided for patients with advanced maternal age or other high-risk indications at 16 to 18 gestational weeks. Gestational diabetes mellitus (GDM) is assessed as well dur-

ing 24 to 28 gestation weeks.

As most pregnant women tend to be concerned with the health and safety of their babies, we also do offer a variety of self-paid laboratory exams. These include non-invasive prenatal testing (NIPT), early Down's screening, early prediction for preeclampsia, spinal muscular atrophy (SMA) testing, Fragile-X testing, TORCH screen, and array CGH. Level II ultrasound, 3D/4D ultrasounds, and a series of further ultrasounds to assess for fetal development and growth not included in the health exams can also be performed upon patient's request.

Here, we present the current situation of the pyramid of prenatal care in Taiwan.

## International Workshop for Junior Fellows (IWJF) :

### 1. Cross-country Differences in Routine Prenatal Examinations

## 3) The Current Status of the Guidelines of Non-invasive Prenatal Testing (NIPT) in Japan, South Korea and Taiwan

Joseph J. Noh, Soo-Young Oh, Suk-Joo Choi, Cheong-Rae Roh, Jong-Hwa Kim

*Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

KSOG

#### **【Purpose】**

Non-invasive prenatal testing (NIPT) for chromosomal aneuploidy became commercially available in Japan, South Korea and Taiwan in 2013. We explored the current status of the development of guidelines in regards to NIPT use in the three nations.

#### **【Methods】**

A PubMed search of the literature using the pertinent keywords was undertaken, and 15 journal articles published in the three nations were reviewed.

#### **【Results】**

In Japan, prenatal genetic screening is performed in less than 5% of all pregnancies and is mostly performed as second-trimester maternal serum screening. With a growing interest in prenatal screening in recent years however, the Japan Society of Obstetrics and Gynecology published clinical guidelines in 2013 recommending NIPT for women who meet the following conditions : (1) the fetal ultrasound suggests the possibility of a fetal chromosomal abnormality ; (2) maternal serum screening suggests the possibility of a fetal chromosomal abnormality ; (3) a previous pregnancy had a fetal chromosomal abnormality ; (4) pregnancy occurs at an older age ; (5) trisomies 21 and 13 in the fetus are considered possible due to a balanced Robertsonian translocation in either parent. It also recommends undergoing NIPT only after receiving genetic counseling from an obstetrician and pediat-

ric genetic specialist or an approved genetic counselor. These guidelines are similar to those published by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.

Guidelines similar to the Japanese that emphasize the use of the test in high risk pregnant women as a screening method are currently being developed in South Korea, but there are no official guidelines by professional societies or organizations in regards to the use of NIPT yet. Taiwan is in similar conditions to South Korea. In Taiwan, prenatal genetic screening has been mandated by law since 1985, but at present, the first trimester combined test and second trimester quadruple test are the main tools for routine prenatal care and it recently began integrating NIPT in prenatal care.

#### **【Conclusion】**

The three nations are all avidly adopting the NIPT in prenatal screening. Japan has been the most active not only in evaluating the performance of the test but also in providing clinical guidelines that consider psychological and social issues ensued from performing the test. It was observed in all three nations that a high proportion of pregnant women favored the introduction of the test in obstetrical care. Therefore, it seems necessary for professional societies to establish clear guidelines that take into account of the ethical, legal, social and economic aspects of the test.

## International Workshop for Junior Fellows (IWJF) :

### 1. Cross-country Differences in Routine Prenatal Examinations

#### 4) Cross-country Differences in Routine Prenatal Examinations

Sayaka Kawashita, Haruhisa Konishi, Mamoru Shigeta

*JSOG*

The latest maternal mortality rate in Japan is 3.4 per 100,000 deliveries in 2015. That has been decreasing consistently since the 1980s and is sufficiently low. Furthermore, the perinatal mortality rate is 3.6 per 1,000 live births. The demographic statistics reveal a high level of safety of pregnancy and childbirth in Japan. In this presentation, we review our characteristic prenatal examinations compared with foreign countries.

In Japan, municipalities take charge of maternal and child health. Pregnant women usually go to regular medical checkups using the public health system. We perform a total of 14 checkups until delivery, once every 4 weeks until the 23<sup>rd</sup> week, every 2 weeks until the 35<sup>th</sup> week and every week after the 36<sup>th</sup> week. The content is almost identical throughout the entire nation. The result of the prenatal checkup is recorded in the maternity passbook published by municipalities. The passbook is systematically used through the duration of the pregnancy.

Patients are usually managed at primary medical institutions from the confirmation of intrauterine pregnancy until delivery. However, we evaluate their perinatal risks such as complications and their course of pregnancy each time, and we decide whether to introduce them to appropriate advanced medical institutions, namely regional perinatal medical centers (191 centers nationwide) and comprehensive perinatal medical centers (91 centers nationwide). High-risk pregnancies are managed at fully-equipped ad-

vanced medical institutions with massive manpower in collaboration with other departments such as neonatology, anesthesiology and so forth.

One of the characteristics of prenatal examinations in Japan is the high frequency of ultrasound examinations. It is common practice to examine fetal development and amniotic fluid volume by ultrasonography every checkup. Detailed examinations focusing on organic diseases in fetuses have also been emphasized recently. Although a review is necessary for the purpose of effective utilization of limited medical resources, it is definitely useful for the discovery of fetal growth restriction, large babies, non-reassuring fetal status and infant diseases that require postnatal early treatment. In conclusion, the reduction of regional disparities by public expenditure and the established system of managing high-risk pregnancies lead to a high level of safety for pregnancy and childbirth in Japan.

In association with women's social advancement, the average age of first childbirth has been rising in Japan. There is a growing demand for prenatal diagnosis including non-invasive prenatal genetic testing (NIPT) started in 2013. However, some matters remain unresolved such as shortage of genetic counselors and insufficient support systems for eligible patients.

It is important for us to make further progress in prenatal management through examining ourselves and learning from foreign countries on this occasion.



International Workshop for Junior Fellows (IWJF) :

2. Work-life Balance for OB/GYN Doctors : Pregnancy and Parenthood with Careers

1) Work-life Balance for OB/GYN Doctors :  
Managing Pregnancy and Parenthood with Careers

Alison Dixon

*Loyola University Medical Center, USA*

ACOG

Being a parent is difficult no matter what career you choose. Balancing work-life demands, including pregnancy and parenting, is especially difficult in OB/GYN, with busy inpatient services and surgery schedules. This talk is a gather-

ing of reflections on work-life balance in OB/GYN from a group of American OB/GYN residents and attendings. We will discuss overall challenges in the field and some limitations specific to American work-life balance.

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International Workshop for Junior Fellows (IWJF) :

## 2. Work-life Balance for OB/GYN Doctors : Pregnancy and Parenthood with Careers

### 2) The Challenges of Work-life Balance for Female Physicians in OB-GYN versus Other Specialities : Managing Pregnancy and Parenthood with Careers

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TAOG

#### 【Background】

As the increasing numbers of female physicians and the pressure to choose between competing in career and being a dedicated mother, the issue of coordinating family and career become important. Women physicians may encounter more challenges in childbirth and parenthood, especially in women obstetricians and gynecologists (OB-GYNs). In this study, we assessed and compared experiences of managing work-life balance, pregnancy, childbirth, and parenthood between women OB-GYNs and other specialties.

#### 【Methods】

An anonymous survey questionnaire including factors affecting specialty or workplace chosen and childbearing timing, work-life balance, and satisfaction with the policy of maternal and parental leaves was mailed to 25-40 years female physicians in the study institute. Mann-Whitney test was used to identify and compare the career and life choices and the difficulties in pregnancy and parenthood with careers between women OB-GYNs and other specialties.

#### 【Results】

A total of 93 women physicians responded, 47 (50.5%) and 40 (43%) of whom thought more barriers in career and life, respectively compared with their male coworkers. Among 43 married physicians, 23 (53.5%) reported delayed family planning and childbirth because of training. Twenty-two women physicians had at least one child and took 8 weeks maternity leave. Although 13 women (59%) were unsatisfied with the short maternal leave, only 2 (9%) had parental leave. Comparing women OB-GYNs with other specialties, more OB-GYNs chose to work in medical centers and had more working hours and night shifts. However, the attitude towards family planning and maternal leave had no significant difference.

#### 【Conclusions】

Women physicians conflicted more challenges in workplace and delayed childbirth with dissatisfaction of 8 weeks of maternal leave. The study suggested more strategies to lessen the child-bearing burden in training and practice.

## International Workshop for Junior Fellows (IWJF) :

## 2. Work-life Balance for OB/GYN Doctors : Pregnancy and Parenthood with Careers

## 3) Reality of Young Korean Doctors' in Marriage, Childbirth, and Child-rearing : A Comprehensive Interview Survey

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KSOG

**【Objective】**

Korea is rapidly becoming an aging society because of its declining birth rate combined with an increasing life expectancy. The total fertility rate of the Korean women, at 1.24, is one of the lowest. This study aimed to investigate the young Korean doctors' current state of marriage, childbirth, and child-rearing.

**【Methods】**

A comprehensive interview survey was conducted on trainee of the Department of Obstetrics and Gynecology in two institutional hospitals, Seoul National University Hospital and Seoul National University Bundang Hospital. Presently, 41 residents and 15 fellows work and all of them were enrolled.

**【Results】**

In total, 56 young doctors responded the survey (response rate, 100%). Mean age was 31.8 years (range, 26.4–39.1) and male doctors accounted for 14.3% : two are residents and six are fellows. Of the doctors, 23 (41.1%) were married and only 8 (14.3%) gave birth with the mean num-

ber of 1.4 (range, 1–2). Three female doctors and spouses of the two male doctors were pregnant at the time of survey. The reasons behind low marriage and birth rates were various. Doctors commonly responded that hospital's welfare programs are insufficient : female doctors can use only three months on maternity leave. Married doctors requested child care facilities in hospital. In addition, many reported that they are not financially stable enough to get married or raise a child, putting off marriage and/or childbirth until they finish training and get a secure job. Some young single doctors complained of lack of dating due to overwork.

**【Conclusion】**

From the interview survey, we could recognize the young Korean doctors' current state and worrisome regarding marriage, childbirth, and child-rearing. Young Korean doctors showed low marriage and birth rates. Hospital's welfare supports as well as Korean government's policies which encourage young Korean doctors to get married and to have more children are needed.

## International Workshop for Junior Fellows (IWJF) :

### 2. Work-life Balance for OB/GYN Doctors : Pregnancy and Parenthood with Careers

#### 4) Actual Condition of Work-life Balance of OB&GY Doctors in Japan

Ranka Kanda, Naoyuki Iwahashi, Masumi Ishibashi

*JSOG*

From the 1990s onward, the support of work-life balance (harmonization of work and lifestyle) has drawn much attention in Japan. To improve female workers' work-life balance is considered as one of the solution strategies to Japan's problems that include a declining birthrate and aging society.

The number of OB&GY doctors in Japan, both male and female has been decreasing year by year since its peak in 2010. The number of female doctors aged less than 40 has exceeded the male doctors of the same generation since 2013. More female doctors tend to leave their positions due to childbirth and childcare than male doctors. To avoid female doctors leaving their positions, the Japanese Society of Obstetrics Gynecology has advocated the importance of work-life balance.

Many female doctors have to leave their positions due to childbirth and childcare in Japan. And after they return to work, they are obliged to limit their working hours, accept decreased income, and suspend their careers in order to raise their children. On the other hand, to support female doctors raising their children with limited work time, the other doctors have been burdened with a heavy workload. As the current systems of encouraging work-life balance particularly support female doctors during pregnancy or child raising in Japan, other doctors feel unfairness in the contents and volume of work and appraisal of their performances.

To achieve a comfortable work-life balance, it is necessary to understand the diversity of life styles of individual doctors, and secure economic stability, a healthy, enriched life, and availability of flexible and diversified working styles for all doctors, not only for female doctors raising their children.

To create a good work-life balance for all workers, the term "IKUBOSS" was generated in 2013. "IKU" stands for "ikuji", which means raising a child, and "IKUBOSS" means a supervisor who takes the initiative in creating a workplace environment supportive of work life balance. "IKUBOSS" is responsible for supporting the private lives and careers of subordinates, while also enjoying a work-life balance fully, obtaining profits for the organization, and solving the problems of conflict between the supporter side and doctors who need support.

However, "IKUBOSS" is not yet appreciated in the OB&GY field and there are quite a few senior supervisors who feel confused about the practice on the site. This is because the supervisors who are expected to play the role of "IKUBOSS" have too much work as OB&GY doctors, and some senior supervisors do not understand the sense of values that places importance on personal and family life, as well as atmosphere of workplace. There are few supervisors who can serve as role models.

We expect the work-life balance of all OB&GY doctors to be improved.

## Luncheon Seminar 31

## Are Environmental Toxics Affecting Reproductive Health Globally —What is the Evidence?

Linda Giudice

*University of California, USA*

The past 70 years have demonstrated an alarming global increase in developmental abnormalities, intellectual disabilities, reproductive compromise, respiratory, endocrine and metabolic disorders, and cancer. As these changes have occurred in a relatively short time frame, it is unlikely that genetics is their sole cause, and it is likely that environmental factors are significant contributors. Globally, chemicals in agriculture, pesticides, industrial waste, personal care products, household cleaning agents, and nearly ubiquitous plastics, along with particulate matter in indoor and outdoor air pollution are of great concern. Human epidemiologic studies and wildlife and laboratory data support risks and plausible causation of these agents in human disease risk. Exposures to environmental toxics at

critical windows of development have adverse effects on reproductive tract development and function through epigenetic and other mechanisms, resulting in or exacerbating, e.g., male and female infertility, endometriosis, polycystic ovarian syndrome, uterine fibroids, and per-term delivery. Additionally, disadvantaged populations have higher likelihood of living in contaminated communities and higher risk occupations, augmenting their risks of poor reproductive outcomes. This lecture will review relevant data supporting environmental toxics as putting world reproduction at risk and highlight how reproductive and other healthcare professionals are well positioned to advocate for global solutions to prevent these growing harms to the health of this and future generations.

## IS-AC-1-1

**Uterine progesterone signaling is a mechanistic target for metformin therapy in polycystic ovary syndrome** Linus R Shao<sup>1</sup>, Yuehui Zhang<sup>1,2</sup>, Min Hu<sup>1</sup>, Hakan Billig<sup>1</sup> *The Sahlgrenska Academy at the University of Gothenburg, Sweden<sup>1</sup>, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, China<sup>2</sup>*

**Background** Impaired progesterone (P4) signaling is linked to endometrial dysfunction and infertility in women with polycystic ovary syndrome (PCOS). However, the molecular mechanisms behind this association are not well characterized. Metformin is one of the primary therapeutic drugs for PCOS patients, where beneficial treatment of endometrial dysfunction is observed clinically, but the effects of metformin on the regulation of the P4 signaling pathway are not fully understood. **Objective** The present study sought to establish how the P4 signaling pathway is involved in improved uterine function in PCOS patients treated with metformin. **Study design** Differential expression of two progesterone receptor (PR) isoforms in endometria samples from non-PCOS and PCOS patients was observed. Using an established PCOS-like rat model, which exhibits similar pathological alterations of both uterine morphology and function, we determined the molecular mechanism underlying metformin-induced alterations of P4 signaling molecules before and after implantation. To determine whether metformin directly regulates PR, we evaluated PR-targeted and implantation-related gene expression in an in vitro study of rat uterine tissues. **Results** We found that in the absence of P4 or to sustained low levels of P4, both uterine PR isoforms were elevated in PCOS patients and in PCOS-like rats in vivo. This was positively associated with the high levels of estrogen receptor (ER) expression. Consistent with mouse knockout studies, decreased or increased expression of Fkbp52 and Nco2, two genes that contribute to uterine P4 resistance, was observed in PCOS-like rats before and after implantation. Our data showed that metformin directly suppressed uterine PR isoform expression along with the correction of aberrant expression of PR-targeted and implantation-related genes in PCOS-like rats. Abnormal cell-specific regulation of PR and ER, paralleling the aberrant expression of PR-targeted and implantation-related genes, was retained in some PCOS-like rats with implantation failure. In addition, while increased PR expression was associated with inhibition of the MAPK/ERK/p38 signaling pathway, metformin treatment mainly restored the MAPK/p38 signaling pathway in PCOS-like rat uterus. **Conclusion** Our results suggest that the P4 signaling pathway might constitute the target of metformin treatment in PCOS patients with uterine dysfunction.

## IS-AC-1-2

**Quantification of primordial follicle using optical coherence tomography intended for investigating effective ovarian tissue transplantation** Seido Takae<sup>1</sup>, Kosuke Tsukada<sup>2</sup>, Yorino Sato<sup>1</sup>, Naoki Okamoto<sup>1</sup>, Chie Nishijima<sup>1</sup>, Nobuhito Yoshioka<sup>1</sup>, Yodo Sugishita<sup>1</sup>, Yuki Horage<sup>1</sup>, Haruhiro Kondo<sup>1</sup>, Junichi Hasegawa<sup>1</sup>, Kazuhiro Kawamura<sup>1</sup>, Nao Suzuki<sup>1</sup> *St. Marianna University School of Medicine<sup>1</sup>, Keio University Graduate School of Science and Technology<sup>2</sup>*

**Objective** Assessment of ovarian reserve on each ovarian tissue will enhance the effect of ovarian tissue transplantation. Nevertheless, there are no established noninvasive techniques for quantification of primordial follicles in fresh ovarian tissue. Optical coherence tomography (OCT) is high resolution imaging technique equivalent to microscope with near-infrared ray (NIR). In present study, we verified potency of OCT for clinical application. **Methods** OCT with ovaries from each life stage mice was performed to establish standard follicle images. To

verify the safety of OCT, outcome of in vitro fertilization (IVF) was compared among follicles from day3 mice ovaries irradiated stepwise NIR (60 to 250 mW/cm<sup>2</sup>). Also, day3 mice ovaries with/without OCT were transplanted under kidney capsule of host mice. Two weeks later, outcome of IVF with transplanted ovaries were confirmed, and newborns were bred. Finally, OCT was performed using human ovary tissues which obtained from two hematological disease girls who received ovarian tissue cryopreservation as fertility preservation. And follicle count was performed with OCT as quantification of follicle numbers. **Results** The standard OCT images were established including primordial follicle. And NIR irradiation and OCT examination did not affect for IVF outcome. Furthermore, all of newborns were shown normal appearances including reproductive ability. Finally, OCT images of human ovarian tissues were well-accorded with histological images. As the result of follicle count, there were no significant differences between histology and OCT (p=0.98). **Conclusion** In present study, potency of OCT for clinical application was demonstrated to quantify of follicles aimed at effective ovarian tissue transplantation.

## IS-AC-1-3

**The PGC-1 $\alpha$ -mediated pathway as a potential therapeutic target in endometriosis** Hisashi Kataoka, Taisuke Mori, Fumitake Ito, Akemi Koshihara, Osamu Takaoka, Hiroyuki Okimura, Eiko Maeda, Takuya Sugahara, Yosuke Tarumi, Izumi Kusuki, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** Previously, we reported that PGC-1 $\alpha$  stimulates aromatase activity to promote local estrogen biosynthesis in ovarian endometrioma. In this study, we investigated the potential of PGC-1 $\alpha$  as a molecular target for endometriosis treatment. **Methods** Stromal cells (SCs) from ovarian endometrioma (OE, n=21) and normal endometrium (NE, n=8) tissue were cultured. The SCs were transfected with PGC-1 $\alpha$  or knocked down for PGC-1 $\alpha$  using siRNA. The expression level of PGC-1 $\alpha$  and other factors during endometriosis was examined by real-time PCR and western blotting. Cell proliferation was measured by the WST-8 assay. Transcriptional activity was examined by a luciferase reporter assay. HX531, a selective Retinoid X Receptor (RXR) antagonist, was used post transfection with PGC-1 $\alpha$ . **Results** PGC-1 $\alpha$  overexpression promoted the proliferation of OESCs, but not of NESCs, in a time-dependent manner (P<0.01). PGC-1 $\alpha$  stimulated the expression of aromatase, IL-6, IL-8, and VEGF (P<0.05). Phosphorylated I $\kappa$ B was observed post transfection with PGC-1 $\alpha$ . The expression of XIAP and survivin, inhibitors of apoptotic proteins, was also upregulated (P<0.05). HX531 suppressed the PGC-1 $\alpha$ -induced cell proliferation (P<0.05); this compound also suppressed the expression of the factors listed above (P<0.05). Moreover, transcriptional reporter activity was inhibited by HX531 in a dose-dependent manner (P<0.05). PGC-1 $\alpha$  knockdown reduced the expression of aromatase, IL-6, IL-8, and anti-apoptotic factors (P<0.05). The immunostaining intensity of RXR in OE was significantly greater than that in NE. **Conclusion** PGC-1 $\alpha$  plays important roles during cell proliferation in endometriosis. Thus, the PGC-1 $\alpha$ -mediated pathway could be a potential molecular target for endometriosis treatment.

## IS-AC-1-4

**HSD3B1 and Androgenetic alopecia in polycystic ovarian syndrome women** Yi-An Tu, Mei-Jou Chen *National Taiwan University Hospital, Taiwan*

**Objective** Androgenetic alopecia (AGA) is a common phenotype in women with PCOS. However, the mechanism of AGA is still unknown. *HSD3B1* (1245A>C) has been mechanistically linked

to polycystic ovarian syndrome (PCOS) because it encodes an altered enzyme that augments dihydrotestosterone synthesis from non-gonadal precursors. We postulated that women inheriting the *HSD3B1* 1245C allele would exhibit specific phenotypic variances in PCOS. **Methods** Between 2004 and 2011, in the single center, we included 472 women with PCOS and determined their *HSD3B1* genotype and correlated genotype with phenotypic outcomes, including androgenetic alopecia, acne, hirsutism, obesity, hypertension, and laboratory evidence of androgen excess and dyslipidemia. **Results** We included and genotyped 472 PCOS patients. Androgenetic alopecia was significantly increased ( $p=0.046$ ) in women with heterozygous variant genotype ( $n=56$ , 23.2%), compared to that with homozygous wild-type genotype ( $n=416$ , 13.5%). In PCOS women with AGA, we found significantly higher BMI (26.9 vs. 23.0 kg/m<sup>2</sup>,  $p<0.001$ ), lower sex hormone binding globulin (22.5 vs. 31.7 nmol/L,  $p<0.001$ ), higher free androgen index (9.6 vs. 8.4,  $p=0.034$ ), and more hypertension (15.9 vs. 7.7%,  $p=0.037$ ). The frequency of *HSD3B1* 1245C allele (0.076) in this PCOS cohort was similar in previous reported Asian ethnicity (0.072). **Conclusion** Inheritance of the *HSD3B1* 1245C allele that enhances peripheral dihydrotestosterone synthesis is associated with AGA phenotype in PCOS. This is the first study elucidating the possible genetic contribution of AGA phenotype in PCOS women.

### IS-AC-2-1

**Clinical outcomes and risk of recurrence among patients with vaginal intraepithelial neoplasia** Mi-Kyung Kim<sup>1</sup>, In Ho Lee<sup>2</sup>, Ki Heon Lee<sup>3</sup> *Ewha Womans University of Korea, Korea<sup>1</sup>, Cheil General Hospital and Women's Healthcare Center, Dankook University of Korea, Korea<sup>2</sup>*

**Objective** To evaluate the clinical outcomes of vaginal intraepithelial neoplasia (VAIN) and to assess the risk of recurrence and progression to invasive vaginal carcinoma. **Methods** A retrospective review of the clinicopathologic data and clinical outcomes was performed on patients who were diagnosed with VAIN at a single center between January 2000 and July 2016. Demographics, treatments, and clinical outcomes were abstracted from medical records. **Results** A total of 576 patients with VAIN1-3 were included in the study analysis. The distribution of VAIN1-3 was as follows : VAIN1 31.1%, VAIN2 45.3%, and VAIN3/in situ carcinoma (CIS) 23.6%. In VAIN1 patients, observation was performed in 29.1% of the cases and 48.8% obtained regression. In VAIN2+ patients, management included observation (3.5%), topical management (6.5%), laser ablation (75.3%), excision (14.1%), and radiotherapy (0.5%) with the following rates of recurrence/progression : 46.2%, 62.5%, 26.4%, 32.7%, and 0%, respectively. Four patients among VAIN3/CIS patients (3.2%) developed invasive vaginal cancer during the follow-up period with a median time to cancer diagnosis of 21.4 months (range, 5.0-44.8 months). On multivariate analysis, high-risk HPV positivity and treatment method were found to be independent risk factors for recurrence and progression ( $p=0.003$  and  $p=0.001$ ). **Conclusion** Patients with VAIN are at high risk of recurrence, but the risk of progression to vaginal cancer is relatively low. Laser or excision provides higher regression rate than topical agent or observation, and high-risk HPV positivity is a risk factor for recurrence. Whatever the treatment method is used, however, the high rate of recurrence warrants long-term follow-up surveillance.

### IS-AC-2-2

**Acceptability and thoughts about Multipurpose Human Papillomavirus Vaccines in Korean physicians and mothers of Adolescent Girls : What to consider when introducing a new vaccine** Hyewon Seo, Jahyun Koo, Minjin Jeong, Keunho Lee,

Taecheul Park, Jongsup Park, Chanjoo Kim *Catholic University of Korea, Korea*

**Objective** Cervical HPV infection is a common sexually transmitted infection. In Korea, given the high priority of preventing HPV-associated cervical disease including cancers, HPV vaccines were integrated into national vaccination programs in 2016. The importance of vaccines is emerging as the age of first sexual experience is getting younger. Multipurpose vaccines (MPVs) could be formulated to prevent multiple sexually transmitted infections. This study was five countries' collaborative study (Argentina, Malaysia, South Africa, South Korea, and Spain) on MPVs acceptability led by the US in 2013. We aimed to assess the acceptability of hypothetical MPVs for STI prevention. And further, what to consider when introducing a new vaccine. **Methods** We conducted in-depth interview with 30 physicians for the acceptability of MPVs. We conducted focus group discussion (FGD) with the 31 mothers of adolescent daughter. Focus group discussion (FGD) with 31 mothers of adolescent girls was done in 4 groups according to their daughter's HPV vaccination status and social status. One group was consisted with mothers of vaccinated daughters and the other 3 groups were mothers of un-vaccinated daughters. **Results** We found out the research about MPV showed 71% of the mothers preferred single-purpose HPV vaccines over MPVs. 'too much' 'sounds too dangerous' 'sounds less effective and more expensive'. Concerns about Safety and efficacy was common barriers to accepting MPVs. More mothers of vaccinated girls have pros for the MPV (vaccinated vs unvaccinated 37.5% [3/8] vs. 26.1% [6/23]) but it was not statistically significant. Providers have positive attitude (62%) toward MPVs. 'expect less follow up vaccination loss' 'convenient' are the main reasons. They said the biggest problem with introducing a new vaccine was its cost and lack of publicity, mentioned television advertisement as the most effective way to promote. **Conclusion** Effective recommendation and guideline should be promoted in more detail at the specialized subcommittee when we accept new vaccine, and all these activities will need national support. Publicity and effort will be needed to change the viewpoint on obstetrics and gynecology at the national level as well. If we give information to the people with sufficient understanding of the disease and to recognize the need for a vaccine, the introduction of new vaccines is expected to be successful in the future.

### IS-AC-2-3

**Contribution of T helper 17 in peripheral blood to expression of PD-L1 in ovarian cancer** Aeri Aotsuka<sup>1</sup>, Yoko Matsumoto<sup>1</sup>, Ayumi Taguchi<sup>2</sup>, Takahide Arimoto<sup>3</sup>, Juri Ogishima<sup>4</sup>, Akira Kawata<sup>1</sup>, Katsutoshi Oda<sup>1</sup>, Kei Kawana<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo Hospital<sup>1</sup>, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital<sup>2</sup>, Toranomon Hospital<sup>3</sup>, Nihon University Itabashi Hospital<sup>4</sup>*

**Objective** The PD-1/PD-L1 pathway has shown promising clinical success as a cancer immunotherapy target. T helper 17 cells (Th17) inducing Interleukin-17 (IL-17) are known as cause of autoimmune diseases. In this study, we aimed to analyze the role of Th17 in peripheral blood in the regulation of PD-L1 expression in human ovarian cancer. **Methods** Blood samples of 30 ovarian cancer patients and 18 healthy controls (HC) were collected under approval of our institutional ethics committee. Ratio of Th17 in peripheral blood mononuclear cells (PBMCs) and expression level of IL-6 in plasma were analyzed by multi-color flow cytometry and enzyme-linked immunosorbent assay. Expression levels of PD-L1 mRNA in PBMCs was quantified by real-time polymerase chain reaction. We refer to the clinical record of neutrophil-to-lymphocyte ratio (NLR) which can be a prognostic marker in ovarian cancer. **Results** Flow cytometry



revealed that the ratio of Th17 of ovarian cancer patients were significantly higher ( $p=0.002$ ) than HCs. The ratio of Th17 was associated with NLR in ovarian cancer patients ( $p=0.023$ ). Moreover, Th17 and NLR were also correlated with concentration of IL-6 ( $p=0.003$  and  $p=0.008$ , respectively). Quantitative real-time PCR analysis revealed that the expression of PD-L1 mRNA of ovarian cancer patients was not significantly distinct from that in HCs. However, we observed that IL-17 induced both PD-L1 and IL-6 mRNA expressions with upregulation of PD-L1 protein expression in a human ovarian cancer cell line. **Conclusion** Our data suggest that increase of Th17 ratio in PBMCs contributes to the upregulation of PD-L1, which may lead to immune tolerance in ovarian cancer.

### IS-AC-2-4

**Microsatellite instability is a potential biomarker for immune checkpoint inhibitor (anti PD-1/PD-L1 antibody) in endometrial cancer** Hitomi Yamashita, Kentaro Nakayama, Masako Ishikawa, Tomoka Ishibashi, Kohei Nakamura, Kaori Ohnishi, Ruriko Ono, Hiroki Sasamori, Kouji Iida, Razia Sultana, Toshiko Minamoto, Satoru Kyo *Shimane University*

**Objective** Tumor cells have immune escape mechanism and immune checkpoint inhibitor therapy (anti PD-1/PD-L1 antibody) has shown benefit in various cancers. Somatic mutations have the potential to encode non-self immunogenic antigens and lymphocytes infiltrate tumor cells in microsatellite-unstable (MSI) endometrial cancers. Therefore, immune checkpoint inhibitor therapy might be effective in MSI endometrial cancers. **Methods** Mismatch repair protein (MLH1, PMS2, MSH2, and MSH6), tumor-infiltrating lymphocytes (CD8), and PD-1/PD-L1 expression were assessed by immunohistochemistry in 60 patients with endometrial cancer. We examined whether MSI status have enhanced immune microenvironment and become the therapeutic effect predictor of PD-1/PD-L1 immunotherapy in endometrial cancer. **Results** Loss of mismatch repair protein (MSI group) was identified in 42 (27.2%) of 154 patients with endometrial cancer. Expression of tumor-infiltrating lymphocytes (CD8) and PD-1/PD-L1 were significantly higher in MSI group compared to MSS group ( $p=0.007$ ,  $p=0.010$  and  $p<0.001$ ). **Conclusion** These results suggested that immune checkpoint inhibitor (anti PD-1/PD-L1 antibody) is effective in endometrial cancers with MSI. MSI testing is likely to be a biomarker for PD-1/PD-L1 immunotherapy in endometrial cancer.

### IS-AC-3-1

**Nationwide cohort study of the risk of major adverse cerebrovascular and cardiovascular events in the Asian women with endometriosis** Hsin-Ju Chiang<sup>1</sup>, Kuo-Chung Lan<sup>1</sup>, Yao-Hsu Yang<sup>2</sup>, Pei-Hsun Sung<sup>3</sup> *Kaohsiung Chang Gung Memorial Hospital, Taiwan<sup>1</sup>, Department of Traditional Chinese Medicine, Health Information and Epidemiology Laboratory, Chang Gung Memorial Hospital, Taiwan<sup>2</sup>, Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan<sup>3</sup>*

**Background** Emerging evidence shows growing cardiovascular risk in a number of women's disease. Based upon positive correlation of anti-Müllerian hormone to cardiovascular disease in recent studies, we investigated the association between endometriosis and major adverse cerebro-/cardio-vascular events (MACCE) in an Asian population. **Method** Taiwan National Health Insurance Research Database (NHIRD) was utilized for this retrospective population-based cohort study (1997-2013). A total of 17,543 patients with endometriosis and age between 18 and 50 years were identified from 1,000,000 general populations after excluding initially concomitant diagnoses of MACCE. The MACCE was defined as major cardiovascular disease (ma-

ajor CVD, comprising myocardial infarction and heart failure) and cerebrovascular accident (CVA, including ischemic and hemorrhagic strokes). The comparison group ( $n=70,172$ ) without endometriosis was selected matching study cohort with age, gender, income and urbanization in a 1 : 4 ratio. We compared the demographic data, frequency of comorbidities, incidence of and risk of MACCE between the disease and non-disease groups. **Results** With a median follow-up of 9.2 years, the endometriosis patients had significantly higher frequency and cumulative incidence of MACCE than non-endometriosis counterparts (2.76% vs. 2.18%,  $p<0.0001$ ). After adjusting with multivariate analysis, the patients with endometriosis had 1.17-fold greater risk for future development of MACCE (95% CI 1.05-1.29,  $p=0.0053$ ). In further, the adjusted hazard ratios of endometriosis for major CVD and CVA were 1.19 and 1.16, respectively (all  $p<0.04$ ). Apart from endometriosis, older age, lower urbanization level, hypertension and diabetes were identified as risk factors for MACCE occurrence as well. On the contrary, neither medication nor surgery for endometriosis increased the risk of MACCE. **Conclusion** The risk of MACCE including major CVD or CVA increases in the Asian women at reproductive age. There is no concern of increasing MACCE risk regarding medication and surgery for endometriosis.

### IS-AC-3-2

**Mediator complex subunit 1 (MED1) is a novel binding partner of BRCA1 and regulates homologous recombination repair** Harunori Honjoh, Michihiro Tanikawa, Osamu Hiraike, Katsutoshi Oda, Yoshiko Kawata, Machiko Kojima, Shinya Oki, Kenbun Sone, Kazunori Nagasaka, Yoko Matsumoto, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Homologous recombination (HR) is a major repair pathway of DNA double strand breaks and closely correlated with carcinogenesis of breast and ovarian cancer. HR deficiency has now been established as a therapeutic target. The aim of this study was to elucidate functions of a novel HR factor, MED1, and its association with BRCA1. **Methods** Novel HR candidate genes, including MED1, were identified through genome-wide siRNA screening. The complex formation of MED1 and BRCA1 (the central integrator of HR and transcription) was analyzed by immunoprecipitation and GST pull down assay. The role as transcription cofactors of BRCA1 was analyzed by luciferase assay. The roles in DNA damage response and HR pathway were analyzed by immunofluorescence and HR assay. **Results** Among several HR candidate genes, we identified MED1 as a novel binding partner of BRCA1, which binds to BRCT domain of BRCA1. Luciferase assay showed MED1 potentiate the transcription ability of BRCT by 1.5 folds. In MED1 depleted cells, recruitment of HR genes, such as RPA and  $\gamma$ H2AX, to DNA damage sites were severely impaired. HR assay showed strong deficiency of HR in MED1 depleted cells. **Conclusion** We identified MED1 as a transcription cofactor in HR pathway. The impaired interaction of MED1 and BRCA1 may be an alternative mechanism of HR deficiency in cancer cells.

### IS-AC-3-3

**Lack of interval cytoreductive surgery after neoadjuvant chemotherapy in peritoneal, ovarian, or fallopian tube cancer: a description of reasons and treatment outcomes** Myong Cheol Lim<sup>1,2</sup>, Snag-Soo Seo<sup>1</sup>, Sokbom Kang<sup>1</sup>, Sang-Yoon Park<sup>1</sup>, Robert E. Bristow<sup>2</sup> *National Cancer Center (NCC), Korea<sup>1</sup>, Irvine Medical Center, University of California, USA<sup>2</sup>*

**Objective** To investigate the reasons for lack of interval cytoreductive surgery and subsequent treatment outcomes of patients with ovarian cancer who underwent neoadjuvant chemotherapy. **Methods** We conducted a retrospective study of women



with advanced ovarian cancer who never had interval cytoreductive surgery, by using medical chart reviews between September 2001 and December 2015. **Results** Of 470 women who received neoadjuvant chemotherapy as an initial treatment, 110 (23.4%) women did not undergo interval cytoreductive surgery. Of the 110 women, 45 (40.9%) and 65 (59.1%) patients had stage III and IV disease, respectively. The median age was 65.6 years (range, 30.6–86.4 years). The main reason for not undergoing the recommended interval cytoreductive surgery was patient refusal ( $n=29$ ; 26.4%). Other reasons included progressive disease after neoadjuvant chemotherapy (19.1%), chronic illness and/or old age (17.3%), death during neoadjuvant chemotherapy (10.9%), and persistent extraperitoneal disease (10.0%). The median overall survival for these groups was 21.8, 16.7, 14.7, 9.7, and 0.9 months for patients who refused surgery, had chronic illness and/or due to old age, had extraperitoneal disease, had progressive disease, and died during chemotherapy, respectively. In the multivariate analysis, age was the only prognostic factor for women who did not undergo interval cytoreductive surgery. **Conclusion and Relevance** Patients' refusal to undergo interval cytoreductive surgery was the main reason for the lack of surgery, resulting in a median overall survival of 21.8 months. The survival benefit of an intentionally planned treatment package, including interval cytoreductive surgery, needs to be carefully discussed with patients before administration of neoadjuvant chemotherapy.

#### IS-AC-3-4

##### **Differential localization of extracellular matrix related proteins in the uterine cervix of female pelvic organ prolapse**

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**Objective** Pelvic organ prolapse (POP) is multifactorial disorder which impairs the quality of the life of the elderly women. Although mechanical pelvic floor damage is a direct trigger of the progression of POP, genetic and molecular biological pathogenesis of POP has not been clarified yet. **Methods** POP patients ( $n=29$ ) were classified into two groups by with ( $n=13$ ) or without cervical elongation ( $n=16$ ) by POP-Q assessment. We investigated the expression of extracellular matrix (ECM) related proteins, elastin, fibulin-5 (FBLN5), integrin  $\beta 1$  (ITG $\beta 1$ ), lysyl oxidase like 1 (LOXL1) and collagen in human vaginal mucosa (VM), uterosacral ligament (USL) and uterine cervix (UC). Samples were obtained during pelvic reconstructive surgery from 29 women suffering from POP under permission of institutional IRB (2199). Localization of ECM proteins were immunohistochemically evaluated and their mRNAs were quantified by real-time polymerase chain reaction technique and correlation between mRNA level of each protein and severity of POP. **Results** FBLN5 and elastin were localized at lamina propria and fibromuscular layer of VM and USL. FBN5 gene expression was positively correlated to the advance of POP in USL of cervical elongation group, while negative correlation was observed in those of normal cervix group. ITG $\beta 1$  and LOXL1 mRNAs from UC samples significantly increased with POP-Q staging in the cervical elongation group. Expression of elastin and collagen also significantly increased in cervical elongation group. **Conclusion** The correlation between progression of POP and mRNAs of ECM related proteins was different from the existence of cervical elongation of POP. Differential expression of ECM proteins will affect the phenotype of POP.

#### IS-AC-4-1

##### **The discovery of new biomarkers for preterm birth prediction**

Hyun Joo Shin, Young-Ah You, Eun Jin Kwon, JiEun Doo, Kyung Ju Lee, MiHye Park, Young Ju Kim *Ewha Womans University Medical School, Korea*

**Objective** We aimed to investigate biological biomarkers in maternal blood, amniotic membrane, amniotic fluid, urine, and vaginal discharge to prevent preterm birth. **Methods** To determine the biomarkers for early detection of preterm delivery, 40 cytokines were measured with amniotic fluid of pregnant women using cytokine array and we screened cytokines of amniotic fluid between preterm women and normal pregnant women. Next, the 16S rRNA sequencing method using the next generation sequencing with urine, blood, and vaginal fluid in pregnant women was used to compare metagenomes that differed between preterm and normal groups. Lastly, we identified the biomarkers in maternal blood and amniotic membrane using methylation array. After screening, we performed the experiments for the validation in large samples. **Results** After cytokine array in amniotic fluid, the 15 pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-7, IL-8, TNF- $\alpha$ , MMP3, MMP8, MMP9, MIP-1 $\alpha$  and MIP-1 $\beta$ ) were significantly higher in preterm birth group. IL-10, IL-13, IL-15, IL-17 $\alpha$ , and G-CSF were significantly different among the 15 pro-inflammatory analyzed by ELISA. In urine metagenome of 73 non-pregnant women and 74 pregnant women, *Bacillus* was increased about 374 times in maternal urine, and *Lactobacillus* and *Atopobium* was increased in preterm women. Specially, premature babies born to mothers with increased *Lactobacillus*, *Ureaplasma*, *Megashaera*, *Apotobium*, *Fusobacterium*, *Sneathia* and *Prevotella* in the urine showed diseases such as hyaline membrane disease, germinal matrix hemorrhage, pneumomediastinum, respiratory distress syndrome and urinary tract infection. We tried to find metagenome related to preterm birth in maternal vaginal fluid. In this study, it was found that *Bacteriodes* and *Prevotella* were significantly increased in vaginal fluid of preterm pregnant women. One of the probiotics found in Kimchi and *Lactobacillus* were significantly decreased in vaginal fluid of preterm pregnant women. Furthermore, IL-7 was correlated with a decrease in *Lactobacillus* and an increase in *Bacteriodes*. After methylation array and experiments for validation, there were significant differences in the methylation of the KIMB gene in the maternal blood between preterm and normal groups and in the methylation of the KIMC and KIMD in the amnion ( $p<0.05$ , respectively). **Conclusion** We found several candidate biomarkers related to preterm birth in amniotic fluid, urine, blood, and amniotic membrane. We are trying to do experiments to identify candidate markers in the population. In near future, we hope the development of biomarker to predict preterm birth using non-invasive method from pregnant women.

#### IS-AC-4-2

##### **Comparison of pregnancy outcome among nulliparas with and without microalbuminuria at the end of the second trimester**

Maryam Kashanian, Shohreh Bahasadri, Zahra Khosravi *Iran University of Medical Sciences, Iran*

**Introduction** Poor pregnancy outcome and complications during pregnancy such as pre-eclampsia, preterm delivery, preterm premature rupture of membranes (PPROM) and intra uterine growth restriction (IUGR), are very important and the finding of new methods for their prediction has always been a matter of serious concern. **Objective** To evaluate the rate of poor pregnancy outcome among nulliparas who had microalbuminuria at the end of the second trimester of their pregnancy. **Methods** A prospective cohort study was performed on 490 nulliparous women who were at the end of the second trimester of

pregnancy. Urine tests for albuminuria and creatinine measurements were performed in all women and the albumin to creatinine ratio (ACR) was calculated. The women with microalbuminuria (exposed group) and those without microalbuminuria (nonexposed group) were monitored until the end of their pregnancy and compared for pregnancy outcome. **Results** Preterm labor (57.9% versus 13.5%), preeclampsia (50.0% versus 8.6%), intrauterine growth restriction (42.1% versus 6.4%), and preterm premature rupture of membranes (31.6% versus 10.2%) were significantly more common in the exposed group. The rates of gestational diabetes did not differ significantly between the 2 groups. In multivariate logistic regression analyses, microalbuminuria increased the risks for preterm labor (adjusted OR 2.4; 95% CI 1.1–5.5,  $P=0.03$ ) and preeclampsia (adjusted OR 9.5; 95% CI 4.6–19.3,  $P=0.001$ ). **Conclusion** Microalbuminuria at the end of the second trimester of pregnancy might increase the risks of preterm labor, preeclampsia, intrauterine growth restriction, and preterm premature rupture of membranes.

### IS-AC-4-3

**Causes and risk factors for singleton stillbirth in Japan : an analysis using the Japan Society of Obstetrics and Gynecology Perinatal Database, 2013-2014** Rei Haruyama<sup>1</sup>, Naoyuki Miyasaka<sup>2</sup> *The University of Tokyo<sup>1</sup>, Tokyo Medical and Dental University<sup>2</sup>*

**Objective** Although Japan has achieved one of the lowest perinatal mortality rates in the world, more than 80% is due to stillbirths after 22 weeks of gestation with one in 300 families experiencing fetal loss every year. This study aimed to assess causes and risk factors for singleton stillbirth in Japan. **Methods** A retrospective cross-sectional study was conducted using the Japan Society of Obstetrics and Gynecology (JSOG) Perinatal Database from January 2013 to December 2014. A total of 379,211 births including 2,133 stillbirths were analyzed. Causes of death were examined by the JSOG clinical death classification system and reclassified according to the level I categories of the Cause of Death and Associated Conditions classification system by gestational age. A multi-level Poisson regression model was used to assess the relationship between stillbirth and key maternal, fetal, and facility factors. **Results** Causes of death were unknown in 25–45% of stillbirths. Among the known cause, placental abnormality accounted for the most, followed by umbilical cord abnormality and congenital malformation. Stillbirth risk was increased among small-for-gestational-age infants (adjusted relative risk (ARR) : 3.8, 95% confidence interval (CI) : 3.3–4.3) and nulliparous women (ARR : 1.2, 95% CI : 1.1–1.3). By contrast, maternal underweight, pregnancy-induced hypertension and oligohydramnios showed a protective effect. **Conclusion** This study suggests that stillbirths occurring among women with known complications are likely already being prevented in Japan. Further reduction in stillbirths must target small-sized fetuses and nulliparous women. Improved recording of the causal pathways of stillbirths is also needed to explain stillbirths with unknown cause of death.

### IS-AC-4-4

**Risk factors for congenital cytomegalovirus infection in pregnant women with non-primary infection** Akiko Uchida<sup>1</sup>, Kenji Tanimura<sup>1</sup>, Shinya Tairaku<sup>1</sup>, Kana Ozaki<sup>1</sup>, Satoshi Nagamata<sup>1</sup>, Mayumi Morizane<sup>1</sup>, Masashi Deguchi<sup>1</sup>, Yasuhiko Ebina<sup>1</sup>, Ichiro Morioka<sup>1</sup>, Toshio Minematsu<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University Hospital<sup>1</sup>, Aisenkai Nichinan Hospital<sup>2</sup>*

**Objective** Not only primary cytomegalovirus (CMV) infection during pregnancy but also non-primary infection can cause congenital CMV infection (CCI). The aim of this prospective cohort study was to determine clinical factors that were associated

with the occurrence of CCI in pregnant women with non-primary CMV infection. **Methods** This study was approved by the institutional ethic boards, and written informed consent was obtained from all participants. One thousand two hundred and eighty-seven pregnant women with non-primary CMV infection were enrolled. Positive CMV IgG, avidity index >45% and negative IgM were defined as non-primary infection. Clinical factors assessed were as follows : hypertensive disorders, diseases requiring immunosuppressive medication, abnormal glucose tolerance, threatened premature labor, and multiple pregnancy etc. To determine risk factors for CCI, logistic regression analyses were performed. **Results** Seven (0.5%) of the 1,287 pregnant women with non primary infection were found to have newborns with CCI. Univariate logistic regression analyses demonstrated that threatened premature labor (OR 10.6, 95%CI 2.0–55.0;  $p<0.01$ ) and multiple pregnancy (OR 7.1, 95%CI 1.4–37.4;  $p<0.05$ ) were associated with the occurrence of CCI. Multivariable logistic regression analyses revealed that threatened premature labor was a significant risk factor of CCI (OR 8.4, 95% CI 1.5–48.1;  $p<0.05$ ). **Conclusion** The present study demonstrated for the first time that the threatened preterm labor was a risk factor for the occurrence of CCI from mothers with non-primary CMV infection.

### IS-AC-5-1

**Pre-pregnancy factors associated with development of hypertension in women with preeclampsia** Hye Jin Choi<sup>1</sup>, Geum Joon Cho<sup>1</sup>, Min Jung Oh<sup>1</sup>, Jong Heon Park<sup>2</sup>, Ki-Hoon Ahn<sup>1</sup>, Soon-Cheol Hong<sup>1</sup>, Hai-Joong Kim<sup>1</sup>, Sung Won Han<sup>2</sup> *Korea University, Korea<sup>1</sup>, Big Data Steering Department, National Health Insurance Service, Korea<sup>2</sup>*

**Objective** The aim of our study was to investigate the pre-pregnancy characteristics that are risk factors for the development of hypertension (HTN) and identify pre-pregnancy factors for the development of HTN in women affected by preeclampsia in their first pregnancy. **Study design** We enrolled 1,910 women who had undergone a National Health Screening Examination through the National Health Insurance Corporation between 2002 and 2003, and who had their first delivery affected by preeclampsia in 2004. Women were classified as having HTN if they were newly diagnosed with HTN from 2005 through 2012. **Results** After 8 years of follow-up, 7.7% (148/1,910) of preeclamptic women developed HTN. Using the Cox proportional hazards model, old age (hazard ratio [HR] 3.92, 95% confidence interval [CI] 2.47–6.23), a family history of HTN (HR 2.28, 95% CI 1.46–3.58), pre-pregnancy obesity (HR 3.74, 95% CI 2.50–5.59), and high blood pressure (BP) (HR 2.78, 95% CI 1.85–4.19), were independently associated with the development of HTN. **Conclusion** The results show the development of HTN in preeclamptic women is related to pre-pregnancy factors. This suggests that the monitoring and management of these factors during pre-pregnancy and/or early pregnancy may facilitate a reduction in the likelihood of developing preeclampsia and HTN in the future.

### IS-AC-5-2

**Antenatal ultrasound findings and hemorrhagic outcomes in suspected abnormally invasive placenta** Su Kyeong Kong, Suk Young Kim, Eun Suk Seo, Mee Hyang Ko *Gil Medical Center Gachon University, Korea*

Abnormally invasive placenta (AIP) is a clinical term used to describe a placenta that does not separate spontaneously at delivery and cannot be removed without causing high blood loss. Because of potentially life-threatening, accurate antenatal diagnosis in suspected AIP allows improved pregnancy outcomes. Our aim was to evaluate association between ultrasound find-

ings and hemorrhagic outcomes in suspected AIP. Between 2016 and August, 2017, distribution of ultrasound signs and pregnancy outcome were examined in patients with suspected AIP. We used the Pro forma for ultrasound reporting. The report include appropriate demographics and risk factors and ultrasound signs to evaluate AIP. There were 6 parameters of grayscale and 4 parameters of color Doppler ultrasound. During this period 862 living singleton births had occurred and they had at least one scan in our ultrasound unit. Finally 41 cases were enrolled in prospective observational study. The majority of patients had placental lacunae of grayscale parameters and subplacental hypervascularity of color doppler ultrasound. The prevalence of loss of clear zone and all parameters of color doppler ultrasound was association with high blood loss at delivery. There was a significant relationship between subplacental hypervascularity and blood loss ( $p=0.003$ ). Antenatal ultrasound findings has a clinical significance to predict high blood loss. Further studies using a standardized approach in suspected AIP to evaluate correlation between ultrasound sings and hemorrhagic outcomes are needed.

### IS-AC-5-3

**Obstetric outcome and use of medications during pregnancy with systemic lupus erythematosus, rheumatoid arthritis and inflammatory bowel disease in Japan : A nationwide retrospective descriptive study** Sayaka Tsuda<sup>1</sup>, Azusa Sameshima<sup>1</sup>, Haruna Kawaguchi<sup>2</sup>, Shintaro Makino<sup>3</sup>, Daisuke Fujita<sup>4</sup>, Shigeru Saito<sup>1</sup> *University of Toyama<sup>1</sup>, Osaka Medical Center and Research Institute for Maternal and Child Health<sup>2</sup>, Juntendo University<sup>3</sup>, Osaka Medical College<sup>4</sup>*

**Objective** To describe obstetric outcome and medications during pregnancy with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Crohn's disease (CD) and ulcerative colitis (UC). **Methods** We conducted questionnaire survey to the hospitals listed in the Japan Maternal Fetal Intensive Care Unit Network. It inquired the number of the pregnancy with those diseases for two years, obstetric outcome and medications. **Results** Among 69,810 deliveries, pregnancy with SLE, RA, CD and UC were 282 (0.4%), 203 (0.3%), 68 (0.1%) and 302 (0.4%), respectively. Compared with before conception, the proportion of patients with active disease increased during pregnancy in SLE (4.8% vs 15.0%,  $p=0.003$ ) but not in others. In SLE, incidence rates of preterm delivery, preeclampsia (PE), fetal growth restriction (FGR) and thromboembolism were higher than that of general population (9.6% vs 5.6%  $p=0.017$ , 14.4% vs 5.6%  $p=0.0002$ , 11.2% vs 4.1%  $p<0.0001$ , 2.7% vs 0.1%  $p<0.0001$ ). Incidence rates of preterm delivery in RA and FGR in CD were also significantly higher (12.9% vs 5.6%  $p=0.0002$ , 20.7% vs 4.1%  $p=0.001$ ). Anti-TNF inhibitors users during pregnancy were 0.0% of SLE, 15.0% of RA, 65.5% of CD and 3.9% of UC. Immunosuppressive agents users were 19.3%, 2.9%, 17.2% and 3.3%, respectively. To estimate the birth rate, that of RA women was 42.2% (95% CI : 24.1–60.2) of general population. **Conclusion** Frequency of obstetrical complications was the highest in SLE. We showed that despite pregnancy increased the rate of active disease just in SLE but not in RA, CD and UC, the birth rate of RA were fewer than that of general population in Japan.

### IS-AC-5-4

**Antenatal anti-arrhythmic treatment for fetal tachyarrhythmias : a prospective multicenter trial in Japan** Takekazu Miyoshi<sup>1</sup>, Haruhiko Sago<sup>2</sup>, Hitoshi Yoda<sup>3</sup>, Makio Shozu<sup>1</sup>, Shinji Katsuragi<sup>1</sup>, Tomoaki Ikeda<sup>5</sup> *National Cerebral and Cardiovascular Center<sup>1</sup>, National Center for Child Health and Development<sup>2</sup>, Toho University Omori Medical Center<sup>3</sup>, Chiba University<sup>4</sup>, Mie University<sup>5</sup>*

**Objective** To evaluate the efficacy and safety of the protocol-defined transplacental treatment of fetal tachyarrhythmias. **Methods** This was a multicenter, single-arm interventional study. A total of 50 fetuses were enrolled at 15 Japanese institutions from October 2010 to January 2017. The protocol-defined treatment was performed for singletons with sustained fetal tachyarrhythmia  $>180$  bpm, with a diagnosis of supraventricular tachycardia (SVT) or atrial flutter (AFL). Digoxin, sotalol, flecainide or a combination was used for transplacental treatment. The primary endpoint was disappearance of fetal tachyarrhythmias. **Results** SVT shortVA ( $n=17$ ), SVT longVA ( $n=4$ ) and AFL ( $n=29$ ) were diagnosed at  $30.4 \pm 3.2$  weeks of gestation. Fetal hydrops at diagnosis was found in 5 cases. Maternal adverse event was observed in 43/50 (86.0%), however, each event was minor, thus transplacental treatment could be continued. The treatment effect was analyzed in 49 cases excluding 1 case of dropout. Fetal tachyarrhythmia disappeared in 41/49 (83.7%) ; 39/44 (88.6%) of non-hydrops and 2/5 (40.0%) of hydrops fetuses. Fetal demise was found in 2 cases ; AFL with suspected Costello syndrome and advanced hydrops, and SVT shortVA (suspected ventricular tachycardia) with progression of fetal hydrops. Mean gestational age was  $37.0 \pm 1.9$  weeks and preterm birth was 8/47 (17.0%). Neonatal tachyarrhythmia was found in 17/47 (36.2%). **Conclusion** Our protocol-defined transplacental treatment of fetal tachyarrhythmias is effective and tolerable in more than 80% of cases. However, it is necessary to take notice of serious fetal adverse events and recurrence of tachyarrhythmias after birth.

## JKT-YD-1

**The prognostic role of pre-treatment complete blood count profiling in early cervical cancer** Joseph J. Noh, Chel Hun Choi, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

**Objective** To investigate the prognostic role of pre-treatment complete blood count (CBC) profiling as a predictive marker of survival, recurrence and death in early stage adenocarcinoma and squamous cell carcinoma of the cervix. **Methods** The CBC profiles of the patients from eight tertiary medical centers in South Korea who were treated surgically for early stage cervical cancer were reviewed. The blood samples were collected within two weeks prior to the initial operation. **Results** A total of 1,441 patients were included in the study and the median follow-up was 58 months with a range of 3–181 months. They were classified according to the disease status – no evidence of disease (NED), hematogenous recurrence, lymphatic recurrence or death. Those who recurred within five years from the initial treatment showed lower hemoglobin levels and higher platelet levels in pre-treatment CBC compared to the NED group (hemoglobin in g/dL, 12.4 vs. 12.7,  $p < 0.01$ ; platelet in multiple of 103/microliter, 273 vs. 250,  $p < 0.01$ ). The patients who died within five years from the initial treatment also showed lower hemoglobin levels and lymphocyte percentage levels compared to those who survived (hemoglobin in g/dL, 12.4 vs. 12.7,  $p < 0.01$ ; lymphocyte in percentage, 1.7 vs. 1.9,  $p < 0.01$ ). Further analyses revealed that low hemoglobin and high platelet levels were predictive markers of overall recurrence including both hematogenous and lymphatic while low white blood cell (WBC), neutrophil levels and high platelet levels were predictive of hematogenous recurrence. Pre-treatment low hemoglobin levels were also shown as a prognostic marker of death in this population. **Conclusion** Pre-treatment CBC profiling including WBC, hemoglobin, neutrophil, lymphocyte and platelet levels were found to be a potential biomarker for survival prognosis in early cervical cancer.

## JKT-YD-2

**Clinical significance of p53-binding protein 1 nuclear foci in cervical squamous intraepithelial lesions** Sayaka Kawashita, Kiyonori Miura, Yuri Hasegawa, Takako Shimada, Michio Kitajima, Hideaki Masuzaki *Nagasaki University*

**Objective** As p53-binding protein 1 (53BP1) localizes at the sites of DNA double strand breaks and forms nuclear foci (NF), the presence of 53BP1 NF can be considered as an indicator of endogenous genomic instability. We previously reported the number of 53BP1 NF in cervical squamous intraepithelial lesions (SIL) increased with tumor progression. In this study, to clarify the significance of 53BP1 NF in SILs, we analyzed the distribution of 53BP1 NF in a series of SILs and compared with the expression of P16, which is a useful diagnostic marker of SIL reflecting the proliferative stress caused by HPV infection. **Methods** We performed double-label immunofluorescence for 53BP1 and P16 in 64 cases of SILs (CIN1 : 22 cases, CIN2 : 21 cases, and CIN3 : 21 cases). Correlation between the expressions of 53BP1 NF and P16 in epithelial layers was analyzed. **Results** P16 was negative in 10 cases of SILs (15.6%). In 54 cases of SILs with a positive expression of P16, a strong correlation between the expressions of 53BP1 NF and P16 was detected ( $P < 0.0001$ ), suggesting that 53BP1 NF could be a potential diagnostic marker for SILs as well as p16. Furthermore, when 53BP1 NF was detected over 1/3 layer of epithelium, the presence of SILs referring to ROC curve showed highest sensitivity and specificity. Especially, five of 10 cases with a negative result of P16 (50%) were diagnosed as SILs correctly. **Conclusion** 53BP1 NF immunofluorescence

may be a potential diagnostic marker for SILs, especially in the cases with a negative result of P16.

## JKT-YD-3

**The expression of glucagon-like peptide-1 receptor could be a novel biomarker of endometrial cancer possibly by stimulating autophagy via AMPK signaling pathway** Ranka Kanda<sup>1</sup>, Haruko Hiraike<sup>1</sup>, Yasuhiro Matsumoto<sup>1</sup>, Yuko Sasajima<sup>2</sup>, Kazunori Nagasaka<sup>1</sup>, Osamu Hiraike<sup>3</sup>, Eiji Ryo<sup>1</sup>, Yutaka Osuga<sup>3</sup>, Tomoyuki Fujii<sup>3</sup>, Takuya Ayabe<sup>1</sup> *Teikyo University<sup>1</sup>, Department of Diagnostic Pathology, Teikyo University<sup>2</sup>, The University of Tokyo<sup>3</sup>*

**Objective** A previous report suggested that glucagon-like peptide-1 receptor (GLP-1R) agonist exenatide induced apoptosis in endometrial cancer cells. However, pathophysiological role of GLP-1R in endometrial cancer is not fully elucidated. Here, we aimed to further investigate the effects of GLP-1R agonist liraglutide in endometrial cancer cells, and examined the association between GLP-1R expression and clinicopathological characters in endometrial cancer patients. **Methods** Ishikawa cells were treated with liraglutide of different concentrations. Cell viability assay, colony formation assay, flow cytometry, Western blotting, and immunofluorescence were used to assess the effects of liraglutide. The induction of autophagy was examined by analyzing the expression levels of LC3 and p62, and the accumulation of autophagosome. Moreover, using tissue microarray, we analyzed the GLP-1R expression status in 154 endometrial cancer tissues by immunohistochemistry. **Results** In concordance with previous report, liraglutide inhibited the growth of cancer cells in a dose-dependent manner. We revealed that the treatment with liraglutide significantly induced autophagy, and phosphorylated AMPK expression was elevated in Ishikawa cells. The immunohistological analysis of GLP-1R revealed that the expression of GLP-1R was associated with positive estrogen and progesterone receptor status, and higher expression of GLP-1R was significantly correlated with better progression-free survival. **Conclusion** The application of liraglutide to target autophagy in endometrial cancer cells may provide a new potential treatment for endometrial cancer. Furthermore, higher expression of GLP-1R may be associated with better prognosis in endometrial cancer patients.

## JKT-YD-4

**The clinical prognostic correlation of CypB in epithelial ovarian carcinoma patients** Heng-Cheng Hsu<sup>1,2</sup>, Chi-An Chen<sup>2</sup>, Chang-Yao Hsieh<sup>2</sup>, Wen-Fang Cheng<sup>2,3,4</sup> *National Taiwan University Hospital Hsin-Chu Branch, Taiwan<sup>1</sup>, College of Medicine, National Taiwan University, Taiwan<sup>2</sup>, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taiwan<sup>3</sup>, Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taiwan<sup>4</sup>*

**Objective** To investigate the role of CypB as a clinical prognostic biomarker for patients with epithelial ovarian carcinoma. **Methods** We measured CypB expression with quantitative real time-polymerase chain reaction (qRT-PCR) in 201 women with EOC and 36 woman with normal/benign ovaries and evaluated correlations between CypB expression, clinicopathological characteristics, and the outcomes of the patients. **Results** The expression of CypB was higher in cancerous tissues than in normal tissues. The expression of CypB were especially elevated in patients with ovarian clear cell carcinoma ( $p < 0.001$ ), high grade ( $p < 0.001$ ), and lymph node metastasis ( $p = 0.044$ ). **Conclusion** The results suggest that CypB could be a potential marker to predict ovarian cancer cell type and be a predictor of lymph node metastasis.



## JKT-YD-5

**Laparoscopic cornuostomy versus cornual resection using hemostatic suture : interstitial ectopic pregnancy** Bo Ram Yu, Chul Hee Rheu, Jong Hyun Kim *Chonbuk National University of Korea, Korea*

**Objective** To evaluate outcomes of two surgical management (cornuostomy, cornual resection) of interstitial ectopic pregnancies. **Methods** Retrospective case review of patients with cornual pregnancy which treated by laparoscopy. The charts of thirty five patients managed by laparoscopic cornual resection or cornuostomy at Chonbuk National University Hospital, Korea, from 2010 to 2017 were reviewed. The primary outcomes were operation time, hemoglobin level difference after surgery, blood transfusion, postoperative methotrexate (MTX) injection, postoperative acute complication (infection, bleeding, etc.). The secondary outcomes were pregnancy outcomes like full term delivery, another ectopic pregnancy, etc. The primary outcomes were processed by paired t-test. **Results** Seventeen patients were treated by cornual resection using hemostatic suture. Sixteen patients were treated by cornuostomy using hemostatic suture. Between cornual resection group and cornuostomy group, the values of operation time, hemoglobin level difference after surgery, blood transfusion, postoperative MTX injection, postoperative acute complication (infection, bleeding, etc.) are statistically not significant. 1 case of continuous abdominal pain after cornual resection was managed by bed rest & pain killer only. 1 case of vaginal bleeding after cornuostomy which suspected as uterine subinvolution was treated by uterotonic agents. Only 1 case of 21 unruptured interstitial ectopic pregnancies was transfused blood after cornual resection. Only 3 patients were pregnant after laparoscopy (one after cornual resection, two after cornuostomy). No one has recurred yet. **Conclusion** Cornual resection is not superior to cornuostomy with regard to postoperative outcomes. Cornuostomy would be considered as a first line surgical treatment.

## JKT-YD-6

**Porphyromonas gingivalis-lipopolysaccharide enhances inflammation in amniotic mesenchymal cells** Haruhisa Konishi<sup>1</sup>, Satoshi Urabe<sup>1</sup>, Yuko Teraoka<sup>1</sup>, Mutsumi Miyauchi<sup>2</sup>, Hiroshi Miyoshi<sup>3</sup>, Takashi Takata<sup>2</sup>, Yoshiki Kudo<sup>1</sup> *Hiroshima University<sup>1</sup>, Department of Oral and Maxillofacial Pathobiology, Hiroshima University<sup>2</sup>, Hiroshima Prefectural Hospital<sup>3</sup>*

**Objective** Inflammation is known to induce preterm delivery. We previously reported that mice with dental *Porphyromonas gingivalis* (*P.g* ; a common pathogen of dental disease) infection could be used as an effective model of preterm delivery. In this model, *P.g* colonies were observed in the fetal membrane, and inflammation on the fetal membrane is thought to be the main cause of preterm delivery as COX-2 and interleukin (IL)-1b levels are highly upregulated. However, whether *P.g* induces inflammation in the fetal membrane remains unknown. We aimed to investigate the association of *P.g* infection with the human amniotic membrane in vitro. **Methods** Amniotic membranes were obtained at normal delivery under protocols approved by the Institutional Review Board in our hospital. The amniotic membrane was isolated to epithelial cells (AEC) and amniotic mesenchymal cell (AMC) with trypsin and collagenase, and primary cell cultures were carried out. Confluent cells were stimulated with *P.g* lipopolysaccharide (LPS) (1ng, 10ng, 100ng, 1µg/ml, 12hours). The mRNA expression of IL-1b, IL-8, and COX-2 were investigated by realtime RT-PCR. **Results** Initially, the mRNA expression of IL-1b, IL-8 was observed only in AMC, and the mRNA expression of COX-2 was observed in both cells. Following stimulation with *P.g*-LPS, the expressions in AMC were enhanced in a concentration-dependent manner, and those

in IL-1b, IL-8, and COX-2 were increased by 2.7, 3.7, and 3.6 fold with 1µg/ml, respectively. By contrast, there were no significant changes in AEC. **Conclusion** *P.g*-LPS might enhance inflammation in AMC, leading to preterm birth.

## JKT-YD-7

**Comparisons of the effects of estradiol valerate and medroxyprogesterone acetate versus tibolone on menopausal symptoms, lower urinary tract symptoms and female sexual function : A preliminary report** Pei-Ling Chen, Sheng-Mou Hsiao *Far Eastern Memorial Hospital, Taiwan*

**Objectives** Treatment-related effects are important for pre-treatment counseling. Thus, our aim was to compare the effects of different hormone therapies on menopausal symptoms, lower urinary tract symptoms and sexual functions in women with menopausal syndrome. **Methods** Between December 2012 and August 2017, women with menopausal syndrome were invited to receive estradiol valerate (E<sub>2</sub>V, 1 mg) & medroxyprogesterone acetate (MPA, 2.5 mg) or tibolone (2.5 mg) per day. Women who were willing to pay an extra fee took tibolone, which is not covered by the National Health Insurance in Taiwan ; others got E<sub>2</sub>V/MPA. **Results** A total of 68 women had a follow-up visit after 1 month's treatment, including E<sub>2</sub>V/MPA (n=39) and tibolone (n=29). Thirty-three women received a follow-up visit after 3 months' therapy, including E<sub>2</sub>V/MPA (n=22) and tibolone (n=11). Baseline characteristics did not differ between the two groups. At the visit after one-month treatment, most domains of modified Greene Climacteric Scale and some domains of Female Sexual Functional Index improved. Significant improvements in diastolic blood pressure were found in both groups. Besides, endometrial thickness did not increase in either group. However, the quality of life score of International Prostate Symptoms Score improved with E<sub>2</sub>V/MPA treatment exclusively. At the three-month visit, most domains of modified Greene Climacteric Scale, as well as some domains of Female Sexual Functional Index and International Prostate Symptoms Score, improved after hormone therapy. However, dizziness was significantly reduced with tibolone, but not with E<sub>2</sub>V/MPA. **Conclusions** Both regimens give rise to similar improvements in menopausal symptoms. In addition, they both improve lower urinary tract symptoms and some domains of female sexual functions. E<sub>2</sub>V/MPA is superior in the improvement in quality of life affected by urinary symptoms, while tibolone has superiority in the reduction of dizziness.

## JKT-YD-8

**The effectiveness of laparoscopic ultrasonography during LM operation to reduce residual myomas** Mamoru Shiget, Yasushi Kotani, Kiko Yamamoto, Masato Aoki, Shiro Takamatsu, Yoshie Yo, Kosuke Murakami, Hisamitsu Takaya, Masao Shimaoka, Takako Tobiume, Isao Tsuji, Noriomi Matsumura *Kindai University Hospital*

**Objective** LM (Laparoscopic Myomectomy) has been more often performed than before. The problem of postoperative recurrence in both LM and OM (Open Myomectomy) sometimes occurs. In our prior retrospective study the cumulative recurrence rates of 8 year after LM and OM operation were 76.2% and 59.6% respectively. The postoperative recurrence rate of LM was significantly higher than that of OM. There is a possibility that the lack of palpation during operation in LM causes residual myomas and results in the recurrent. Therefore we have used LUS (Laparoscopic ultrasonography) to reduce residual myomas since 2015. In this study, we will introduce the effectiveness of LUS. **Methods** Between February 2015 and September 2016, in LM after all the myomas detected by preoperative MRI were removed, with LUS we checked and removed residual myomas if

any. We used LUS in 26 patients and examined the patient characteristics and surgical outcomes. **Results** In the patients who underwent LM, 26 patients underwent LUS. The total number of removed myomas was 135. The mean number was 5.2 per patient. The mean diameter of the largest myoma was 68mm. In 6 out of the 26 patients, residual myomas were detected by LUS and removed additionally (7 myomas were detected and all removed). The mean diameter was 5.7mm and all the myomas were less than 10mm. **Conclusion** The myomas that would be left behind without LUS can be removed during operation. We believe LUS will contribute to decreasing postoperative recurrence rate in LM.

## IS-WS-1-1

**Comparison of MRI, PET-CT, and frozen biopsy in the evaluation of lymph node status before fertility-sparing radical trachelectomy in early stage cervical cancer** Geon-Woo Lee, Jeong-Yeol Park, Dae-Yeon Kim, Dae-Shik Suh, Jong-Hyeok Kim, Yong-Man Kim, Young-Tak Kim, Joo-Hyun Nam *University of Ulsan College of Medicine, Asan Medical Center, Korea*

**Objective** Apply of frozen biopsy is more accurate than MRI or PET-CT when trachelectomy is performed in early cervical cancer. **Materials and Methods** This was a retrospective study including 132 young women with early-stage cervical cancer who tried fertility-sparing laparoscopic or robotic radical trachelectomy between July 1, 2004 and April 30, 2017. All patients underwent preoperative MRI and/or PET-CT. Pelvic lymphadenectomy was performed during surgery, and all retrieved lymph nodes were sent to frozen biopsy before proceeding radical trachelectomy. Paraaortic lymphadenectomy was performed when metastasis was suspected in the paraaortic lymph node. The diagnostic accuracy of MRI, PET-CT, and frozen biopsy was compared using McNemar test and logistic regression using generalized estimating equation. The final pathologic report on lymph nodes was the gold standard for diagnosis. **Results** A total number of retrieved lymph node stations was 697, and mean retrieved lymph nodes was 20 (range 2-61). Lymph nodes were positive in 20 patients (14.3%). Sixteen patients underwent radical hysterectomy with lymphatic metastasis in frozen biopsy. In comparison between patients, there was significant difference in sensitivity (95.0% vs. 40.0%,  $P < 0.001$ ), specificity (100.0% vs. 80.0%,  $P < 0.001$ ), accuracy (99.2% vs. 73.8%,  $P < 0.001$ ) of frozen biopsy versus MRI. There was significant difference in specificity (100.0% vs. 84.3%,  $P < 0.001$ ), accuracy (99.2% vs. 82.5%,  $P < 0.001$ ) of frozen biopsy versus PET-CT. **Conclusion** Although sensitivity is not statistically significant in PET-CT, lymph node metastasis is very important for prognosis. Therefore, frozen biopsy of all retrieved lymph nodes during surgery is still the best way to evaluate lymph node status before fertility-sparing radical trachelectomy.

## IS-WS-1-2

**The study about anti-cancer mechanism of tetraarsenic oxide in cervical cancer using cell line and PDX model** Jeong-Won Lee, Jun Hyeong Seo, Jee Youn Hong, Jihye Kim, Hyunjin Choi, Jae Ryoung Hwang, Young-Jae Cho, Chel Hun Choi, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

**Objective** Current standard therapy for advanced or recurrent cervical cancer is combination chemotherapy with paclitaxel or topotecan based on cisplatin chemotherapy. However, these combination chemotherapy show only 27-36% response rate. Therefore, there have been many efforts to discover other combination therapeutic agents for cervical cancer. Tetraarsenic oxide (TAO) showed the possibility of therapeutic effect in previous in vitro and in vivo studies with cervical cancer cell lines. The purpose of this study was to investigate the anticancer effect of TAO in an in vivo study using patient derived xenograft (PDX) mouse model and reveal the mechanisms of TAO acting on tumor cells. **Methods** We performed in vivo experiments with subrenal injection of three different squamous cell carcinoma PDX models of uterine cervix. TAO was administered to each group to compare the antitumor effect with control. We also did in vitro studies using cervical cancer cell lines, in order to understand the mechanism of anticancer effect of TAO. TAO was treated with SiHa, HeLa and HUVEC cells, and western blot was performed. In addition, to investigate the effect of TAO on cell migration, we performed MMP2 and 9 ELISA assays using HUVEC and SiHa cells. **Results** In vivo studies with PDX mouse

model, all three showed significant tumor volume reduction in TAO treated group. Furthermore, the tumor volume decreased more significantly in cisplatin combination group than in single agent and control group. In vitro studies with SiHa and HeLa cells, TAO decreased the phosphorylation of Akt. In HUVEC cells, TAO decrease VEGF receptor 1 expression. Furthermore, the same results were obtained after processing with VEGF in HUVEC cells. Also, MMP2 was decreased in HUVEC cells. **Conclusion** TAO reduces tumor volume in cervical cancer PDX mice, which is more pronounced in the cisplatin combination group. TAO inhibits phosphorylation of Akt and decreases VEGF receptor 1 expression. However, these mechanisms differ depending on the cell line. These results indicate the reduction of VEGF-related signaling pathway plays an important role in anti-cancer mechanism of TAO in cervical cancer.

## IS-WS-1-3

**Increased myeloid derived suppressor cells during pregnancy promotes cervical cancer progression** Katsumi Kozasa<sup>1</sup>, Seiji Mabuchi<sup>1</sup>, Naoko Komura<sup>1</sup>, Eriko Yokoi<sup>1</sup>, Akihiko Yoshimura<sup>1</sup>, Hiromasa Kuroda<sup>2</sup>, Yuri Matsumoto<sup>1</sup>, Michiko Kodama<sup>1</sup>, Kae Hashimoto<sup>1</sup>, Kenjiro Sawada<sup>1</sup>, Tadashi Kimura<sup>1</sup> *Osaka University<sup>1</sup>, Kansai Rosai Hospital<sup>2</sup>*

**Objective** Myeloid derived suppressor cells (MDSC) were known to be involved in the progression of human malignancies including cervical cancer (CC). Recently it is reported that 17 $\beta$ -estradiol (E2) increase MDSC. It is also reported that women diagnosed with cervical cancer during pregnancy may have an increased mortality. We hypothesized that elevated E2 level during pregnancy promotes cervical cancer progression by the induction of MDSC. **Methods** BALB/c nude mice, subcutaneously inoculated with HeLa cells (known estrogen-receptor negative CC), were impregnated and then, tumor growth and the number of MDSC were examined. In order to investigate the effect of pregnancy induced increment of E2 on the frequency of MDSC and tumor growth, we carried out the following experiments. The effect of E2 on the differentiation of bone marrow cells into MDSC was examined by flow cytometry. We examined the effect of E2 on the STAT3 activation in MDSC by western blotting. We examined the effect of E2 on the suppressive effect of MDSC on the proliferation of CD8<sup>+</sup> T cells by flow cytometry. **Results** The number of MDSC was increased in bone marrow, peripheral blood mononuclear cells and tumor in pregnant mice. The tumor growth was also enhanced in pregnant mice. E2, that is elevated during pregnancy, stimulated the differentiation of bone marrow cells into MDSC. E2 also enhanced the STAT3 activation in MDSC and the suppressive effect of MDSC on CD8<sup>+</sup> T cells. **Conclusion** Pregnancy might promote cervical cancer progression by the induction of MDSC.

## IS-WS-1-4

**MicroRNAs in the cervical mucus are promising biomarkers for cervical cancer and cervical neoplasia** Satoshi Kawai, Sayaka Ootani, Ryoko Ichikawa, Yutaka Torii, Eiji Nishio, Takuma Fujii *Fujita Health University*

**Objective** MicroRNAs (miRNAs) play important roles in the regulation of gene expression during cervical carcinogenesis. The aim of this study was to examine whether the detection of specific miRNAs could be a biomarker for cervical cancer. **Methods** Cervical mucus was collected using a cotton swab from 230 patients with a normal cervix, cervical intraepithelial neoplasia (CIN), squamous cell carcinoma (SCC), and adenocarcinoma (AD), and cellular miRNA levels were quantified by miRNA array and real-time RT-PCR. Cytology and human papillomavirus (HPV) infection statuses were also used as clinical parameters. **Results** We found that four miRNAs (miR-126-3p,

-20b-5p, -451a and -144-3p) were significantly upregulated in SCC and AD compared with normal, and that their expression levels correlated with the disease severity and with high-risk HPV infection. Receiver operating characteristic curve analyses revealed that the area under the curve values for miR-126-3p, -20b-5p, -451a, and -144-3p were 0.91, 0.94, 0.96, and 0.95, respectively, for SCC compared with normal, and 0.89, 0.90, 0.94, and 0.93, respectively, for SCC plus AD compared with normal, showing high accuracy of cancer detection. When comparing normal with CIN3 and worse, these values for miR-126-3p, -20b-5p, -451a, and -144-3p were 0.80, 0.82, 0.87, and 0.87, respectively, showing moderate accuracy. Real-time RT-PCR analyses confirmed the expression of these four miRNAs in frozen tissues of cervical cancer. **Conclusion** miR-126-3p, -20b-5p, -451a, and -144-3p, which are upregulated in cervical mucus from cervical cancer and its precursor lesions, are promising biomarkers for cervical cancer detection.

### IS-WS-1-5

**Reduced serum miR-100 as a potential biomarker for cervical cancer** Zenta Yamanaka, Yuzo Nagamitu, Toru Sasaki, Hirotaka Nishi *Tokyo Medical University*

**Objective** MicroRNAs (miRNAs) regulate various physiological activities in living organisms. Recent studies have reported that the expression of miR-100 decreased in cervical cancer tissues. In this study, we measured the expression level of miR-100 in the sera and tissues of individuals with cervical cancer to investigate whether miR-100 can be used as a biomarker for cervical cancer. **Methods** From April 2010 to April 2012, we extracted total RNA from the sera and cervical tissues of 46 cervical cancer patients (CC), 64 cervical intraepithelial neoplasm patients (CIN), and 34 normal controls (NC). The expression level of miR-100 was investigated in each sample using quantitative real-time RT-PCR. The cutoff value of miR-100 in serum was set based on a ROC curve. We also examined the correlations of miR-100 expression levels with clinicopathological factors and prognosis. **Results** The relative levels of miR-100 in serum were  $5.32 \pm 3.39$  in the NC,  $3.93 \pm 2.52$  in the CIN, and  $1.84 \pm 1.72$  in the CC, indicating that significantly lower levels were present in patients with CC ( $p < 0.001$ ). The levels of miR-100 in cervical tissues were also significantly lower. According to the ROC curve, the AUC was 0.879, and the cutoff value was set at 2.451. The level of miR-100 in the lymph node metastasis-positive group was significantly lower than that in the negative group ( $0.98 \pm 0.36$  and  $2.13 \pm 2.15$ , respectively;  $p < 0.01$ ). Also, cervical cancer patients with lower miR-100 levels tended to have a poorer prognosis than those with higher miR-100 levels in serum. **Conclusion** Serum miR-100 level may be used as a biomarker for cervical cancer.

### IS-WS-1-6

**HPV E1 is dispensable for low and high-risk HPV maintenance and latent replication in keratinocytes but is necessary for genome amplification** Isao Murakami, Takashi Iwata, Masaru Nakamura, Tohru Morisada, Kyoko Tanaka, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** E1 and E2 play a direct role in viral replication. In contrast, the E6, E7 and E5 proteins act indirectly to drive the infected cell into cell cycle. To establish the minimal requirement of low and high-risk viral proteins in genome maintenance and latency, we have developed a genome maintenance model system, and have compared replication mechanisms between low and high-risk HPV. **Methods** Normal immortal keratinocytes (NIKS) transfected wild-type or mutated HPV11/16 genomes were cultured pre- or post-confluence. Genome copy number and viral gene expression were subsequently ana-

lyzed using qPCR. **Results** Both wild-type HPV11 and HPV16 genomes were maintained during cell division, despite different growth rates and patterns of transcription. However, HPV16 genome levels rose three fold post-confluence, while in contrast, HPV11 genome copy number declined dramatically. Both HPV 11 and HPV16 E1-deficient genomes were maintained pre-confluence, reinforcing the emerging view that maintenance-replication is E1-independent. Loss of functional E1 prevented HPV 16 confluence-dependent genome amplification. Exogenous E6 and/or E7 expression recovered HPV11 replication post-confluence, but was not sufficient to elevate HPV11 E1-deficient episomal copy number. **Conclusion** Our results show that both low and high-risk HPVs switch their replication mode from E1-independent replication to E1-dependent replication as cell density increases and cells commit to differentiate. Moreover, it appears that both of HPVs can replicate in the absence of the E1 viral helicase during genome maintenance, and during latent replication in the basal layer. The methodologies and observations described here have implications for drug therapeutic strategies designed to clear viral episomes.

### IS-WS-1-7

**Intra-patient variation of human papillomavirus genomes revealed by deep sequencing** Yusuke Hirose<sup>1</sup>, Yuri Tenjimbayashi<sup>1</sup>, Mamiko Onuki<sup>1</sup>, Takeo Minaguchi<sup>2</sup>, Takashi Iwata<sup>3</sup>, Koji Matsumoto<sup>1</sup>, Akihiko Sekizawa<sup>1</sup> *Showa University Hospital<sup>1</sup>, University of Tsukuba<sup>2</sup>, Keio University<sup>3</sup>*

**Objective** Persistent infection with oncogenic HPV causes invasive cervical cancer (ICC), accompanied with the accumulation of somatic mutations into the host genome. However, genetic changes in the HPV genome during HPV infection and their relevance to cervical carcinogenesis are not fully understood. The aim of this study was to investigate the intra-patient variation of HPV genomes by performing deep sequencing analysis of the viral whole genome. **Methods** The whole genome of HPV 16, 52 and 58 was amplified by HPV type-specific PCR from total cellular DNA of cervical exfoliated cells collected from CIN/ICC patients, and subjected to deep sequencing on a MiSeq (Illumina). The viral genome positions showing base substitutions of more than 0.5% read-counts in the total read-count at each position were determined for individual clinical specimens. **Results** In total, 896 positions of base substitutions were detected throughout HPV16/52/58 genomes from 118 patients samples (CIN1, n=47. CIN2/3, n=48. ICC, n=24), with varying numbers and frequencies for individual samples. Overall, C-to-T substitutions were predominantly detected across HPV types and histological grades, followed by C-to-A substitutions. The analysis of trinucleotide motifs covering substitution bases revealed that TCW (W : A or T), a preferred target sequence for APOBEC proteins, was a primary site for C-to-T substitutions in HPV genomes. Interestingly, the relative frequency of C-to-T substitutions decreased with lesion severity, whereas that of C-to-A substitutions increased. **Conclusion** These results strongly imply that APOBEC proteins, cellular cytidine deaminases that mediate antiviral immunity, are primarily involved in introducing mutations into the HPV genome, particularly in CIN1 lesions.

### IS-WS-1-8

**Involvement of transcription factor HOXD9 in the malignant phenotype of cervical cancer through direct binding to HPV P97 promoter** Naohiko Saiki, Takashi Iwata, Kohsei Tanaka, Tomoko Iijima, Masaru Nakamura, Shigenori Hayashi, Tohru Morisada, Kyoko Tanaka, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** We previously showed that apoptosis is induced by



suppression of transcription factor HOXD9 in cervical cancer cell lines, and that cell growth was also markedly inhibited. In this study, we examined the genetic basis of these results. **Methods** (1) HOXD9 expression was suppressed by shRNA in cervical cancer cell lines SKG-I and SKG-IIIb. Changes in all genes in the two cell lines were analyzed by microarray analysis and intracellular signals that changed in both lines were identified. (2) HOXD9 expression was suppressed in SKG-IIIb and Siha cell lines and expression of p53 at the gene and protein levels was examined. (3) Luciferase assays using the HPV16 E6/7 gene promoter (P97 promoter) were performed to examine whether HOXD9 induced E6/7 gene expression via the P97 promoter. (4) A chromatin immunoprecipitation (CHIP) assay was performed to examine whether HOXD9 binds to the P97 promoter. **Results** (1) P53 signaling was activated after suppression of HOXD9 expression in SKG-I and SKG-IIIb cells. (2) P53 gene expression did not change, while the P53 protein level was elevated in HOXD9 suppressed SKG3B and Siha cells. (3) Luciferase activity was significantly decreased after HOXD9 expression was suppressed in SKG-IIIb cells ( $p < 0.05$ ). (4) In the CHIP assay in SiHa cells (HPV16 positive), HOXD9 was shown to bind to the P97 promoter. **Conclusion** HOXD9 is involved in the malignant phenotype of cervical cancer through direct binding to P97 promoters, which facilitates expression of E6/7 and promotes degradation of P53.

### IS-WS-2-1

**Antitumor effect of XCT790, an estrogen-related receptor  $\alpha$  inverse agonist, on uterine endometrial cancer cells and a xenograft mouse model** Tetsuya Kokabu, Taisuke Mori, Hiroshi Matsushima, Hisashi Kataoka, Kaori Yoriki, Haruo Kuroboshi, Hiroshi Tatsumi, Morio Sawada, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** Estrogen-related receptor (ERR)  $\alpha$  is structurally similar to estrogen receptors. We previously demonstrated tumor progression caused by ERR $\alpha$  in endometrial cancer. This study investigated the efficacy of XCT790, a selective inverse agonist of ERR $\alpha$ , on endometrial cancer. **Methods** HEC-1A and KLE, endometrial cancer cells showing high ERR $\alpha$  expression, were treated with XCT790. Xenograft model mice inoculated with HEC-1A were treated with XCT790. Cell proliferation was measured with WST-8 and colony formation assays. Transcriptional activity was examined with a luciferase assay. The cell cycle was examined with flow cytometry, fluorescent immunocytochemistry, and western blotting. The apoptotic effect was determined with the caspase-3/7 assay. **Results** XCT790 (1.25–10  $\mu$ M) significantly inhibited ERR $\alpha$ -induced transcriptional activity in a concentration-dependent manner, regardless of the upregulation of ERR $\alpha$  at mRNA level ( $P < 0.01$ ). XCT790 reduced colony formation and suppressed cell proliferation in a dose- and time-dependent manner without cytotoxicity ( $P < 0.01$ ), and induced apoptosis supported by accumulation in the sub-G1 phase and stimulation of caspase-3/7 activity ( $P < 0.01$ ). Flow cytometry and fluorescent immunocytochemistry revealed that XCT790 caused cell cycle arrest at the mitotic phase. Western blotting used to analyze induction of histone H3 phosphorylation after treatment with XCT790 demonstrated the mitotic arrest. XCT790 in combination with paclitaxel produced a synergistic inhibitory effect. Significant inhibition of tumor growth without reduction of body weight was observed in a xenograft mouse model treated with XCT790 ( $P < 0.01$ ). **Conclusion** XCT790, a selective ERR $\alpha$  inverse agonist, may be a novel therapeutic agent for endometrial cancer.

### IS-WS-2-2

**A novel epigenetic therapy with inhibition of histone methyltransferase, SETD8, for endometrial cancer** Shinya Oki<sup>1</sup>, Kenbun Sone<sup>1</sup>, Katsutoshi Oda<sup>1</sup>, Asako Kukita<sup>1</sup>, Machiko Kojima<sup>1</sup>, Michihiro Tanikawa<sup>1</sup>, Kazunori Nagasaka<sup>1</sup>, Yoko Matsumoto<sup>2</sup>, Osamu Hiraie<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Kanagawa Health Service Association<sup>2</sup>*

**Objective** Dysregulation of histone methyltransferases is known to be associated with human cancers. One of the methyltransferase, SETD8, is a key regulator of DNA replication and its overexpression is reported in various types of cancers. Here, we investigated the role of SETD8 expression and anti-tumor effect of SETD8 inhibition in endometrial cancer. **Methods** SETD8 expression was analyzed by quantitative real-time PCR in 52 clinical endometrial cancer specimens under informed consent and approval of our ethics committee. SETD8 was inhibited by either knockdown of SETD8 with siRNA or treatment with UNC0379, a selective SETD8 inhibitor, in 8 endometrial cancer cell lines. The anti-tumor effects were examined with immunoblotting, MTT assay, colony formation assay, cell cycle analysis, and Annexin V-FITC. Anti-proliferative effect of UNC0379 was assessed by combination with other anti-cancer drugs (cisplatin or doxorubicin). **Results** SETD8 expression was elevated in endometrial cancer specimens, compared with control (normal endometrium) ( $P < 0.05$ ). Knockdown of SETD8 by siRNA induced significant growth suppression (90% of suppression) and caused G1 arrest in 8 endometrial cancer cell lines. In addition, knockdown of SETD8 increased the number of apoptotic cells (15–35%) and reduced the level of H4K20 methylation, accompanied with gamma-H2AX accumulation (DNA damage marker). UNC0379 suppressed cell proliferation (IC50 : 0.6–2.5  $\mu$ M in MTT assay) by itself, and showed additive anti-proliferative effects when combined with either doxorubicin or cisplatin. **Conclusion** The present findings highlight that SETD8 overexpression is involved in endometrial cancer, and that SETD8 might be a promising epigenetic target against endometrial cancer.

### IS-WS-2-3

**Long-term outcomes of medroxyprogesterone acetate plus metformin as fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer** Akira Mitsuhashi, Yuji Habu, Hirokazu Usui, Makio Shozu *Chiba University*

**Objective** This study aimed to analyze the long-term outcomes of MPA plus metformin as fertility-sparing treatment for atypical endometrial hyperplasia (AEH) and endometrial cancer (EC). **Methods** We analyzed 56 patients (37 with EC and 19 with AEH) who underwent fertility-sparing management using MPA plus metformin. MPA (400 mg/day) and metformin (750–2250 mg/day) were administered to achieve a complete response (CR). Metformin was administered until conception, even after MPA discontinuation. We compared these patients with 19 patients who received MPA alone. **Results** The body mass index was  $> 25$  kg/m<sup>2</sup> in 42 patients (75%) (mean, 30.5 kg/m<sup>2</sup>; range, 19–51 kg/m<sup>2</sup>). Fifty-four (96.4%) showed CR within 18 months. The CR rates at 6, 8–9, 12 months were 58.9%, 80.4%, and 89.3%, respectively. During a median follow-up period of 57 months (range, 13–88 months), relapse was confirmed in 7 of 54 patients (12.9%) who had achieved CR. Two patients who failed to achieve CR and 3 of 7 recurrent patients underwent hysterectomy. Four of 7 patients with recurrence underwent re-treatment with MPA, and all achieved CR. Relapse-free survival in all patients at 3 years was 44% in the MPA alone group and 85.4% in MPA+metformin group ( $p = 0.003$ ). **Conclusion** The con-

comitant use of metformin can achieve long-term remission for patients who desire fertility sparing.

#### IS-WS-2-4

**Screening of Endometrial Cancer Using Cervical Swab** Ling Lim<sup>1</sup>, Yuh-Cheng Yang<sup>1</sup>, Chao-Chih Wu<sup>2</sup>, Yun-Ting Hsu<sup>1</sup>, Chih-Long Chang<sup>1,2,3</sup> *MacKay Memorial Hospital, Taiwan<sup>1</sup>, MacKay Memorial Hospital, Department of Medical Research, Taiwan<sup>2</sup>, MacKay Medical College, Taiwan<sup>3</sup>*

**Objective** The Papanicolaou test (Pap test) reduced cervical cancer since it was introduced in screening program in 1991. However, cervical cancer remains the only gynecologic cancer that is screenable till now. Endometrial cancer is the most common gynecologic cancer in developed countries. It is often discovered only when patients presented with symptom of vaginal bleeding and had underwent invasive procedure to extract tissues from endometrium. Our study aims to establish a screening tool for endometrial cancer based on current infrastructure using cervical swab. **Methods** Fresh tissues from 108 endometrial cancer patients were screened for gene mutations. Besides, white blood cells of 60 of these patients were collected as control. The gene mutations were determined by capture probes and next generation sequencing (NGS). Afterwards, a panel of mutated genes was established through data processing. Subsequently, this panel of mutated genes was tested in cells obtained from cervical swabs of 138 endometrial cancer patients and 50 healthy participants by amplicon-based multiplex polymerase chain reaction and NGS. All participants were enrolled from two medical centers in Taiwan. **Results** A total of 1,635 amplicons from 36 genes were determined as final markers for screening of endometrial cancer. The detection rate for endometrial cancer was 86% when validating the panel genes using cervical swab in 188 cases. However, up to 14% of the normal cases were found to have gene mutations. **Conclusion** In conclusion, our data indicated that screening of endometrial cancer might be feasible using cervical swab. However, further investigation is needed to improve the specificity of the test. Furthermore, cost reduction of this screening test is necessary to enhance its accessibility.

#### IS-WS-2-5

**Genomic analysis of cell-free DNA in plasma using NIPT platform by massively parallel sequencing for a prognostic factor : gynecological tumor associated copy number variants : a prospective study** Makoto Nakabayashi<sup>1</sup>, Akihiro Kawashima<sup>1</sup>, Hanako Shimizu<sup>2</sup>, Shingo Miyamoto<sup>1</sup>, Chiaki Iitsuka<sup>1</sup>, Koji Matsumoto<sup>1</sup>, Akihiko Sekizawa<sup>1</sup> *Showa University<sup>1</sup>, National Cancer Center Hospital<sup>2</sup>*

**Objective** The discovery of circulating tumor DNA (ctDNA) molecules has created a paradigm shift in tumor biomarker. In the other hands, non-invasive prenatal testing (NIPT) for detecting circulating cell-free fetal DNA in maternal plasma has been increasingly recognized as a valuable substitute to perceive fetal copy number variations (CNVs). We hypothesized that CNVs of ctDNA detected by NIPT methods would be detectable in the plasma of gynecological cancer patients collected before primary surgery and be predictable for their recurrence. The aims of this study were whether the use of NIPT platform for ctDNA in the plasma of gynecological cancer patients could serve as a predictive marker of patient outcome. **Methods** We used NIPT platform to detect CNVs of ctDNA in the plasma of patients with gynecological cancers. Samples were collected from 100 patients who underwent surgery at a single institution. Progression-free survival (PFS) and overall survival (OS) were analyzed according to the presence of CNVs of ctDNA. **Results** Among the 100 cases, CNVs of ctDNA was detected in 32 plasma sam-

ples. Patients with CNVs of ctDNA had a significantly poorer prognosis in all stages concerning PFS (P=0.002) and OS (P=0.043), and even in early stages concerning PFS (P=0.034). **Conclusion** We proved that the existence of CNVs of ctDNA in plasma samples could be a powerful predictor of poor survival in patients with gynecological cancer. Accordingly, CNVs of ctDNA detection might be a promising approach for the management of gynecological cancer.

#### IS-WS-2-6

**The malicious role of immune-reaction in Uterine Serous carcinoma** Yuka Mise, Tsukasa Baba, Junzo Hamanishi, Kaoru Abiko, Ryusuke Murakami, Noriomi Matsumura, Masaki Mandai *Kyoto University*

**Objective** Uterine serous adenocarcinoma (USC) has the worst prognosis in endometrial cancer exhibiting chemo-resistant and progressive property, and thereby a novel therapeutic strategy has been desperately required. Recently, anti-tumor immunity evasion (ATIE) is known to play crucial roles in refractory cancers, but ATIE in USC has not been clarified so far due to lacking immunocompetent assessment models. The aims of this study are to evaluate local immunological features of human USCs and to develop an immuno-competent mouse USC model for future investigation. **Methods** Clinical samples from 42 surgically treated USC patients were served for clinicopathological analysis. Tumor infiltrating CD8<sup>+</sup>T cells (TILs) and CD33<sup>+</sup> cells (MDSC) were counted and MDSC-TIL ratio was calculated to assess tumor microenvironmental immunity. A mouse endometrial cancer cell line, ppp268, was established by conditional uterine deletion of Pten and Trp53 using the Cre/loxP approach, and murine cMyc was further introduced to develop ppp268-cMyc cells for assessing immunocompetent tumorigenicity on C57BL6 mice. **Results** TILs were more frequently observed in the center of tumor without recurrence (p<0.05). Overall survival was significantly better in cases with low MDSC-TIL ratio. Immunocompetent tumorigenicity got superior by transduction of cMyc, and cMyc tumor exhibited highly nuclear atypia and glandular structure mimicking USC. In cMyc tumors, MDSCs were more frequently observed (p<0.05), and MDSC-TIL ratio was also high. **Conclusion** TILs and MDSCs are prognostic factors of human USC. ppp268-cMyc cells can be designated as a mouse USC mimicking cell line suitable for investigating a new therapeutic strategy conquering ATIE.

#### IS-WS-2-7

**Surgical technique and outcomes of uterus retrieval from brain-dead multi-organ donors : a preclinical research of human living uterine transplantation** Gaowen Chen<sup>1</sup>, Yifeng Wang<sup>1</sup>, Xiangyuan Li<sup>2</sup>, Youhong Zheng<sup>1</sup>, Xiaoxuan Li<sup>1</sup>, Ying Zhu<sup>1</sup>, Zengying Cui<sup>1</sup>, Chenyuan Hao<sup>1</sup> *Zhujiang Hospital, Southern Medical University, China<sup>1</sup>, Department of Reproductive Medical Center, Guangdong Women and Children Hospital, China<sup>2</sup>*

**Objective** To evaluate the surgical technique and outcomes of deceased donor uterine transplantation, which is a preclinical research of human living uterine transplantation. **Methods** From May, 2015 to August, 2017, four uterine retrieval procedures, characterized with radical hysterectomy and uterine vascular pedicles dissection, were performed in multi-organ brain-dead donors. The uterus was the third authorized organ after the kidney and liver retrieval procedures. The uterine pedicles included the uterus, ovarians, fallopian tubes, the upper one-third of the vagina and internal iliac vessels or external iliac vessels. The perfusion of the uterus was conducted after the retrieval for evaluating the availability, followed by histopathological examination of the harvested uterus per 30 minutes.

**Results** Since the uterine vein was quite difficult to identify and dissect in the first two cases, which result in the rupture of triple uterine veins. Therefore, the uterine venous vessels, including uterine vein connected with internal iliac vein, and internal iliac arteries as well as uterine arteries were selected as vascular grafts and dissected successfully in the last two cases. The last two harvested uteri could be perfused with the mixture of 4 degree heparinized physiological saline through each artery following shortening the surgical time. Mean (SD) operative time was  $68.7 \pm 9.3$  mins (60–85 mins, n=4). **Conclusion** Our preliminary experience indicated that the uterus could be retrieved from the brain-dead multi-organ donors and transplanted to the recipient. The attempt of purely dissecting the uterine veins should be replaced by dissection of internal iliac vein.

### IS-WS-2-8

**Analysis of paternal contribution of genetic partial hydatidiform mole using subtraction B allele frequency plotting of SNP array** Hirokazu Usui, Asuka Sato, Makio Shozu *Chiba University*

**Objective** Partial hydatidiform mole (PHM) is genetically diandric monogynic triploid. Two haploids of paternal contribution are estimated. The aim of this study is to elucidate the clarify the detailed paternal contribution of PHM, especially which did not have three allelic loci in short tandem repeat (STR) polymorphism analysis. **Methods** The paired genomic DNA of eight cases of genetic PHM diagnosed by STR analysis and their maternal blood were analyzed using single nucleotide polymorphism (SNP) array (Illumina HumanCore v1.0) to get the log R ratio and B allele frequency (BAF) parameters. We developed the subtraction BAF plotting, which could estimate their paternal haploid contribution. Further, the SNP array data were explored with subtraction BAF plotting. **Results** Four PHM cases showed two paternal haploid contributions and one maternal contribution. Centromeric region analysis indicated that two paternal haploids were from two mature sperms but not a diploid sperm. The rest of four cases without three allelic loci on STR analysis were confirmed as triploid. They showed the mono haploid of paternal contribution (self-duplication) and one maternal haploid. **Conclusion** We developed the new method as a subtraction BAF plotting. We identified the diandric monogynic triploid PHM with the paternal contribution from one mature sperm. This methodology could be applied to determine the parental origin of trisomy and to analyze the villous samples with maternal contamination.

### IS-WS-3-1

**Genomic landscape of ovarian clear cell carcinoma via next generation sequencing** Se Ik Kim, Maria Lee, Hee Seung Kim, Hyun Hoon Chung, Jae-Weon Kim, Noh Hyun Park, Yong-Sang Song *Seoul National University College of Medicine, Korea*

**Objective** To obtain whole exome sequencing (WES) data of OCCC via next generation sequencing (NGS) technique. Genomic profiles were compared between EMS-associated OCCC (EMS-OCCC) and non-EMS associated OCCC (Non-EMS-OCCC). **Methods** We used serum samples and cancer tissues collected from the female patients who were diagnosed with OCCC between 2012 and 2016, and stored at the Seoul National University Hospital Human Biobank. In total, 15 patients were enrolled : 5 were pathologically confirmed EMS-OCCC cases and the other 10 were Non-EMS-OCCC cases. We performed WES for 15 OCCC tissues with matched serum samples, and analyzed NGS data for comprehensive genomic characterization of OCCC. **Results** OCCC was characterized by complex genomic alterations, with a median of 178 exonic mutations (range, 111–25,798) and a median of 343.0 (range, 43.0–1,820.0) so-

matic copy number variations per tumor sample. Top three statistically recurrent somatic mutations were PIK3CA, ARID1A, and KRAS. Somatic copy number alterations were frequently detected on the region of MUC1, GATA2, NTRK1, and ATM. And we also identified that significantly altered pathways included cell proliferation/survival (PI3K-AKT pathway, TP53 pathway and ERBB2 pathway) in 87% and chromatin remodeling in 47% of tumors. However, we could not find the statically difference between EMS-OCCC and Non-EMS-OCCC groups on genetic alteration analyses. **Conclusion** We successfully obtained genomic landscape of 15 patients with OCCC. We identified a potential therapeutic target in most tumors for the treatment of OCCC. Further studies with whole transcriptome sequencing to discover the effect of genetic alterations are warranted.

### IS-WS-3-2

**Gene Methylation Panel of CDH1, DLEC1 and SFRP5 as Prognostic Marker in Advanced Epithelial Ovarian Cancer** Ying-Cheng Chiang<sup>1</sup>, Wen-Fang Cheng<sup>1</sup>, Chi-An Chen<sup>1</sup>, Heng-Cheng Hsu<sup>2</sup> *National Taiwan University Hospital, Taiwan<sup>1</sup>, National Taiwan University Hospital, Hsin-Chu Branch, Taiwan<sup>2</sup>*

**Background** Aberrant gene methylation is crucial in carcinogenesis and related to the clinical outcomes. This study aimed to investigate the prognostic value of the gene methylation panel (CDH1, DLEC1 and SFRP5) in the advanced epithelial ovarian cancer. **Methods** Totally 177 epithelial ovarian cancer specimens were evaluated by methylation-specific polymerase chain reaction and capillary electrophoresis. The correlation of gene methylation and clinico-pathological parameters were analyzed. The panel was also validated by TCGA dataset. **Results** Patients with tumor recurrence had higher frequency of two or more methylated genes (37.8% versus 12%,  $p=0.001$ , Chi-square test) than patients without tumor recurrence. Chemo-resistant patients had higher frequency of two or more methylated genes (43.3% versus 22.7%,  $p=0.004$ , Chi-square test) than chemo-sensitive patients. The patients with two or more methylated genes had a significantly shorter disease-free survival (DFS) ( $p<0.001$ , log-rank test) and overall survival (OS) ( $p=0.001$ , log-rank test) than those with only one or no gene methylation. In multivariate Cox regression, two or more methylated genes was independent factor for recurrence (HR : 1.79 [1.19–2.69],  $p=0.005$ ) and death (HR : 1.96 [1.26–3.06],  $p=0.003$ ). In the TCGA dataset, patients with two or three methylated genes had a significantly shorter DFS ( $p=0.023$ , log-rank test) and OS ( $p=0.003$ , log-rank test) than those with only one or no gene methylation. **Conclusion** Our gene methylation panel can be a prognostic biomarker of advanced epithelial ovarian cancer.

### IS-WS-3-3

**GSTP1 rs1695 is a predictive indicator of both hematological toxicity and prognosis of ovarian cancer treated with paclitaxel plus carboplatin** Tomoko Yoshihama<sup>1</sup>, Akira Hirasawa<sup>1</sup>, Hiroyuki Nomura<sup>1</sup>, Tomoko Akahane<sup>1</sup>, Fumio Kataoka<sup>1</sup>, Wataru Yamagami<sup>1</sup>, Taisei Mushiroad<sup>2</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, RIKEN<sup>2</sup>*

**Objective** To identify genetic variants that are associated with toxicity and/or efficacy of paclitaxel plus carboplatin combination chemotherapy (TC therapy), so that we are able to predict the likelihood of severe toxicity or efficacy in patients before treatment. **Methods** In a retrospective case-control study, we analyzed 320 patients who had received TC therapy for gynecological cancers (ovarian, fallopian tube, peritoneal, uterine, and cervical cancers) and collected their germline DNA from archived samples. We performed a comprehensive pharmaco-

genomic analysis by targeted resequencing of 100 pharmacogenes using next-generation sequencer. For all 1,188 genotyped variants with minor allele frequency  $\geq 0.001$  and missing genotype rate  $< 10\%$ , case-control association studies and survival analyses were conducted. Next, we assessed 5-year progression-free survival (PFS) and overall survival (OS) in 56 advanced ovarian cancer patients who had received tri-weekly TC therapy as a first-line chemotherapy. **Results** *GSTP1* (glutathione S-transferase P1) rs1695 showed the smallest p value for hematotoxicity association, and the A allele (wild type) had a significantly higher risk of severe hematotoxicity (neutropenia  $\geq G3$ , thrombocytopenia  $\geq G3$  and anemia  $\geq G3$ ) than the G allele (variant type) did ( $p=0.00034$ , odds ratio=5.71 (95% confidence interval : 1.77-18.44)). In a prognosis analysis, patients with *GSTP1* rs1695 AA genotype showed significantly better PFS ( $p=0.00070$ ) and OS ( $p=0.0012$ ) than those with the AG or GG genotype did. **Conclusion** Our study indicates that the *GSTP1* rs1695 AA genotype is associated with both severe hematotoxicity and high efficacy of TC therapy, identifying a possible prognostic indicator for patients with TC therapy.

### IS-WS-3-4

**Inactivation of ZNF671 by DNA methylation is closely associated with early recurrence of serous ovarian cancer** Shoko Mase<sup>1</sup>, Ryutaro Nishikawa<sup>1</sup>, Atsushi Arakawa<sup>1</sup>, Mayumi Sugiura<sup>1</sup>, Yutaka Kondo<sup>2</sup> *Nagoya City University<sup>1</sup>, Nagoya University, Department of Cancer Biology<sup>2</sup>*

**Objective** The aim of this study is to examine epigenetic alterations, which are associated with early recurrence of SOCs. **Methods** We use TCGA database to identify the methylated genes in early recurrence of SOCs. We analyze DNA methylation of the identified gene in our SOC cohort and perform the functional analysis of the identified gene using SOC cell lines. **Results** We analyzed DNA methylation using Infinium 27K data of 209 SOCs in The Cancer Genome Atlas : 51 showed early ( $< 12$  months) and 158 showed late ( $> 12$  months) recurrence, respectively. Among 14,475 genes, we identified 11 genes which were differentially methylated between the two groups. ZNF671 was the most frequently methylated in the early recurrence group and showed inverse correlation between DNA methylation status and gene expression. In validation group of SOCs ( $n=85$ ), the sensitivity of this marker for detection of early recurrence was 82.1% (DNA methylation cut off was 10.85%). And patients with high methylation of ZNF671 significantly showed worse overall survival compared with those who with low methylation ( $p<0.05$ ). Inhibition of DNA methyltransferase by 5-aza-2-deoxycytidine induced ZNF671 expression in SOC cell lines (JHOS-2, JHOS-4, OVCAR3). Further, inhibition of ZNF671 by siRNA increased cell proliferation as well as invasion and migration in SOC cell lines. **Conclusion** Our data indicated that ZNF671 may act as a tumor suppressor and that methylation of this gene might be a useful biomarker for prediction of early recurrence of SOCs.

### IS-WS-3-5

**MiR-522 modulates paclitaxel resistance in ovarian cancer cells** Mayuko Miyamoto, Kenjiro Sawada, Akihiko Yoshimura, Erika Nakatsuka, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Tadashi Kimura *Osaka University*

**Objective** The overcome of paclitaxel resistance is a critical issue in ovarian cancer treatment. The aim of this study is to identify key microRNAs (miRNAs) which regulate paclitaxel resistance and to pursue those potential as therapeutic targets. **Methods** Using two serous ovarian cancer cell lines, SKOV3ip1 and HeyA8, paclitaxel resistant cell lines were established by a continuous exposure of paclitaxel. The miRNA PCR arrays were

performed and miR-522 was found to be one of downregulated miRNAs in paclitaxel-resistant cell lines. The expression level of miR-522 was analyzed among 7 ovarian cancer cells and the relationship between miR-522 and IC50 value of paclitaxel was examined. The effect of miR-522 on paclitaxel resistance was assessed by transducing the precursor miRNA into ovarian cancer cells. Using laser microdissection technique, the precise carcinoma tissues were extracted from paraffine-embedded materials and the expression level of miR-522 was examined by real-time miRNA PCR. **Results** In paclitaxel resistant cell lines (HAC2, KOC7C, OVISe, RMG-1, RMG-2), of which IC50 values were higher than 50nM, the expression level of miR-522 was down-regulated than paclitaxel sensitive SKOV3ip1 cells (0.003, 0.627, 0.608, 0.009, and 0.066, respectively). In vitro cell viability assay revealed that transduction of miR-522 into paclitaxel resistant SKOV3ip1 cells sensitized resistant cells to paclitaxel. In paclitaxel resistant clear cell carcinoma, miR-522 expression was significantly down-regulated compared with contralateral normal ovary (0.042). **Conclusion** MiR-522 modulated sensitization to paclitaxel in ovarian cancer cells and can be considered as a therapeutic target to overcome paclitaxel resistance.

### IS-WS-3-6

**Elevated level of serum miR-1290 is correlated with high grade serous epithelial ovarian cancer and can be a potential biomarker** Masaki Kobayashi, Kenjiro Sawada, Aasa Shimizu, Mayuko Miyamoto, Kyoso Ishida, Akihiko Yoshimura, Erika Nakatsuka, Koji Nakamura, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Tadashi Kimura *Osaka University*

**Objective** There is a critical need for improved diagnostic markers detecting ovarian high grade serous ovarian cancer (HGSOC). MicroRNAs (miRNAs) stably exist in circulating blood, reflecting tissue conditions and present in circulating microvesicles like exosomes. The aim of this study is to identify which miRNAs are highly produced from HGSOCs and analyze whether serum miRNA can discriminate HGSOC patients from healthy controls. **Methods** Secreted exosomes from ovarian cancer cell lines were collected and exosomal miRNAs extracted. miRNA microarray was performed and several elevated miRNAs specific to HGSOCs were picked up. Among these, we focused on miR-1290. Serum from 71 pre-operative, 46 post-operative ovarian cancer patients and 13 healthy controls were gathered and its expression levels were detected by quantitative real time PCR. Further, CA125 value of each patient was collected and the potential of miR-1290 as a novel biomarker examined. **Results** In HGSOC patients, miR-1290 emerged overexpressed compared to healthy controls (3.52-fold) unlike other types of epithelial cell ovarian cancer patients. In advanced stage HGSOC patients, its expression was higher than that in early stage (4.23 VS 1.58 ;  $P=0.23$ ). Its expression significantly decreased after operation (5.87 to 1.17 ;  $P<0.01$ ), indicating that this miRNA is produced from cancer tissues. ROC analysis showed that at the cut-off of 1.61, the sensitivity and specificity were 63% and 85% respectively for detecting HGSOCs (AUC=0.71). Combining CA125 and miR-1290 values, AUC value significantly improved (0.972 to 1.00). **Conclusion** Serum miR-1290 can be a potential diagnostic biomarker for HGSOC.

### IS-WS-4-1

**Cyberknife Therapy for Locally Recurrent Gynecologic Cancers After External-beam Radiation Therapy** Courtney Griffiths<sup>1</sup>, Roseanna Valant<sup>1</sup>, Jonathan Haas<sup>1</sup>, David Ebling<sup>1</sup>, Melissa Fazzari<sup>1</sup>, Jeanine Villella<sup>2</sup>, Eva Chalas<sup>1</sup>, Edward Jimenez<sup>1</sup> *NYU-Winthrop University Hospital, USA<sup>1</sup>, Lenox Hill Hospital, USA<sup>2</sup>*

**Objective** Management of locally recurrent gynecologic cancers



following external-beam radiation (RT) presents a therapeutic dilemma. Treatment options usually involve an exenterative procedure or palliative chemotherapy due to the risk of toxicity with re-irradiation. This study aims to analyze the efficacy of re-irradiation using Cyberknife for local recurrences. **Methods** A retrospective chart review of patients treated with Cyberknife at NYU Winthrop between 2005-2015, identified 29 patients with prior RT and locally recurrent gynecologic cancer: endometrial (n=22), cervix (n=1), ovary (n=2) and vulvar (n=4). Recurrences were radiologically confirmed. Median dose of pelvic RT given prior to the recurrences was 60 Gy and the median Cyberknife dose delivered was 25 Gy. Kaplan-Meier estimates for progression-free (PFS) and overall survival (OS) were calculated. Associations between survival was determined using Cox proportional hazards regression models. **Results** 27 of the 29 patients had follow up data and were included. Median time between primary RT and Cyberknife treatment was 24 months. Seventeen recurrences were located in the central pelvis, 4 in the pelvic sidewall, and 9 in the PA region. Median follow up was 13.7 months. Overall response rate to Cyberknife at 12 months was 89 (9 complete response, 8 partial response, and 7 stable disease). The median PFS and OS were 11.7 months and 20.5 months, respectively. Only 6 in-field disease progressions were observed. **Conclusion** Our results suggest that use of Cyberknife for locally recurrent gynecologic cancers in a prior radiated field can be an effective non-surgical salvage option providing local control with acceptable toxicity.

#### IS-WS-4-2 Withdraw

#### IS-WS-4-3

**Frzb is induced by RAS-MAPK signaling and contributes to transformation** Ichiro Onoyama, Keisuke Kodama, Hiroshi Yagi, Masafumi Yasunaga, Tatsuhiro Ohgami, Kazuo Asanoma, Kenzo Sonoda, Kiyoko Kato *Kyushu University Hospital*  
**Objective** RAS-MAPK signaling is aberrantly activated in variety kinds of human cancers. In gynecologic oncology field, KRAS activating mutation is one of the most frequent alterations reported in ovarian cancers and endometrial cancers. However, KRAS mutation alone cannot transform normal cells and needs another oncogene activation and/or tumor suppressor genes inactivation for carcinogenesis. To fully understand RAS-MAPK downstream signaling pathways we performed RNA-sequencing using mouse embryonic fibroblasts (MEFs) isolated from BrafV600E knock-in mice, and tried to find unknown pathways that promote or suppress carcinogenesis. **Methods** MEFs are isolated from BrafV600E knock-in mice, and analyzed them with RNA-sequencing. Upregulated or downregulated genes are validated with MEFs from BrafV600E and KrasG12D knock-in mice, and biological significance of those genes were investigated with knockdown experiments. **Results** We have got many genes with their expressions increased or decreased after BrafV600E activation from RNA-sequencing analysis, and focused on Frzb among the validated genes, because oncogenic Braf and Kras induced massive expression of Frzb two or three weeks after activation of each oncogene. KrasG12D knock-in MEFs with Frzb knockdown showed suppressed cell growth and reduced focus formation ability, indicating that Frzb induced by Kras activation would play a role in carcinogenesis. **Conclusion** Frzb was induced by oncogenic Kras activation, and could contribute to carcinogenesis in Kras-activated cells. Besides Frzb, the expression of many genes which are not known to be involved in RAS-MAPK pathway, changed following oncogenic Kras activation. RAS-MAPK signaling has been studied vigorously so far, however, it is still worth investigating those genes to understand the pathway.

#### IS-WS-4-4

**Lovastatin induced KLF2, KLF6 and RHOB genes and preferentially led to viability reduction of cisplatin-resistant cells** Chiho Koi, Tomoko Kurita, Taeko Ueda, Seiji Kagami, Toshinori Kawagoe, Toru Hachisuga *University of Occupational and Environmental Health*

**Objective** Recently, statin has been reported to have an antitumor activity and also pointed out the association with drug-resistance. We investigated the antitumor activity of statins in cisplatin-resistant cells and elucidated the mechanism. **Methods** (1) We performed the cell viability of 7 statins in cisplatin-resistant HCP4 and PCDP5 cells compared with parent HeLa and PC3 cells by WST-8 assay. We also examined cell cycle analysis after treatment to HeLa and HCP4 cells with lovastatin. (2) We investigated cDNA microarray analysis with HCP4 cells treated or untreated 1uM lovastatin, and we focused on KLF2, KLF6, and RHOB genes thought to be tumor suppressor genes. We examined whether statins induced these genes by real-time PCR, and evaluated the effect on cell survival and cell cycle due to overexpression of these genes, by cell counting and cell cycle analysis, respectively. **Results** (1) HCP4 cells and PCDP5 cells were 20.8-33.4-fold more resistant to cisplatin but 1.02-68.3-fold more sensitive to 7 statins. Lovastatin significantly increased the sub-G1 population of HCP4 cells more rapidly and to greater extent than in HeLa cells. (2) KLF2, KLF6, and RHOB genes were induced by a low concentration of lovastatin in HCP4 cells compared with HeLa cells. Overexpression of these genes led to viability reduction. Cell cycle analysis revealed that KLF2 and RHOB significantly induced an increase in the populations of sub-G1. **Conclusion** It was suggested that statins induced tumor suppressor genes such as KLF2, KLF6, and RHOB and sensitized cisplatin resistant cells with low concentration.

#### IS-WS-4-5

**Anticancer effect by curcumin is both associated with caspase-dependent and caspase-independent cell death in gynecological cancer cells** Tzefang Wong, Atsushi Uekawa, Shiho Kuji, Norihito Yoshioka, Tatsuru Ohara, Imari Deura, Akiko Tozawa, Nao Suzuki *St. Marianna University School of Medicine*  
**Objective** Curcumin is widely reported to have a vast repertoire of molecular targets within the cell, despite its low toxicity in normal cells. As curcumin's multitude targets within the cell was touted to circumvent resistance to treatment, we chose three distinct pathways within cancer that have shown to contribute to resistance to standard clinical therapies when either of which was inhibited, i.e. the RAS-MEK-ERK1/2, PIK3CA-AKT-mTOR and JAK2-Stat3 pathways. Association with both caspase-independent and classical apoptosis was also investigated. **Methods** Gynecological cancer cell lines RMG-I, RMG-V, SNG-II, SNG-M, HeLa and SiHa were used. Curcumin was added to cultured cells and IC50 were derived from cell proliferation assays using alamarBlue (manufactured by Bio-Rad), based on the protocol provided. Western blots were performed to detect apoptotic markers such as cleaved PARP and cleaved caspases, phosphorylated kinases and other pathway markers. **Results** Curcumin inhibits cell proliferation in a dose-dependent manner. Lower IC50 seems to be associated with a higher AKT activity, as shown by AKT phosphorylation. Cervical cancer cell-lines, HeLa and SiHa, tend to show caspase-independent cell death, whereas the endometrial cancer (SNG-II and SNG-M) and ovarian cancer cell lines (RMG-I and RMG-V) tend to show both caspase-dependent and independent apoptosis. **Conclusion** Resistance to standard cytotoxic chemotherapy and molecular targeted treatment is an urgent problem. This investigation aims to fine-tune our understanding on curcumin's mechanism of action, therefore will potentially prove (or dis-

prove) the usefulness of curcumin for cancer treatment.

### IS-WS-4-6

**The spliceosome U2 snRNP factors promote genome stability through distinct mechanisms : transcription of repair factors and R-loop processing** Michihiro Tanikawa<sup>1</sup>, Osamu Hiraike<sup>2</sup>, Katsutoshi Oda<sup>2</sup>, Harunori Honjoh<sup>2</sup>, Machiko Kojima<sup>2</sup>, Shinya Oki<sup>2</sup>, Kenbun Sone<sup>1</sup>, Kazunori Nagasaka<sup>1</sup>, Yoko Matsumoto<sup>1</sup>, Yutaka Osuga<sup>2</sup>, Tomoyuki Fujii<sup>2</sup> *The University of Tokyo<sup>1</sup>, Graduate School of Medicine, The University of Tokyo<sup>2</sup>*

**Objective** Whole-exome sequencing in various cancers identified recurrent somatic mutations in U2 snRNP components of the spliceosome. Accumulating evidences have implied that the spliceosome plays an important role in genome stability and DNA repair processes. The aim of this study is to clarify the functions of U2 snRNP splicing factors, especially SNRPA1 (Small Nuclear Ribonucleoprotein Polypeptide A1) in DNA damage repair (DDR) pathway. **Methods** SNRPA1 and other splicing factors were identified as Homologous Recombination (HR) repair genes by genome-wide screens. Each splicing factor was depleted by siRNA knockdown and their functions in DNA repair were analyzed by HR assay, immunofluorescence, real-time laser micro-irradiation and comet assay. R-loop formations, deleterious transcription by-product for the genome, were also analyzed. **Results** HR assay showed strong HR deficiencies in splicing factor's depleted cells. In these cells, accumulation of BRCA1 and Rad51 to DNA damage sites were severely impaired. Live cell imaging showed recruitment of SNRPA1 to laser induced DNA damage sites, indicating its direct involvement to DNA damage repair. Comet assay showed that depletion of SNRPA1 markedly caused DNA damage. Immunofluorescence detected R-loop formation in splicing factors depleted cells as cause of DNA damage. **Conclusion** Recruiting HR factors to DNA damage sites and R-loop processing were identified as novel tumor suppressive function of the spliceosome U2 snRNP factors. Our data also suggest U2 snRNP of spliceosome can be therapeutic target in HR deficient cancers (i. e. BRCAness).

### IS-WS-5-1

**Trends in maternal mortality in Mongolia in year 2016** Munkhtsetseg Davaatseren<sup>1</sup>, Yanjinsuren Darmaa<sup>1</sup>, Enkhtsetseg Jamsranjav<sup>1</sup>, Bolormaa Narantuya<sup>2</sup>, Buyanjargal Yadamsuren<sup>2</sup>, Bolorchimeg Baldandorj<sup>1</sup>, Amartuvshin Tumenjargal<sup>1</sup> *Mongolian National University of Medical Sciences, Mongolia<sup>1</sup>, Ministry of Health, Mongolia<sup>2</sup>*

**Aim** Maternal mortality remains a major challenge to health systems in Mongolia. In this study, we investigated the causes of maternal death in 2016, Mongolia. **Methods** We retrospectively analyzed 38 maternal mortality cases in 2016. The information was obtained from pregnancy observation card, birth history, verbal autopsy study, and reports of the chief expert of the Ministry Health for Obstetrics and Gynecology. **Results** In the year 2016, there were 72,000 deliveries in Mongolia. The overall maternal mortality ratio (MMR) was 26.0 per 100,000 live births in 2015 and increased significantly to 48.6 per 100,000 live births in 2016. Further, seven (18.4%) of maternity died at home without any healthcare service. However, our antenatal care rate was 76.3%. Among the 38 cases, there were 22 (57.9%) direct maternal deaths and 16 (42.1%) indirect. The main causes of direct maternal deaths were in a category of amniotic fluid embolism (n=8, 36.4%), and sepsis (n=7, 31.8%). In the indirect causes of maternal deaths, most often were a cardiovascular disorder (n=5, 31.3%), neurological disorders (n=4, 25%), followed by respiratory system disease was two (n=2, 12.5%). Most of the maternal deaths were in age group 30-34 years old (n=16, 42.1%). **Conclu-**

**sion** Available data showed that the leading causes of maternal mortality are amniotic fluid embolism, sepsis, and cardiovascular disorders. Besides, recent changes in mortality distribution highlight current characteristics of pregnancy care in Mongolia and may help identify strategies for future improvement.

### IS-WS-5-2

**Factors affecting maternal and neonatal morbidity planned for cesarean delivery** Young Mi Jung, Su Ah Kim, Ji Hyun Ahn, Jina Youm, Seung Mi Lee, Chan-Wook Park, Joong Shin Park, Jong Kwan Jun *Seoul National University College of Medicine, Korea*

**Objective** Previous studies have indicated that the risk of adverse neonatal outcomes in term cesarean deliveries (CD) increases progressively as gestational age (GA) at birth declines. So it has recently been recommended to perform CD after 39 weeks of gestation. We analyzed factors affecting maternal and neonatal morbidity in term cesarean section. **Methods** The relationship between the GA, maternal age, indication of CD, whether elective or emergent and adverse neonatal/maternal outcomes were compared in 1,035 term pregnant women who were booked for CD. Adverse neonatal outcomes were defined as the presence of mortality, adverse respiratory outcomes, sepsis, hypoglycemia, seizures, necrotizing enterocolitis, hypoxic ischemic encephalopathy, cardiopulmonary resuscitation, cord pH<7, 5min AS below 3, admission to NICU, or prolonged hospitalization. Adverse maternal outcomes included a primary composite of death, uterine atony, need for transfusion, uterine artery embolization, peripartum hysterectomy, cystostomy, broad ligament hematoma, uterine artery ligation, uterine rupture, wound dehiscence, admission to ICU, endometritis, thromboembolic complications, or postoperative ileus. **Results** 1) The frequency of adverse neonatal and maternal outcomes were 5% (52/1,035), and 6% (61/1,035) in all CD. 2) Neonatal complications decreased as the GA increased in all patients. 3) The maternal age and whether the cesarean section was an emergency or scheduled were the two factors that adversely affect maternal outcomes. **Conclusion** The risk of neonatal complications decreased as the GA increased. But GA was not related with adverse maternal outcome. Maternal age and whether elective or emergent were the factors related with adverse maternal outcome. The risk of emergency CD increased as the GA\_planned increased, so clinicians should remember when planning the date of elective CD.

### IS-WS-5-3

**How do we reduce further maternal deaths in Japan? : Recommendations from the Maternal Death Exploratory Committee** Junichi Hasegawa<sup>1</sup>, Hiroaki Tanaka<sup>2</sup>, Shinji Katsuragi<sup>2</sup>, Kazuhiro Osato<sup>2</sup>, Takeshi Murakoshi<sup>2</sup>, Masahiko Nakata<sup>2</sup>, Masamitsu Nakamura<sup>2</sup>, Jun Yoshimatsu<sup>2</sup>, Akihiko Sekizawa<sup>2</sup>, Isamu Ishiwata<sup>2</sup>, Tomoaki Ikeda<sup>2</sup> *St. Marianna University School of Medicine<sup>1</sup>, The Maternal Death Exploratory Committee in Japan<sup>2</sup>*

**Objective** To clarify the problems related to maternal deaths in Japan, we made recommendation for further reduction of maternal deaths. **Methods** Descriptive study was performed in maternal death registration system established by the Japan Association of Obstetricians and Gynecologists (JAOG). Women who died during pregnancy or within a year after delivery between 2010 and 2016 throughout Japan (n=277) were analyzed. This study was approved by institutional ethical board. **Results** Maternal deaths were frequently caused by obstetric hemorrhage (23%), stroke (15%), amniotic fluid embolism (13%), cardiovascular disease (10%) and pulmonary disease (8%). The committee considered that it was impossible to prevent death in 51% of

the cases due to their severity especially in cases of amniotic fluid embolism and stroke. In contrast, half of the deaths due to obstetric hemorrhage were considered possible to prevent with quick response or enough medical resource. Frequency of epidural labor analgesia in the subjects was as same as that in population in Japan (5%). Whereas only a death was associated with analgesia itself, obstetric hemorrhage involved by instrumental delivery was strongly associated with deaths. 10% of the subjects had got pregnant by ART, however one-third of them had already had severe complications before ART. Suicide was reported only 5% of the subjects, however this incidence is estimated lower than certain population. **Conclusion** Recommendations for further reduction of maternal deaths in Japan include to improve primary care for patients with maternal hemorrhage, longitudinal mental care from pregnant to puerperal period, and pre-conceptional evaluations for each complication and care.

### IS-WS-5-4

**Prevention of hypothermia is important in early mother-infant skin-to-skin contact** Kentaro Kurasawa<sup>1</sup>, Yoshinobu Sugo<sup>1</sup>, Mizuha Odagami<sup>1</sup>, Shigeru Aoki<sup>1</sup>, Etsuko Miyagi<sup>1</sup> *Yokohama City University<sup>1</sup>, Yokohama City University Medical Center<sup>2</sup>*

**Objective** The points of attention in "Early Mother-Infant Skin-to-Skin Contact" was published in 2012. We describe the current status of implementing early mother-infant skin-to-skin contact in Japan and identify factors associated with sudden changes in the conditions of newborns. **Methods** The Maternal and Child Health Division of the Ministry of Health, Labour and Welfare conducted a questionnaire survey focusing on early mother-infant skin-to-skin contact during the early neonatal period in full term infants born in 2014. The questionnaire was delivered to 2,839 maternity facilities throughout Japan. Replies were obtained from 1,680 facilities (60.4%), and 627,593 deliveries were analyzed based on the responses obtained. **Results** The proportions of facilities implementing early mother-infant skin-to-skin contact overall and in accordance with the Points of Attention in "Early Mother-Infant Skin-to-Skin Contact" were 88.2% and 36.0%, respectively. Early mother-infant skin-to-skin contact time is most often less than 30 minutes (38.9%). The number of events of sudden change requiring resuscitation including positive pressure ventilation during early mother-infant skin-to-skin contact was 149 (0.027%). Of these 149 events, 97 (65.1%) occurred within 10 minutes after birth. There was no association between the event occurrence rate and facility types ( $p=0.56$ ), although fewer events were observed in the general and regional prenatal care centers. In addition, the event rate was significantly lower in facilities providing hypothermia prevention ( $p<0.01$ ). **Conclusion** All newborns may show sudden changes, necessitating careful observation of mothers and children. Prevention of hypothermia in newborns contribute to reducing the risk of needing urgent care.

### IS-WS-5-5

**Population-based trends and risk factors of early- and late-onset preeclampsia in Taiwan 2001-2014** Shu-Han You, Hsien-Ming Wu, Pao-Hsien Chu, Ting-Ting Chung, Chang-Fu Kuo *Chang Gung Memorial Hospital, Taiwan*

**Objective** Preeclampsia is strongly correlated with maternal and fetal complications in pregnancy, especially the early onset (<34 weeks of gestation) preeclampsia, which contributes to poorer pregnancy outcomes. Besides, the incidences between early and late onset of preeclampsia were differed among populations. The established risk factors of preeclampsia included advanced maternal age, nulliparity, chronic hypertension, and

diabetes mellitus. In this study, we evaluated the incidences, trends, and risk factors of early and late onset preeclampsia in Taiwan. **Methods** The population-based prospective cohort study included all >20 weeks singleton deliveries in Taiwan from 2001 to 2014 ( $n=2,884,347$ ) according to the Taiwanese Birth Register. The preeclampsia was determined from hospital records, reporting to National Health Insurance Research Database. The standardized preeclampsia incidence was adjusted based on the age distribution in 2014, the trends were analyzed through Joinpoint Trend Analysis Software, and multivariate logistic regression was used to evaluate the adjusted relative risks (ARR) of clinical factors of early- and late-onset preeclampsia. **Results** The total incidence of preeclampsia increased from 1.11 to 1.69% with the early onset from 0.47 to 0.83% and late onset from 0.66 to 0.89%, respectively during the study period. The significant annual percentage change was noted in early-onset preeclampsia, especially from 2012 to 2014 (22.5%/year; 95% confidence interval [CI], 7.5-39.6%). Advanced maternal age, primiparity, previous stroke, diabetes mellitus, chronic hypertension, and hyperthyroidism were associated higher risk of preeclampsia. Comparing early- versus late-onset disease, two groups were similar to clinical risk factors, and chronic hypertension had stronger association with early-onset preeclampsia (ARR, 16.8; 95%CI, 15.7-18.0). **Conclusion** The incidences of early- and late-onset preeclampsia were increasing between 2001 and 2014 in Taiwan, especially early-onset preeclampsia. Pregnant women who were advanced maternal age, primiparity, or had stroke, diabetes mellitus, chronic hypertension, or hyperthyroidism should be aware of higher risk of early- and late-onset preeclampsia, particularly in women with chronic hypertension.

### IS-WS-5-6

**EEG changes and sleep/wakefulness behaviors in Pregnancy-Associated Hypertensive mice** Haruna Komiya, Hiromi Hamada, Miyuki Mayumi, Yuko Nagai, Rena Ohara, Hiroya Yagi, Mana Obata, Toyomi Satoh *University of Tsukuba*

**Objective** We reported the quantitative/qualitative sleep change during pregnancy in mice at the annual congress last year. Based on these results, we further investigate the effect of EEG changes and sleep/wakefulness behaviors on acute and severe hypertension during late pregnancy using PAH (Pregnancy-Associated Hypertensive) mice, Renin-Angiotensin transgenic mice. **Methods** Human angiotensinogen expressing female mice and C57BL/6 female mice are the subjects. At the age of 9-12 weeks, EEG/EMG recording electrodes were implanted to the skull and neck muscle. After the recovery and acclimation periods, we recorded the basal sleep state. Next, we mated the human angiotensinogen expressing female mice and wild type female mice with human renin expressing male mice and wild type male mice, respectively. The recordings were restarted after the confirmation of vaginal plug. We evaluated 4 days for early, mid, late pregnancy and 2 days for postpartum. Furthermore, we injected Evans blue to the tail vein and removed the brains in late pregnancy to investigate the BBB permeability. **Results** PAH mice exhibited markedly abnormal vigilance states with a generalized slowing of EEG and a drastic decrease in REM sleep during late pregnancy, making it impossible to determine wakefulness and NREMS. Half of the PAH mice shows convulsive seizure conceived as eclampsia. These changes are returned to normal immediately after delivery. All PAH mice exhibited multiple leakages of Evans blue. **Conclusion** PAH mice exhibited a general slowing of EEG accompanied with BBB disruption. This study also suggest the PAH mice as an animal model for eclampsia

## IS-WS-5-7

**Attenuation of angiotensin II-induced preeclamptic symptoms by recombinant thrombomodulin in mice — a novel therapeutic approach for preeclampsia** Hiroko Oda, Takeshi Nagamatsu, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Endothelial dysfunction is known to be a factor of pathoetiology in preeclampsia (PE). Recombinant thrombomodulin (rTm) is reported to have anti-inflammatory function that could modify endothelial damage. We examined the efficacy of rTm administration in a mouse model of PE. **Methods** The osmotic pump was implanted in the pregnant mice or non-pregnant female mice. Angiotensin2 (Ang2) was continuously injected for 7 days from pc 10 to 17 using the osmotic pump. rTm was administered intraperitoneally for 4 days from pc 13 to 16. In the control mice, saline was administered during the same period. Blood pressure (BP) was monitored daily. Blood and urine samples were collected before and after rTm or saline injection. On pc 17, the mice were sacrificed. The fetuses and placentas were excised. **Results** Continuous infusion of Ang2 induced the symptoms mimicking human PE. Significant elevation of BP was confirmed from day 3 after of Ang2 infusion. Hypertension was more obvious in the pregnant mice than the non-pregnant control. Occurrence of proteinuria was limited to pregnant mice. Ang2 infusion caused growth restriction in the fetuses. Administration of rTm significantly attenuated all of the three symptoms of PE. On pc 17, the difference between rTm group and the non-treated control were as follows, SBP (mmHg) : rTm :  $149 \pm 21$  vs control :  $199 \pm 15$ ,  $p < 0.001$ , proteinuria (mg/g CRE) : rTm :  $40 \pm 13$  control :  $78 \pm 12$ ,  $p < 0.001$ , and fetal weight (g) : rTm :  $0.7 \pm 0.07$  control :  $0.61 \pm 0.05$ ,  $p < 0.001$ . **Conclusion** rTm attenuated Ang2-induced PE symptoms in the mouse model. Our findings suggest that rTm might be a novel approach for the therapy of PE.

## IS-WS-5-8

**Possible involvement of RAGE in Hypertensive Disorders of Pregnancy** Juria Akasaka, Taihei Tsunemi, Kazutoshi Nakano, Shunsuke Onishi, Mai Kimura, Kenji Ogawa, Chiharu Yoshimoto, Toshiyuki Sado, Hiroshi Kobayashi *Nara Medical University*

**Objective** Obesity and diabetes mellitus are risk factors of Hypertensive Disorders of Pregnancy (HDP). RAGE is one of the most important receptor related in diabetes mellitus. In this study we investigate the involvement of RAGE in HDP. **Methods** We used primary human preadipocyte and induced them into adipocyte. We cultured adipocyte with medium which contains 10% patient's serum. We used serum of preeclampsia patients (referred to as PE group), and serum of normal pregnancy as a control group (referred to as NP group). After culture, we collected adipocyte for analysis of mRNA expression and collected supernatant for measurement of protein expression. **Results** Using real-time-PCR, we analyzed mRNA expression of adipocyte (about TNF $\alpha$ , IFN $\gamma$ , IL-6, IL-17A). IL-6 mRNA expression was elevated after 6 and 12 hours culture in PE group compared to NP group. Using ELISA, it was also revealed that IL-6 protein expression is elevated in supernatant of PE group compared to NP group. Focusing on IL-6, we furthermore analyzed mRNA expression of HMGB1, RAGE, CCL2. Hereupon, we confirmed that mRNA expression of IL-6 are related to those of HMGB1, RAGE and CCL2. We hypothesize the pathway that HMGB1 elevation cause RAGE elevation and finally cause IL-6 and CCL2 elevation. So using SW872 as human adipocyte cultivated cell line, stimulating SW872 with AGE and HMGB1 lead to elevation of mRNA expression of IL-6 and CCL2. But when siRAGE is introduced, stimulating with AGE and HMGB1 didn't

cause mRNA elevation of IL-6 and CCL2. **Conclusion** In this experiment we revealed that in human adipocyte, AGE and HMGB1 leads to raise of IL-6 and CCL2 through RAGE. It is possible that PE patient serum contains RAGE ligands and play an important role in HDP onset.

## IS-WS-6-1

**Endoplasmic reticulum chaperone calreticulin plays a key role in human placental development** Naoyuki Iwahashi<sup>1</sup>, Madoka Yamamoto<sup>1</sup>, Yoshito Ihara<sup>2</sup>, Kazuhiko Ino<sup>1</sup> *Wakayama Medical University Hospital<sup>1</sup>, Department of Biochemistry, Wakayama Medical University Hospital<sup>2</sup>*

**Objective** Calreticulin (CRT), a molecular chaperone in the endoplasmic reticulum, plays a variety of roles in cell growth, differentiation, and apoptosis. The objective of this study was to investigate the expression and functions of CRT in human placenta, utilizing the human trophoblast cell lines, in which CRT gene expression was knocked down. **Methods** Expression of CRT was examined in human placenta and trophoblast cell lines, such as HTR8/SVneo and BeWo. Stable CRT-knockdown HTR8/SVneo and BeWo cell lines were established, and the effect of CRT downregulation was investigated in respects of cell proliferation, invasion, adhesion, and/or differentiation. This study was approved by the institutional ethics boards, and the informed consent was obtained from all patients. **Results** In western blotting, CRT was strongly expressed in human placenta throughout pregnancy and in trophoblast cell lines. In immunohistochemistry, CRT was mainly expressed in extravillous trophoblasts cells in the first-trimester placenta, and in syncytiotrophoblasts in the third-trimester placenta. In human placenta, the CRT expression levels in fetal growth restriction group were significantly lower than those in control group in the third-trimester. On the other hand, in HTR8/SVneo cells, knockdown of CRT expression suppressed matrigel invasion and the adhesion to fibronectin via the alteration of integrin signaling. Furthermore, in BeWo cells, forskolin-induced expression of  $\beta$ -hCG was significantly suppressed by the CRT knockdown. **Conclusion** The results suggest that CRT is involved in cell invasion and  $\beta$ -hCG expression in trophoblasts. The decrease in CRT expression in fetal growth restriction might be involved in the dysfunction of placental development.

## IS-WS-6-2

**Effectiveness of Nifedipine in threatened preterm labor : a randomized trial** Chatchanawadee Na Nan, Srisuda Songthamwat, Metha Songthamwat *Udon Thani Hospital, Thailand*

**Objective** Threatened preterm labor is the condition which is premature regular uterine contraction at least 1 time in 10 minutes persist for more than 30 minutes before 37 complete weeks of gestation without dilatation of cervix. In the preterm labor with cervical dilatation, the effectiveness of tocolytic was proven. However, in threatened preterm labor, the efficacy of Nifedipine has not yet been well studied. This study aimed to evaluate the effectiveness of Nifedipine versus placebo for inhibiting uterine contraction in threatened preterm labor. **Methods** A randomized, double blind, placebo controlled study of 206 threatened preterm labor participants were randomly allocated into Nifedipine and placebo groups. **Results** After 90 minutes of treatment, 88.3% of the Nifedipine group and 69.9% of the placebo group had no uterine contraction ( $P < 0.001$ ). Nifedipine achieved successful treatment in 77.6% of the participants compared with 49.5% in placebo group ( $P < 0.001$ ). The remainder of participants from both groups needed the second line tocolytic drug. Of these 9.7% of the Nifedipine group delivered in 48 hours compare with 12.6% in the placebo group ( $P > 0.05$ ). Mean gestation age at delivery and neonatal complications of both groups



were not significantly different. **Conclusion** Nifedipine has a higher success rate in inhibiting threatened preterm contraction. However, 60–90 minutes observation before starting tocolytic drug can reduce unnecessary treatment without affecting the outcome.

### IS-WS-6-3

**Involvement of apoptosis signal-regulating kinase 1 (ASK1)-MAPK pathway in inflammation-induced preterm birth** Midori Yoshikawa, Takayuki Iriyama, Kensuke Suzuki, Taiki Samejima, Tatsuya Fujii, Kazuki Morita, Takeshi Nagamatsu, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Oxidative stress is closely associated with the pathophysiology of preterm birth. Apoptosis signal-regulating kinase 1 (ASK1), a member of mitogen-activated protein kinase kinase (MAPKKK), controls oxidative stress-induced cellular responses including inflammation by regulating JNK and p38 MAPK pathways. Here, we aimed to investigate the roles of ASK1-JNK/p38 MAPK pathways in preterm birth. **Methods** Lipopolysaccharide (LPS) was injected transvaginally into cervixes of pregnant ASK1-deficient (ASK1<sup>-/-</sup>) and wild type (WT) mice on day 15 of gestation. Human amniotic epithelial cells (hAEC) isolated from human term placenta were treated with hydrogen peroxide. The research protocol was approved by the Institutional Committee. **Results** ASK1<sup>-/-</sup> displayed a significantly lower incidence of delivery (7/17=41%) at 24 hours following LPS injection when compared with WT (11/15=73%) ( $p < 0.05$ ). Kaplan-Meier analysis revealed that the incidence of delivery within 48 hours following LPS injection was significantly lower in ASK1<sup>-/-</sup> as compared with WT ( $p < 0.05$ ). Immunoblotting analysis showed that LPS injection induced the activation of ASK1 in the cervix, myometrium, and placenta of WT. LPS-induced phosphorylation levels of JNK and p38 in the cervix, myometrium, and placenta were decreased in ASK1<sup>-/-</sup>, compared with WT. In human primary culture of placental membranes, we found that ASK1 was activated in response to hydrogen peroxide in hAEC. **Conclusion** Our results suggested that ASK1 could play a pivotal role in inflammation-induced preterm birth through the activation of JNK and p38 pathways. ASK1 might be a novel therapeutic target for preterm birth.

### IS-WS-6-4

**Amniotic fluid macrophages help the healing of ruptured amnion via epithelial mesenchymal transition (EMT)** Haruta Mogami<sup>1</sup>, Yosuke Kawamura<sup>1</sup>, Shingo Io<sup>1</sup>, Mai Sato<sup>1</sup>, Hiroshi Takai<sup>1</sup>, Yoshitsugu Chigusa<sup>1</sup>, Eiji Kondoh<sup>1</sup>, Masaki Mandai<sup>1</sup>, Ruth Ann Word<sup>2</sup> *Kyoto University<sup>1</sup>, UT Southwestern Medical Center, USA<sup>2</sup>*

**Objective** pPROM is a major cause of preterm birth. However, a small proportion of women remain undelivered after pPROM and spontaneous sealing of the membranes occurs occasionally. Here, we investigated mechanisms of healing of ruptured membrane. **Methods** Fetal membranes of pregnant mice were punctured with a sterile 26G or 20G needle by laparotomy on 15dpc. Ruptured membrane was compared to intact control at each time point. All procedures were approved by the Ethics Committee and Animal Research Committee of our institution. **Results** In the model of non-infectious pPROM by 26G, 83% healed spontaneously within 24h and 98% within 72h, whereas in rupture by 20G, only 7% healed spontaneously within 24h and 50% within 72h. Histologically, massive migration of mesenchymal cells was observed in healing site of amnion. In scanning electron microscope, flap-like structure of amnion was formed at rupture site, and then rupture was completely covered by epithelial cells after 48h. In immunofluorescence, F4/80-positive macrophages were recruited from amniotic fluid to wounded

amnion, and IL-1 $\beta$  and TNF were released. Vimentin-positive mesenchymal cells have appeared in the epithelial layer of healing amnion, which suggested the existence of EMT. In vitro, IL-1 $\beta$  and TNF stimulated the migration of human amnion epithelial cells in scratch assay, and E-cadherin-positive epithelial cells were changed to vimentin-positive mesenchymal cells in the wounded center. **Conclusion** Amniotic fluid-derived macrophages move to ruptured amnion, releasing IL-1 $\beta$  and TNF, which stimulate EMT of amnion epithelial cells and help the healing of the ruptured amnion.

### IS-WS-6-5

**Anti-inflammatory effect of progesterone suppresses the enhancement of inflammatory cytokines on fetal membrane in a preterm birth mouse model with chronic dental infection** Yuko Teraoka<sup>1</sup>, Satoshi Urabe<sup>1</sup>, Haruhisa Konishi<sup>1</sup>, Mutsumi Miyauchi<sup>2</sup>, Hiroshi Miyoshi<sup>3</sup>, Takashi Takata<sup>2</sup>, Yoshiki Kudo<sup>1</sup> *Hiroshima University<sup>1</sup>, Department of Oral and Maxillofacial Pathobiology, Hiroshima University<sup>2</sup>, Hiroshima Prefectural Hospital<sup>3</sup>*

**Objective** Progesterone (P4) is important in maintaining pregnancy via its anti-inflammatory effect in the myometrium; however, this effect is poorly understood in the fetal membrane. We previously reported that mice with dental *Porphyromonas gingivalis* (*P.g*) infection could be useful as a model of preterm birth. In this model, inflammation in the fetal membrane via toll-like receptor 2 is thought to result in preterm birth, as the level of IL-1 $\beta$  is highly up-regulated. We investigated whether P4 prevented preterm birth and the effects of P4 on the fetal membrane. **Methods** *P.g* mice were injected subcutaneously with (*P.g* +P4 mice) or without (*P.g* mice) 1 mg of P4 daily at days 15.5 to 17.5 of gestation. We observed the mice in these gestational periods. Western blot analysis was performed for detection of NF- $\kappa$ B and MAPK on the fetal membrane at day 18 of gestation. We also evaluated inflammatory cytokines (IL-1 $\beta$ , IL-8, TNF- $\alpha$ ) at the same tissues using RT-PCR. **Results** The average gestational period was 20.4 days in *P.g* +P4 mice and 18.3 days in *P.g* mice. The enhancement of NF- $\kappa$ B and MAPK expression levels was decreased in *P.g* +P4 mice, compared with *P.g* mice. Treatment with P4 significantly reduced the enhancement of the expression of IL-1 $\beta$ , IL-8, and TNF- $\alpha$  by 88%, 76% and 59%, respectively. **Conclusion** P4 prevented preterm birth by suppressing the activation of inflammatory signaling pathways in the fetal membrane of a chronic inflammation-induced preterm birth mouse model.

### IS-WS-6-6

**Prevention of LPS-induced preterm labor by the lack of CX3 CLI-CX3CR1 interaction in mice** Mika Mizoguchi, Tamaki Yahata, Madoka Yamamoto, Sawako Minami, Kazuhiko Ino *Wakayama Medical University*

**Objective** We explored the pathological roles of CX3CL1 (fractalkine) and its receptor CX3CR1 in preterm labor (PTL) using *Cx3cr1*<sup>-/-</sup> (KO) mice. **Methods** Pregnant C57BL/6 (WT) and KO mice were injected i.p. 25 $\mu$ g LPS at gestational day (gd) 15.5 and observed until labor followed by the evaluation of PTL rate. Gestational tissues and serum were collected at 6 hrs after LPS. The rate of PTL, count of immune cells, and inflammatory cytokines were compared between WT and KO mice. Anti-CX3CL1 Abs were injected to WT mice at 3 hrs after LPS. **Results** In both mice and human PTL, serum CX3CL1 level was significantly increased. The rate of PTL was significantly inhibited in KO mice, compared with WT ones. Moreover, the lack of CX3CR1 reduced macrophage recruitment into uterus and gene expression of *Il1b*, *Il6*, *Tnfa* and *Ptgs2*. Macrophages were the main cellular source of these cytokines and COX-2. The exogenous

CX3CL1 augmented gene expression of *I1b*, *I16*, *Tnfa* and *Ptgs2* in WT peritoneal macrophages. Finally, anti-CX3CL1 Ab significantly reduced the rate of preterm labor in WT mice. **Conclusion** Collectively, these observations suggested that CX3CL1-CX3CR1 axis would play detrimental roles in LPS-induced PTL through macrophage recruitment and eventually inflammatory cytokine production. Thus, CX3CL1-CX3CR1 systems might be a therapeutic target of PTL.

### IS-WS-6-7

**Elimination of Mother-to-Child Transmission of Human Immunodeficiency Virus: 11-Year Experience in a Single Center in Taiwan** Huang Kuan-Ying, Li Yi-Ping, Shi Chung-Ching, Lee Chien-Nan, Lin Shin-Yu, Ho Hong-Nerng *National Taiwan University Hospital, Taiwan*

**Background** A prenatal "opt-out" human immunodeficiency virus (HIV) screening program in Taiwan has started since 2005. By the end of 2014, the screening rate was approximately 99%. However, after the "opt-out" HIV screening program, only 13 cases of MTCT of HIV infection were diagnosed in Taiwan; an MTCT rate of 3.2%. Here we describe clinical management of the HIV-infected mother and MTCT rate in National Taiwan University Hospital after the "opt-out" HIV screening program was started. **Methods** Retrospective charts of pregnant women infected with HIV managed at NTUH, Taipei, Taiwan, from 2005 to December 2016, were reviewed. HIV infection status was available for 39 infants born to HIV-infected mothers. **Results** There were 50 pregnant HIV-infected women with 57 parities in NTUH from 2005 to December 2016. Fifty-seven living infants were born. However, 18 parities were excluded because of missing data. Maternal antiviral treatment was administered in 92% parities (37/39 infants). Only one child (1/39) was found to be positive for an HIV antibody test at 18 months, but this child showed definitive HIV exclusion at 20 months after a series of tests without antiviral treatment. The MTCT rate was zero. **Conclusion** Successful implementation of available perinatal HIV intervention dramatically reduced the vertical transmission rate. The MTCT rate was zero in NTUH after the "opt-out" HIV screening program. However, as an HIV referral center, several efforts need to be made for achieving the World Health Organization criteria of elimination vertical transmission of HIV to lower than 2% in Taiwan.

### IS-WS-6-8

**Comparison of One-Step Versus Two-Step Screening for Gestational Diabetes Mellitus and Adverse Obstetrical Outcomes at a Single Tertiary Center in Taiwan** Cleo Tsai, Mei-Leng Cheong, Li-Ching Chen, Ming-Song Tsai *Cathay General Hospital, Taipei Branch, Taiwan*

**Objective** To compare the incidence of gestational diabetes mellitus (GDM) diagnosed by the one-step or two-step screening method during 24 to 28 weeks of gestation and its associated adverse obstetrical outcomes. **Materials and Methods** From January 2000 to August 2017, the medical records of 23,517 singleton pregnancies were reviewed retrospectively at Cathay General Hospital, Taiwan. Data for GDM diagnosed by the one-step International Association of Diabetes and Pregnancy study groups (IADPSG) method or the two-step Carpenter and Coustan (CC) criteria were collected. Outcomes including cesarean delivery, macrosomia, large for gestational age (LGA), intrauterine fetal demise (IUFD), and preeclampsia were compared between the two groups. **Results** The incidence of GDM using the one-step criteria (9.21%) had a 2.73-fold increase when compared to the two-step criteria (3.37%). After implementation of the one-step criteria as institutional guidelines since August 2012, decreases in cesarean delivery rate (46.7% to 40.5%,  $p < 0.05$ ), macrosomia

(6.7% to 1.8%,  $p < 0.05$ ), LGA (15.0% to 6.0%,  $p < 0.05$ ), and hypertensive disorders (9.4% to 5.6%,  $p < 0.05$ ) were observed. Our data also showed an increase in vaginal delivery rate (49.4% to 57.8%,  $p < 0.05$ ) in women with GDM diagnosed by the one-step method. **Conclusion** The one-step screening method was associated with a higher incidence of GDM when compared to the two-step criteria. However, decreases in adverse obstetrical outcomes in our population were observed after encouragement of diet control and regular exercise. GDM is a category of high-risk pregnancy that all obstetricians should carefully manage and treat accordingly to reduce the risks of adverse pregnancy outcomes.

### IS-WS-7-1 Withdraw

### IS-WS-7-2

**Anti-cancer effect of axitinib in ovarian cancer** Myeong Seon Kim, Jihye Kim, Seon Mi Kim, Ji Young Hong, E Sun Paik, Tae-Joong Kim, Chel Hun Choi, Byoung-Gie Kim, Duk-Soo Bae, Jeong-Won Lee *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

**Objective** Axitinib (Inlyta®) is a small molecule tyrosine kinase inhibitor developed by Pfizer. It is known that the primary mechanism of axitinib is related to vascular endothelial growth factor receptor 2 (VEGFR2), which is dependent on tumor-associated angiogenesis. We aimed to investigate the anti-cancer effect of axitinib alone or combined with chemotherapeutic drugs against human ovarian cancer cells. **Methods** We treated axitinib in ovarian cancer cells (A2780, HeyA8, A2780-cis, HeyA8-MDR, ES2, RMG1) to evaluate the effect on cell proliferation using MTT assay. To check the VEGFR2, ERK, AKT, and Bcl-2 level and the apoptosis according to Axitinib treatment, we performed the Western blot and ELISA in ovarian cancer cell line. In addition, in vivo therapy experiments of axitinib were done using xenografts using A2780 and RMG1 in nude mice. Tumor cells were injected i.p., the mice ( $n=10$  per group) were randomly assigned to two treatment groups: 0.5% methyl cellulose (control), oral axitinib 30mg/kg twice daily. Moreover, we performed the in vivo therapy experiment in patient-derived xenograft model (PDX) of ovarian clear cell carcinoma (CCC) to confirm these effects. **Results** Axitinib significantly inhibited the cell survival and increased the apoptosis in ovarian cancer cells. Combination treatment of cells with axitinib and cisplatin/paclitaxel significantly inhibited the cell growth and increased the apoptosis compared to the single agent treatment in chemoresistant ovarian cancer cells. In in vivo experiments, axitinib significantly decreased the tumor weight in xenograft models of established cell lines (A2780, RMG1) and a PDX model for CCC compared to control. Moreover, the immunohistochemical analysis using in vivo tumor samples showed that axitinib treated group increased apoptosis revealed by TUNEL assay compared with control. **Conclusion** We found that axitinib have anti-cancer-effects in ovarian cancer cells via inhibition of VEGFR signal to cell proliferation and apoptosis through in vitro and in vivo tests. Also, our results indicated that combined therapy with axitinib and chemotherapeutic drugs could significantly enhance the ovarian cancer cell growth inhibitory effect. We plan further studies using xenograft model for combination effect of axitinib and chemotherapeutic drugs.

### IS-WS-7-3

**Machine Learning-guided Staging in Patients with Epithelial Ovarian Cancer** E Sun Paik<sup>1</sup>, Jeong-Yeol Park<sup>2</sup>, Ju-Hyun Kim<sup>2</sup>, Jihye Kim<sup>1</sup>, Chel Hun Choi<sup>1</sup>, Byoung-Gie Kim<sup>1</sup>, Duk-Soo Bae<sup>1</sup>, Sung Wook Seo<sup>3</sup>, Jeong-Won Lee<sup>1,3</sup> *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea<sup>1</sup>, Univer-*

sity of Ulsan College of Medicine, Asan Medical Center, Korea<sup>2</sup>, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University School of Medicine, Korea<sup>3</sup>

**Purpose** We aimed to use the machine learning classifier, gradient boosting (GB), to predict survival outcomes for epithelial ovarian cancer (EOC) patients using all of available clinical variables. **Methods** Clinical variables including serial CA-125 level in EOC patients from two hospitals were analyzed retrospectively for training/internal validation (Samsung Medical Center, n=1,128) and external validation (Asan Medical Center, n=229). The GB model was optimized using validation data. The performance of final model was tested over external validation set. ROC curves of survival probability were compared to the Cox proportional hazard regression analysis (CoxPHR) model annually over five years after the surgery. **Results** Of initial 34 covariates generated, 19 covariates were optimized for GB model. We used second year survival data as target value with the highest area under the curve (AUC). During internal validation, the AUC of the GB model for predicting second year overall survival was 0.830 (95% C.I. : 0.802-0.853), which was more accurate than CoxPHR (AUC of 0.668 (95% C.I. : 0.617-0.719)). On external validation, GB model also showed higher AUC of 0.816 (95% C.I. : 0.739-0.892) for second year survival after surgery, which was better than the CoxPHR model (AUC of 0.597 (95% C.I. : 0.474-0.719)). A new staging system according to survival probability scores of the GB model identified four distinct prognostic subgroups that classified patients. **Conclusion** Our new GB-guided staging system accurately identified prognostic subgroups of patients with EOC. This approach would be useful for better estimation of individual outcomes of EOC patients.

#### IS-WS-7-4

**Trends and comparative analysis of patients with end-stage ovarian cancer who have received active palliative chemotherapy for the past 10 years** Jeong-Yeol Park, Dae-Yeon Kim, Dae-Shik Suh, Jong-Hyeok Kim, Yong-Man Kim, Tae-Kyu Jang, Young-Tak Kim, Joo-Hyun Nam *Asan Medical Center, University of Ulsan College of Medicine, Korea*

**Objective** We analyzed the pattern of chemotherapy for the last 6 months of patients with end-stage ovarian cancer who have been aggressively treated with palliative chemotherapy for the past 10 years. **Methods** We retrospectively analyzed the patients who died after performing active palliative chemotherapy with end-stage ovarian cancer at Asan Medical Center from 2006 to 2015. From 2006 to 2010 and from 2011 to 2015, we divided into two groups. Based on the electronic medical records, the demographic and basic characteristics of the patients, admission for the last 6 months, invasive procedures, and the time of final chemotherapy were confirmed. **Results** A total of 111 patients with ovarian cancer were eligible for this study. 57 patients died from 2006 to 2010, and 54 patients died from 2011 to 2015. The mean number of hospitalizations during the last 6 months was 4.33 (2006-2010) vs. 5.69 times (2011-2015) ( $p=0.041$ ) and mean number of palliative chemotherapy was 3.88 (2006-2010) vs. 5.06 times (2011-2015). ( $P=0.002$ ) The proportion of patients undergoing invasive procedures was 35.1% (20/57, 2006-2010) vs. 53.7% (29/54, 2011-2015). ( $p=0.048$ ) The number of palliative chemotherapy and the rate of invasive procedures have increased in patients with end-stage ovarian cancer for the recent 5 years compared to 2006 to 2010. **Conclusion** Gynecology oncologists need to evaluate whether active palliative chemotherapy improves patient quality of life at every time and if not helpful, should communicate with patients and caregivers about when to stop the palliative chemotherapy.

#### IS-WS-7-5

**Carcinoma-associated mesothelial cells orchestrate progression of peritoneal dissemination and acquired platinum resistance in epithelial ovarian cancer** Masato Yoshihara<sup>1</sup>, Hiroaki Kajiyama<sup>1</sup>, Mai Sugiyama<sup>2</sup>, Yoshihiro Koya<sup>2</sup>, Shiro Suzuki<sup>1</sup>, Fumitaka Kikkawa<sup>1</sup> *Nagoya University<sup>1</sup>, Bell Research Center, Nagoya University<sup>2</sup>*

**Objective** Based on the "seed and soil" theory, we evaluated interaction of epithelial ovarian cancer cells (EOCs : seed) and mesothelial cells (MCs : soil), and analyzed how they promote tumor microenvironment with innovative experimental models and various in silico omics analyses under approval of ethical committee. **Methods** We compared adhesion and proliferation of EOCs co-cultured with carcinoma associated MCs (CAMs) and non-activated MCs by human omentum ex vivo assay and in vivo imaging system using a mouse dissemination model. We established an in vitro peritoneal metastatic invasion model and visualized fluorescent labeled-cell behavior by 3D-construction. Proteome analysis was used to reveal the feature of CAMs. Cell viability of EOCs co-cultured with CAMs were evaluated by apoptosis detection assay and transcriptome analysis was performed to pursue detailed mechanism. **Results** The EMT-related characteristics were observed in CAMs and its relevance was confirmed by proteome analysis. The growth factor array (ascites : n=17) concluded that CAMs were mainly generated by TGF- $\beta$ 1. Adhesion and proliferation of EOCs on CAMs were increased both in vitro, ex vivo, and in vivo assay. As for invasion, the 3D-construction imaging demonstrated that EOCs invaded with CAMs into extracellular matrix beneath the layer of MCs (846 $\mu$ m vs. 261 $\mu$ m,  $p<0.05$ ). Moreover, we found acquired platinum-resistance in EOCs co-cultured with CAMs by apoptosis detection assay (24.6% vs. 9.93%,  $p<0.05$ ). Transcriptome analysis suggested PI3K/Akt pathway played a crucial role in EOCs induced by stimulation of CAMs. **Conclusion** Our results suggest tumor microenvironment enhanced by mutual association with EOCs and CAMs promotes progression of peritoneal dissemination and acquired platinum-resistance in EOCs.

#### IS-WS-7-6

**Bisphosphonates, new candidate of drug repositioning for ovarian cancer** Yusuke Kobayashi, Kouji Banno, Haruko Kunitomi, Yusuke Matoba, Moito Iijima, Takashi Takeda, Miho Iida, Kanako Nakamura, Kosuke Tsuji, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** Rapid advances in pharmacotherapy and bioinformatics develop drug repositioning that includes re-investigating or recycling of existing drugs for new indications. We have previously demonstrated an antitumor effect of statins, antidiabetic drugs, on ovarian cancer in vitro and in vivo. Bisphosphonates are commonly used as antiosteoporotic drugs, and inhibit mevalonate pathway as same as statins. Antitumor effects of the bisphosphonate were examined in this study. **Methods** Cell counts after administration of alendronate, a second-generation bisphosphonate, were performed to examine inhibitory ability on growth of SKOV3 and OVCAR5 ovarian cancer cells. Autophagy expression was evaluated by western blot. The potential antitumor effect was examined in vivo using transgenic ovarian cancer model mice. The proliferative activity with Ki-67 and quantification of STICs with STIC-associated marker, laminin C1 were evaluated in tissue section by immunohistochemistry. **Results** Alendronate exhibited concentration-dependent inhibition of growth of these cells. Vacuolation was found in cells in a time-dependent, and concentration-dependent expression of autophagy marker, LC3A and LC3B, were induced by alendronate. Treatment with alendronate significantly reduced the total tumor mass in the female reproductive tract,



based on the organ weight. The proliferative activity with Ki-67 was significantly decreased in the alendronate-treated mice compared with that of the control group. The rate of laminin C 1-positive tubal epithelial cells in alendronate-treated mice was also significantly reduced compared with that of the control group. **Conclusion** Alendronate induces autophagy and has an inhibitory effect on cell growth in vitro and an antitumor effect in vivo. Drug repositioning targeting mevalonate pathway for ovarian cancer deserves consideration for clinical application.

### IS-WS-8-1

#### The therapeutic effects of iPS cell-derived myeloid cells producing interferon beta on human ovarian cancer cells in mice

Yuko Imamura<sup>1</sup>, Hironori Tashiro<sup>2</sup>, Junko Tsuboki<sup>1</sup>, Kiyomi Takaishi<sup>1</sup>, Takashi Ohba<sup>1</sup>, Hidetaka Katabuchi<sup>1</sup> *Kumamoto University<sup>1</sup>, Faculty of Life Sciences, Kumamoto University<sup>2</sup>*

**Objective** The microenvironment of metastatic ovarian cancer includes fibroblasts, mesothelial cells, and immune cells with macrophages, the most abundant cell type. Macrophages influence pro-tumorigenic properties. In this study, we focused on examining the cell-to-cell interactions between macrophages and ovarian cancer cells. We examine the mechanism and therapeutic effects of interferon-beta, produced by induced pluripotent stem (iPS-ML/IFN- $\beta$ ) cell-derived myelomonocytic cells, on metastatic ovarian cancer cells. **Methods** The human ovarian cancer cell lines were cultured in the presence or absence of recombinant human IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , and TRAIL. We then established a xenograft model of ovarian cancer metastasis human ovarian cancer cells into the peritoneal cavity of mice. After disseminated tumor formed in the abdomen, IFN- $\beta$  was administered by intraperitoneal injection. SKOV3 and ES2 cells were cultured with or without iPS-ML/IFN- $\beta$ . The injection of iPS-ML/IFN- $\beta$  caused the expression of several macrophage markers, including CD11b and CD68. After a three-day incubation period, luminescence was measured. SCID mice were injected with luciferase-expressing SKOV3 cells. Mice with established tumors were randomly divided into control and treatment groups. The mice in the treatment group were injected with iPS-ML/IFN- $\beta$ . All mice underwent a bioluminescence analysis. **Results** Both IFN- $\alpha$  and IFN- $\beta$  resulted in a decrease in the number of live SKOV3 and ES2 cells in vitro. IFN- $\beta$  showed a clear inhibitory effect on ascites accumulation in vivo. iPS-ML/IFN- $\beta$  significantly inhibited the growth of disseminated ovarian cancer cells in vitro and in vivo, and also successfully reduced ascites in vivo. **Conclusion** This study suggests that iPS-ML/IFN- $\beta$  has therapeutic potential in patients with metastatic ovarian cancer.

### IS-WS-8-2

#### The role of angiopoietin-like protein 2 in serous ovarian carcinoma with peritoneal dissemination

Yuko Takeshita, Isao Sakaguchi, Hidetaka Katabuchi *Kumamoto University*

**Objective** It has been reported that Angiopoietin-like protein 2 (ANGPTL2) is a secretory protein, which is induced from cells under various stress conditions, and also involved in carcinogenesis in skin tissue as well as cancer invasion and metastasis in breast and lung cancer. In this study, we examined the role of ANGPTL2 in peritoneal dissemination of serous ovarian carcinoma. **Methods** We firstly established ANGPTL2-overexpressing cells derived from a human serous ovarian carcinoma cell line, SKOV3. Next, we administered ANGPTL2-overexpressing cells and control cells intraperitoneally to immunodeficient mice, respectively and evaluated the formation of peritoneal dissemination and survival time between two groups. In addition, we performed RT-PCR array focusing on cell motility to examine the key factor of peritoneal dissemination. **Results** *In vivo*

analysis, the number of disseminated nodules in the group of mice transplanted with ANGPTL2-overexpressing cells was larger than the number in the control group significantly ( $p < 0.01$ ). Survival time was significantly shortened in the group of mice treated with ANGPTL2-overexpressing cells compared to control group ( $p < 0.05$ ). In RT-PCR analysis, the expressions of MMP1 and MMP13 increased significantly in ANGPTL2-overexpressing cells ( $p < 0.001$ , respectively), and an increase of dipeptidyl peptidase 4 (DPP4) expression in the cells was also detected by RT-PCR array. **Conclusion** It is proved that ANGPTL2 expression in serous ovarian carcinoma can promote peritoneal dissemination *in vivo* analysis and that the expression of ANGPTL2 in serous ovarian carcinoma might contribute to cell motility in peritoneal dissemination through upregulating the expressions of MMPs and DPP4.

### IS-WS-8-3

#### Unmasking ovarian chemoresistant cancer cells by TSA or 5-AZA reveals new candidates miRNAs involved in chemoresistance development

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**Objective** Ovarian cancer is the most frequent cause of mortality in female gynecological malignancies. The current therapeutic agents face high rate of resistance, pressing the need for novel therapeutics. **Methods** Here, we studied the comparative microarray profiling between the ovarian cancer cells, KF and their taxane-resistance counterparts, KF-TX before and after treatment with the epigenetic modulators TSA or 5AZA, to get novel players involved in ovarian chemoresistance and the mechanism of their expression. After microarray profiling, Quantitative-PCR was used to validate the expression of those miRNAs downregulated in KF-TX and re-expressed after TSA or 5AZA treatment. **Results** We found that miR-7-5p, miR-204-3p, miR-205-5p, miR-365a, miR-387g, miR-501-5p, miR505-3-, miR-1236, miR-3195, miR-3613, miR-3652, miR-4286, miR-4526 and miR-8071 were the most downregulated miRNAs (more than two folds change) in the chemoresistant cells (more than two folds). Of those miRNAs, only miR-204-3p and miR-501-5p were upregulated under TSA treatment, while miR-7-5p, miR-204-3p, miR-365a, miR-4286, miR-4526 and miR-8071 were upregulated after 5AZA treatment in KF-TX cells. **Conclusion** Histone modification study confirmed the promoter acetylation of those miR-501-5p, however DNA methylation of those genes affected by 5AZA, using promoter bisulfate sequencing, confirmed their promoter methylation. Interestingly, combination of TSA and/or 5AZA with taxane significantly restored chemosensitivity as confirmed by viability assay and clonogenic assay. Pathway analysis indicated the major pathways affected by epigenetic changed of miRNA in the chemoresistant ovarian cancer cells. Taken together, our data not only introduced novel suppressors, downregulated during chemoresistance, players in TX resistance but also revealed the mechanism of their downregulation.

### IS-WS-8-4

#### Tumor suppressive roles of MARK3 in high-grade serous ovarian carcinomas

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**Objective** High-grade serous ovarian carcinoma (HGSOC) is the most aggressive histological type, causing approximately 70% of

death by ovarian cancer. The purpose of this study is to identify novel candidate molecular targets and to clarify their functions in HGSOc. **Methods** We analyzed publicly available microarray datasets to identify genes, which are dysregulated and associated with prognosis in HGSOc. We then focused on a microtubule affinity-regulating kinase 3 (MARK3) gene and performed functional analysis by RT-PCR, in vitro kinase assay and cell line based assays, using doxycycline-inducible cell lines. **Results** By analyzing two independent datasets, we identified 6 overlapping genes whose expression was dysregulated in HGSOc. Of them, MARK3 was significantly downregulated in HGSOc cell lines and tissues, and downregulation of MARK3 was associated with poor progression-free survival ( $p < 0.0001$ ). In silico analysis and chemical screening revealed that the mechanisms to repress MARK3 expression in HGSOc are copy number deletion and histone de-acetylation. MARK3 overexpression significantly inhibited tumor proliferation in vitro. MARK3 increased the ratio of cells in the G2/M phase by inhibiting CDC25s activities. **Conclusion** Our data suggests MARK3 is a novel tumor suppressive checkpoint kinase and its downregulation causes tumor proliferation. Dysregulation of MARK3 and CDC25s axis may be a potential therapeutic target against HGSOc.

#### IS-WS-8-5

**Identification of somatic genetic alterations in ovarian clear cell carcinoma with next generation sequencing** Yusuke Shibuya, Hideki Tokunaga, Bin Li, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** Ovarian clear cell carcinoma (OCCC) is the most refractory subtype of ovarian cancer and more prevalent in Japanese than Caucasians (25% and 5% of all ovarian cancer, respectively). The objective of this study is to discover the genomic alterations that may cause OCCC and effective molecular targets for chemotherapy. **Methods** Paired genomic DNAs of 48 OCCC tissues and corresponding non-cancerous tissues were extracted from formalin-fixed, paraffin embedded specimens collected between 2007 and 2015 at our hospital. All specimens underwent exome sequencing and the somatic genetic alterations were identified. **Results** We divided the cases into three clusters based on the mutation spectra. Clinical characteristics such as age of onset and endometriosis are similar among the clusters but one cluster shows mutations related to APOBEC activation, indicating its contribution to subset of OCCC cases. There are three hypermutated cases (showing 12-fold or higher somatic mutations than the other 45 cases) and they have germline and somatic mismatch repair gene alterations. The frequently mutated genes are *ARID1A* (66.7%), *PIK3CA* (50%), *PPP2R1A* (18.8%) and *KRAS* (16.7%). Somatic mutations important for selection of chemotherapeutic agents, such as *BRAF*, *ERBB2*, *PDGFRB*, *PGR*, and *KRAS* are found in 27.1% of OCCC cases, indicating clinical importance of exome analysis for OCCC. **Conclusion** Our study suggests that the genetic instability caused by either mismatch repair defect or activation of APOBEC play critical roles in OCCC carcinogenesis.

#### IS-WS-8-6

**The novel JNK inhibitor AS602801 inhibits ovarian cancer stem cells in vitro and in vivo** Hirotsugu Sakaki, Manabu Seino, Takeshi Sudo, Tsuyoshi Ohta, Satoru Nagase *Yamagata University Hospital*

**Objective** Our recent study released that JNKs (c-Jun NH2-terminal kinases) is a key molecule in the maintenance of ovarian cancer stem cells. A phase 2 clinical trial investigating the efficacy and safety of AS602801, a newly developed JNK inhibitor, in the treatment of inflammatory endometriosis is complete. We

are now examining whether AS602801 acts against human ovarian cancer stem cells in vitro and in vivo. **Methods** Using ovarian cancer stem cells derived from A2780 human ovarian cancer cell line, we examined the effect of AS602801 on the viability as well as on the self-renewal and tumor-initiating capacity. We examined the anti-cancer stem cells effect of AS602801 by trypan blue as a vital dye. We next examined the effect of AS602801 on self-renewal capacity by the expression of stem cell markers with immunoblot assay and flow cytometric assay. We also evaluated sphere formation ability as self-renewal capacity. Lastly, we examined the effect of AS602801 on tumor-initiating capacity by ex-vivo assay. **Results** In vitro, AS602801 exhibited cytotoxicity against both serum-cultured non-stem cancer cells and cancer stem cells derived from human ovarian cancer at concentrations that did not decrease the viability of normal human fibroblasts. AS602801 also inhibited the self-renewal and tumor-initiating capacity of cancer stem cells surviving AS602801 treatment. **Conclusion** These findings suggest AS602801 is a promising anti ovarian cancer stem cell agent, and further investigation of the utility of AS602801 in the treatment of cancer seems warranted.

#### IS-WS-9-1

**Zfp371 is a novel DNA repair gene responsible for genome stability during mitosis** Seiji Ogawa<sup>1</sup>, Mitsutoshi Yamada<sup>1</sup>, Toshio Hamatani<sup>1</sup>, Hidenori Akutsu<sup>2</sup>, Akihiro Umezawa<sup>2</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Department of Reproductive Biology, National Center for Child Health and Development<sup>2</sup>*

**Objective** Chromosomal abnormalities are major obstacle to the assisted reproductive technology (ART). We have previously demonstrated that *Zfp371*, which was identified by in silico analysis, expressed in preimplantation embryos, testis and embryonic stem cells (ESCs), and *Zfp371* knockout somatic cells exhibited several different types of chromosomal abnormalities such as chromosome gap, derivative chromosomes, gain or loss of chromosome, and Robertsonian translocation. *Zfp371* is reported to correlate with *Rad51* and *Brcal*, implying its role of DNA repair. Here we used *Zfp371* knockout mouse to elucidate the etiology of chromosomal abnormalities and clinical phenotype. **Methods** *Zfp371* deficient ESCs (KO-ESCs) were derived from homozygous. To test DNA stress response, KO-ESCs irradiated with a dose of 4-Gy  $\gamma$ -ray were stained by a marker of DNA damage, phosphorylated (Ser139) histone H2A.X ( $\gamma$ H2AX). Protein complex immunoprecipitation (Co-IP) using the protein extracted from ESCs was performed to analyze protein-protein interactions. Teratoma assay was performed to evaluate pluripotency. **Results** Irradiated KO-ESCs showed significantly increased numbers of  $\gamma$ H2AX foci (3.6 per cell) relative to wild-ESCs (1.8 per cell) ( $p < 0.05$ ). Global transcriptional analysis showed elevated expression of DNA repair genes, *Rad51l3* and *Bard1* in *Zfp371* homozygous ES cells. Histone H1.1, H1.2 and H1.4 were detected as the proteins bound with *Zfp371*. KO-ESCs differentiated into choriocarcinoma. **Conclusion** These results suggest that the absence of *Zfp371* results in elevated level of DNA damage, an accumulation of chromosomal abnormalities and eventually carcinogenesis. This is the first report that zygotic gene, *Zfp371*, plays a role in DNA repair and is responsible for genome stability.

#### IS-WS-9-2

**The function of PTENP1 in implantation** Masashi Takamura *Hudson Institute of Medical Research, Australia*

**Objective** Embryo implantation failure is a major cause of infertility. While IVF is an important intervention of implantation failure, the critical regulators remain to be defined. The role of

long non-coding (lnc) RNA in embryo implantation has been poorly defined. We identified that the lncRNA, PTENP1 (Phosphatase-And-Tensin-Homolog-Pseudogene-1), was reduced in primary human endometrial epithelial cells (HEEC) treated with human blastocyst conditioned media (BCM) from embryos that did not implant suggesting a role in implantation. We aimed to investigate the function of PTENP1 in embryo adhesion to endometrium, the initiating event of embryo implantation. **Methods** 1. PTENP1 and PTEN expression in endometrial tissue across the menstrual cycle (N=8) was investigated by RT-qPCR. 2. PTENP1 was localized in human endometrium using in-situ hybridization (N=5). 3. A trophoblast cell-line (HTR8) spheroid adhesion assay was used to model implantation (N=4). 4. miRNA PCR array and fluidigm analysis was used to determine PTENP1 targets in HEEC. **Results** 1. PTENP1 and PTEN levels did not change across the menstrual cycle. 2. Luminal epithelium showed the highest expression in mid-secretory phase. PTENP1 was maximal in the stroma in late secretory phase. 3. PTENP1-silenced HEEC showed less adhesion (reduced by  $21 \pm 4.0\%$ ,  $P < 0.001$ ) 4. PTENP1 knockdown in HEEC the reduction of 100 miRNAs. miR-590-3p was augmented after knockdown ( $2.28 \pm 0.23$  fold,  $p < 0.05$ ). miR-590-3p mimic reduced adhesion ( $0.58 \pm 0.06$  fold  $p < 0.001$ ). Fluidigm analysis detected reduction of LIF, RHOA, ALCAM after knockdown. **Conclusion** Endometrial PTENP1 has pivotal role in successful implantation.

### IS-WS-9-3

**C/EBP $\beta$ , but not HIF1 $\alpha$ , regulates Vegf gene expression in granulosa cells undergoing luteinization during ovulation after the LH surge in female rats** Masahiro Shinagawa, Isao Tamura, Ryo Maekawa, Yuichiro Shirafuta, Maki Okada, Toshiaki Taketani, Hiromi Asada, Hiroshi Tamura, Norihiro Sugino Yamaguchi University

**Objective** Vascular endothelial growth factor (Vegf) expression is increased in granulosa cells (GCs) undergoing luteinization after the LH surge and Vegf plays an important role in rapid vascularization after the LH surge, which contributes to corpus luteum formation. We investigated transcriptional regulation of Vegf in GCs undergoing luteinization. Especially, we focused on transcription factors, HIF1 $\alpha$  and C/EBP $\beta$ , which are involved in angiogenesis. **Methods** GCs were obtained from rats treated with equine chorionic gonadotropin (CG) before (0h) and 4, 8, 12, 24h after human (h) CG injection. 1) Vegf mRNA levels (RT-PCR), 2) HIF1 $\alpha$  and C/EBP $\beta$  protein expressions (Western blot), 3) binding activities of C/EBP $\beta$  to the Vegf promoter region (ChIP assay), 4) transcriptional activity of C/EBP $\beta$  binding site (Luciferase assay), 5) histone modifications (ChIP assay) and chromatin structure (FAIRE-qPCR) in the Vegf promoter region were analyzed. **Results** 1) Vegf mRNA levels were gradually increased and reached a peak at 12h. 2) HIF1 $\alpha$  protein expressions were not detected. The protein levels of C/EBP $\beta$  were increased at 12h. 3) The binding activities of C/EBP $\beta$  were increased at 12h. 4) C/EBP $\beta$  binding site of the Vegf promoter had a transcriptional activity. 5) The levels of H3K9me3 and H3K27me3, which are transcription repressive markers, were significantly decreased at 12h, and the chromatin structure became looser compared with 0h. **Conclusion** We found for the first time that C/EBP $\beta$ , but not HIF1 $\alpha$ , regulates Vegf gene expression by binding to and altering the chromatin structure of the promoter region in GCs undergoing luteinization after the LH surge.

### IS-WS-9-4

**Activation of Endoplasmic Reticulum Stress in Granulosa Cells from Patients with Polycystic Ovary Syndrome Contributes to Ovarian Fibrosis** Nozomi Takahashi<sup>1</sup>, Miyuki Harada<sup>1</sup>, Yasushi Hirota<sup>1</sup>, Osamu Yoshino<sup>2</sup>, Gentaro Izumi<sup>1</sup>, Tetsuya

Hirata<sup>1</sup>, Kaori Koga<sup>1</sup>, Osamu Hiraike<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, University of Toyama<sup>2</sup>*

**Objective** Given the emerging role of unfolded protein response (UPR), activated by endoplasmic reticulum (ER) stress, in regulating tissue fibrosis, we hypothesize that ER stress is activated in granulosa cells (GCs) of PCOS patients, and that activated ER stress induces ovarian fibrosis by modulating pro-fibrotic growth factor expression in GCs. **Methods** The study was approved by IRB. mRNA expression of UPR genes and transforming growth factor (TGF)- $\beta$ 1 in GCs from PCOS patients were examined by quantitative RT-PCR (qPCR). Ovarian fibrosis and expression of UPR and TGF- $\beta$ 1 in the ovary of PCOS patients were examined by Masson trichrome staining (MT) and immunohistochemistry (IHC). The effects of ER stress inducers and inhibitors on mRNA and protein expression of TGF- $\beta$ 1 in cultured human GCs were examined by qPCR and ELISA. The effects of ER stress inhibitors on ovarian fibrosis and ovarian expression of TGF- $\beta$ 1 in PCOS mouse model were examined by MT, qPCR, and IHC. **Results** ER stress was activated in GCs of PCOS patients and PCOS mouse model, accompanied by interstitial fibrosis and an increase in TGF- $\beta$ 1 expression in GCs. ER stress inducers increased the expression of TGF- $\beta$ 1 in human GCs, which was abrogated by a treatment with an ER stress inhibitor. ER stress inhibitors decreased interstitial fibrosis and collagen deposition in PCOS mouse ovaries, accompanied by a reduction in TGF- $\beta$ 1 expression in GCs. **Conclusion** ER stress in GCs of PCOS patients contributes to the induction of pro-fibrotic growth factors during ovarian fibrosis, and that ER stress may serve as a therapeutic target in PCOS.

### IS-WS-9-5

**M2 macrophages play an essential role for successful implantation in mice** Yosuke Ono<sup>1</sup>, Osamu Yoshino<sup>1</sup>, Mutsumi Kobayashi<sup>1</sup>, Masami Ito<sup>1</sup>, Azusa Sameshima<sup>1</sup>, Tomoko Shima<sup>1</sup>, Yasushi Hirota<sup>2</sup>, Akitoshi Nakashima<sup>1</sup>, Shigeru Saito<sup>1</sup> *University of Toyama<sup>1</sup>, The University of Tokyo<sup>2</sup>*

**Objective** Macrophages (M $\phi$ s) play important roles for implantation. M $\phi$ s are classified into M1 and M2 M $\phi$ s. However it is unknown which type of M $\phi$ s play essential roles in implantation. We investigated the role of M2 M $\phi$ s in implantation using CD206-DTR mice. **Methods** The localization of CD206+ M2M $\phi$ s in uterus was studied by immunohistochemical staining. To deplete M2M $\phi$ , diphtheria-toxin (DT) was injected before prior to implantation period in CD206-DTR female B6 mice mated with Balb/c male mice. Decidualization was studied by Ki-67 staining and HE staining on day 3.5. Implantation related mRNAs were evaluated by qPCR on E4.5. **Results** In WT, CD206+ M2 M $\phi$ s were accumulated in uterine stromal lesion at implantation period. In CD206-DTR mice, the number of implantation was significantly lower compared to that of WT ( $1.6 \pm 3.6$  vs  $8.0 \pm 0.7$ ;  $p < 0.01$ ), although the serum levels of estradiol and progesterone were similar to those in WT. Furthermore, decidualization at E3.5 such as Ki-67+ stromal cells were completely impaired in CD206-DTR mice. And the mRNAs level of implantation related genes such as LIF, IL-10, Foxp3, IL-15 on E4.5 in CD206-DTR mice were significantly reduced ( $p < 0.01$ ) compared to WT, while the implantation failure related TNF- $\alpha$  mRNA was increased ( $p < 0.05$ ). In M2M $\phi$  depleted mice, breakdown of tolerance by decreased IL-10 and Foxp3, reduced NK cell differentiation by decreased IL-15, and increased inflammation by accelerated TNF  $\alpha$  could reduce the implantation essential cytokine, LIF expression resulting in implantation failure. **Conclusion** M2 M $\phi$ s are essential for successful implantation.

### IS-WS-9-6

**Analysis of obstetric complications and outcomes related to**

**singleton pregnancy after embryo transfer using a large scale perinatal registry in Japan** Yusuke Kurokawa, Yutaka Kozuma, Toshiyuki Yoshizato, Tatsuyuki Kakuma, Kimio Ushijima *Kurume University Hospital*

**Objective** The aim of this study was to determine the obstetric complications and outcomes related to the singleton pregnancy after embryo transfer (ET) using the large scale perinatal database in Japan. **Methods** The subjects were 215,659 cases of singleton pregnancy delivery at >22 weeks' gestation of the perinatal registry database of the Japan Society of Obstetrics and Gynecology between January and December 2015. There were 16,600 cases of pregnancies after ET (ET group) and 199,059 cases of spontaneous conceptions (SC group) without ovulation induction, artificial insemination with husband's semen or ET. After patients' background characteristics extracted from a univariate analysis between both groups, a multivariate logistic regression analysis was performed to determine obstetric complications and outcomes related to ET. The significance was set at  $P < 0.05$ . **Results** The independent factors related to the singleton pregnancy after ET were maternal and fetal complications including pregnancy-induced hypertension (OR : 1.18, 95% CI : 1.09-1.27), atonic bleeding (OR : 1.37, 95% CI : 1.28-1.46), blood loss at delivery (OR : 2.79, 95% CI : 1.50-4.93) and placenta and cord abnormalities including placenta previa (OR : 1.28, 95% CI : 1.13-1.45), low-lying placenta (OR : 1.27, 95% CI : 1.09-1.47), placenta accreta (OR : 3.23, 95% CI : 2.73-3.84), velamentous cord insertion (OR : 2.14, 95% CI : 1.88-2.41), and marginal cord insertion (OR : 1.44, 95% CI : 1.35-1.55). **Conclusion** The extracted factors were in part related to abnormal implantation, which remains to be elucidated whether ET itself or the maternal background necessary for ET is associated.

**IS-WS-9-7**

**Mdm2-p53 axis is a key machinery of ovulation** Hirofumi Haraguchi, Yasushi Hirota, Leona Matsumoto, Mitsunori Matsuo, Takehiro Hiraoka, Shun Akaeda, Tomoki Tanaka, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Physiological roles of tumor suppressor p53 in the ovary remain unclear. Mdm2 is the negative regulator of p53, and Mdm2 deletion increases p53 expression. We established mice of ovarian Mdm2 deficiency to clarify the influence of excessive p53 on ovarian function. **Methods** We generated mice with deletion of ovarian Mdm2 (KO) and Mdm2/p53 (DKO) by using Pgr-Cre mice. These mice were mated with wild-type fertile males, and reproductive phenotype of KO and DKO mice were evaluated. Microarray analysis and qPCR using mouse cumulus cells (CC), and ChIP assay using human granulosa cell line were performed. **Results** KO mice were infertile due to ovulation failure. In KO mice with superovulation treatment, cumulus cell-oocyte complex (COC) expansion and oocyte maturation were compromised, and numbers of ovulated eggs were markedly decreased. In contrast, DKO were fertile with normal COC expansion and ovulation. Expression of orphan nuclear receptor steroidogenic factor 1 (SF1), a well-known regulator of ovarian function, in CC was not reduced in DKO mice but in KO mice. In addition, p53 was recruited to an SF1 promoter region upon exposure to Nutlin-3, an Mdm2 inhibitor. **Conclusion** Ovarian deficiency of Mdm2 caused infertility due to ovulation failure via p53 induction, and Mdm2-p53 axis in ovarian granulosa cells regulated SF1 transcriptionally, indicating the importance of ovarian Mdm2-p53-SF1 pathway in female fertility. Our findings might help better understanding of human infertility, since p53 inducers such as smoking, obesity, aging, chemotherapy and radiotherapy are linked to the disruption of ovarian function and infertility.

**IS-WS-9-8**

**A National Survey of Cryopreservation of Embryos, Oocytes, and Ovarian Tissue for Cancer Patients** Miyuki Harada<sup>1</sup>, Yuko Sanada<sup>1</sup>, Mayuko Kanatani<sup>1</sup>, Gentaro Izumi<sup>1</sup>, Tetsuya Hirata<sup>1</sup>, Nao Suzuki<sup>2</sup>, Kenichiro Morishige<sup>3</sup>, Minoru Irahara<sup>4</sup>, Daisuke Aoki<sup>5</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, St. Marianna University School of Medicine<sup>2</sup>, Gifu University<sup>3</sup>, Tokushima University<sup>4</sup>, Keio University<sup>5</sup>*

**Objective** To determine the reality of cryopreservation of embryos, oocytes, and ovarian tissue in childhood, adolescent, and young adult cancer patients in Japan. **Methods** Six-hundred and thirteen JSOG-certified ART institutions were sent questionnaires on the experience of cryopreservation for cancer patients between Jan. 2011 and Dec. 2015. Subsequently, the institutions conducting the cryopreservation for cancer patients were sent the second questionnaires. The present survey was conducted as a part of the AMED project Development of the infrastructure of oncofertility in Japan and the research protocol was approved by local IRB. **Results** We received 481 replies (78.5% of 613 institutions). Among them, 126 (26.2%) conducted the cryopreservation for cancer patients. At 108 institutions replied to the second questionnaires (recovery rate : 85.7%), 1,085 cases of embryo or oocyte cryopreservation and 122 cases of tissue cryopreservation were conducted. More than 70% of them were breast cancer patients, followed by patients with hematological malignancy. The median number of patients in each institution was 4 and 2 for breast cancer and hematological malignancy, respectively. Indication for cryopreservation and age limitation varied between institutions. Three-hundred and sixteen embryos and 19 oocytes were already thawed and transferred with resulting pregnancies, while no pregnancy was observed in 7 cases undergoing ovarian tissue transfer. **Conclusion** The present study shows that over 1,000 embryos or oocytes and over 100 ovarian tissues were cryopreserved for cancer patients in Japan. It is urgently needed to establish a national registration system to evaluate the safety and efficacy of the current management.

**IS-WS-10-1**

**Comprehensive analysis of trophoblast lineage cells from human induced pluripotent stem cells (hiPSCs)** Nanae Tsuchida<sup>1</sup>, Hidenori Akutsu<sup>2</sup>, Junya Kojima<sup>1</sup>, Hiroe Ito<sup>1</sup>, Naoki Kuji<sup>1</sup>, Keiichi Isaka<sup>1</sup>, Hirotaka Nishi<sup>1</sup> *Tokyo Medical University<sup>1</sup>, National Research Institute for Child Health and Development<sup>2</sup>*

**Objective** Human induced pluripotent stem cells (hiPSCs) treated with bone morphogenetic protein 4 (BMP4) can differentiate into extra-embryonic tissue. However, the differentiated cells are heterogeneous, which include trophoblast (TB) and mesoderm lineage cells. In order to gain further understanding of early TB differentiation, we collected TB cells using a pan-trophoblast marker, KRT7, and performed comprehensive gene expression analysis. **Methods** Four types of hiPSCs (menstrual blood, two types of uterine endometrium and placental artery endothelium) from four patients were investigated. The hiPSCs were treated with 50ng/ml of BMP4 and differentiated into TB lineage cells. Next, we performed immunofluorescence analysis to confirm the expression of KRT7. We collected KRT7-positive cells using flow cytometry and performed microarray analysis to examine the transcriptome states. We further carried out gene ontology and pathway analysis to compare the gene expression patterns of hiPSCs and differentiated TB lineage cells. **Results** KRT7 was expressed in the BMP4-mediated differentiated cells. Microarray analysis demonstrated that 833 upregulated genes were commonly expressed in all the four hiPSC groups. Of the 259 upregulated genes commonly expressed in the four differentiated groups, some TB-specific genes, such as



CGA, CGB, and syncytin2, were identified. Cluster analysis revealed that most gene clusters were divided into two groups: hiPSCs and KRT7-positive cells. **Conclusion** To the best of our knowledge, this is a first report of comprehensive gene expression analysis of TB lineage cells derived from different types of hiPSCs. The results suggest that the upregulated genes may play an important role in early placental development.

## IS-WS-10-2

**Analyses of FHR parameters and dynamics in normal fetuses according to reactivity related to fetal movement** Jeongkyu Hoh, Eun Saem Choi, Ji Hyun Keum, Young-Sun Park *Hanyang University of Korea, Korea*

**Introduction** The reactive non-stress test (NST) notice the increase of fetal heart rate (FHR) by more than 15 beats/min for longer than 15 seconds following fetal movements, but FHR dynamics according to reactivity related to fetal movement have not yet been identified. **Objective** To compare and analyze differences in antepartal FHR parameters, non-linear indices and pregnancy outcomes in fetuses proven to be normal after delivery according to the reactivity as a result of NST and fetal movement (FM). **Methodology/process** We surveyed 3,295 NST data acquired using a computerized FHR analysis system. First, subjects were divided into two groups by the reactivity as a result of NST (reactive (R) cases, n=1,720 vs non-reactive (NR) cases, n=1,575). Second, each two groups were divided into three groups according to FM: group1 (NR, FM=0), group2 (NR, FM=1), group3 (NR, FM≥2), group4 (R, FM=0), group5 (R, FM=1), and group6 (R, FM≥2). Neonatal outcomes were compared, and FHR parameters analyzed using computerized fetal monitoring system. Non-linear analysis was performed using approximate entropy, ApEn; sample entropy; SampEn, and correlation dimension; CD. **Results/outcome** FHR parameters (mean FHR, FHR variability, Acceleration, and Deceleration) of group3 were the highest among NR groups ( $p<0.01$ ), and FHR parameters of group6 were the highest among R groups ( $p<0.01$ ). The correlation coefficients between FM and FHR parameters were statistically significant ( $p<0.01$ , respectively). However, nonlinear indices among NR group (ApEn, group1=0.92±0.13 vs. group2=0.92±0.13 vs. group3=0.91±0.14;  $p>0.05$ ) and those among R group (ApEn, group4=0.88±0.16 vs. group5=0.89±0.15 vs. group6=0.89±0.15;  $p>0.05$ ) were not statistically different. The correlation coefficients between FM and nonlinear indices were not statistically significant ( $p>0.05$ , respectively). There were no statistically significant differences of perinatal outcomes among 6 groups. **Conclusion** The heart rate dynamics of fetuses are not affected by fetal movement and they are coincidence with fetal and perinatal outcomes.

## IS-WS-10-3

**The hemodynamic influence of twin-twin transfusion syndrome on diastolic function in recipient twins: Insight into pathophysiology** Mayumi Takano<sup>1</sup>, Masahiko Nakata<sup>1</sup>, Sumito Nagasaki<sup>1</sup>, Junya Sakuma<sup>2</sup>, Sadanori Kasai<sup>2</sup>, Rei Ueyama<sup>1</sup>, Eijiro Hayata<sup>2</sup>, Ayako Oji<sup>2</sup>, Toshimitsu Maemura<sup>2</sup>, Mineto Morita<sup>1</sup> *Toho University<sup>1</sup>, Toho University Omori Medical Center<sup>2</sup>*

**Objective** This study was aimed to assess the ventricular filling pressure in twin-twin transfusion syndrome (TTTS) and the impact of fetoscopic laser photocoagulation (FLP) by using E/e' with Dual-gate Doppler method. The relationship between recipient's amniotic fluid N-terminal-prohormone brain-type natriuretic peptide (NT-proBNP) and E/e' was also investigated. **Methods** This is a prospective study involving TTTS patients who underwent FLP for TTTS between 2015 and 2017. Ultrasonography was performed within 24 hours before and 4-7 days

after FLP. The Z-score for E/e' was calculated by using reference ranges of our previous study. Amniotic fluid samples were obtained from recipient's sac at the time of FLP, and NT-proBNP/total protein ratio was assessed. **Results** There were 34 cases. Left ventricular (LV) E/e' of recipients in stage 1, 2 was significantly higher than that of donors ( $p<0.05$ ). RV-E/e' of recipients was elevated in stage 3d and 3r than where in stage 1, 2 ( $p<0.05$ ). Amniotic fluid NT-proBNP was elevated in 3d and 3r, respectively ( $p<0.05$ ), and significantly higher NT-proBNP was observed if recipient's RV-E/e' was more than 1.5 of Z-score (3,475 ng/g vs. 530 ng/g,  $p=0.008$ ). Both LV- and RV-E/e' of recipients significantly decreased after FLP ( $p<0.05$ ). **Conclusion** Recipient heart demonstrates the increase of filling pressure in LV at first, followed by the increase in RV, which is resulted in amniotic fluid NT-proBNP elevation. FLP decreased these elevated biventricular filling pressure within a week, reflecting improvement of pathophysiology of TTTS in recipients.

## IS-WS-10-4

**Fetal baroreceptor activity in preterm fetal sheep with lipopolysaccharide-induced endotoxemia** Hyo Kyojuka, Tsuyoshi Hiraiwa, Shun Yasuda, Keiya Fujimori *Fukushima Medical University*

**Objective** The aim of this study was to investigate the effect of lipopolysaccharide (LPS)-induced endotoxemia on fetal baroreceptor activity in chronically instrumented preterm fetal sheep. **Methods** The changes in fetal baroreceptor activity were measured in six chronically instrumented preterm fetal sheep at days 111-120. Endotoxemia was induced by LPS injection into the amniotic cavity on postoperative days 5 and 6. Fetal baroreceptor activity and fetal heart rate (FHR) were each measured during three phases (A, control phase; B, acute phase; and C, fetal acidosis phase). Baroreceptor activity was determined by the ratio of fetal FHR decrease to mean arterial pressure increase. **Results** Severe chorioamnionitis was confirmed histologically in all cases. Baroreceptor activity was measured a total number of 136 times in this experiment (A, n=63; B, n=54; and C, n=19). There was no significant difference regarding FHR at the time of phenylephrine injection at 3 points (A, 172 [3.3] bpm, B, 176 [4.3] bpm, and C, 162 [4.7] bpm,  $p=0.14$ ). However, the baroreceptor activity showed significant differences at 3 points (A, 2.7 [0.2]; B, 2.5 [0.2]; and C, 1.6 [0.1],  $p<0.05$ ). Post hoc test showed that baroreceptor activity in the fetal acidosis phase significantly decreased compared to that in the control phase. **Conclusion** Baroreceptor activity decreased without FHR change during fetal deterioration induced by LPS. These data suggest that intra-uterine infection may mask variable decelerations or late decelerations

## IS-WS-10-5

**Trial for a new fetal assessment by ultrasound-guided photoacoustic measurement of placental oxygen saturation** Kiguna Sei, Hidenori Sasa, Kenichi Furuya *National Defense Medical College*

**Objective** The sensitivity for fetal hypoxia of fetal heart rate (FHR) monitoring has been questioned. Blood oxygen saturation in placenta (PIO<sub>2</sub>) might provide more objective information about fetal oxygenation than FHR. We performed real-time low-invasive measurement of PIO<sub>2</sub> by ultrasound-guided photoacoustic (PA) technique. **Methods** Established hypoxia rabbit model was applied to seven pregnant rabbits in 28 gestational-day. Fetal hypoxia was made by changing maternal respiration rate and normal, hypoxia, and recovery phase were set. Continuous observation of FHR, fetal tissue oxygen saturation by near-infrared spectroscopy (NIRS), and PIO<sub>2</sub> by PA technique were performed simultaneously. In PA measurement, region of inter-



est (ROI) was set in placenta and maternal tissue. Oxygen saturation of each ROI was calculated from PA signals by the external standard method whose accuracy was proved in our previous study. **Results** The real-time PA measurement was successfully performed. The average  $PIO_2$  in the normal phase was  $57.8 \pm 13.9\%$ , which corresponded to the data in literatures. The recovery of  $PIO_2$  in the recovery phase was observed by PA technique while maternal tissue oxygen saturation and the other index by FHR and NIRS deteriorated. **Conclusion** The result demonstrated that  $PIO_2$  might reflect fetal blood information directly because PA technique could extract the data of placenta due to its high spatial resolution. PA imaging technique can be applied to objects such as umbilical vessels and fetal sagittal sinus by transvaginal detect. PA imaging would be a new device for quantitative fetal assessment and analysis of fetal physiology.

### IS-WS-10-6

**Fetal microglia changes by maternal immune activation**  
Kana Ozaki<sup>1</sup>, Hiroaki Wake<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University<sup>1</sup>, Division of Neuroscience, Kobe University<sup>2</sup>*

**Objective** Maternal immune activation (MIA) triggers developmental disorders and psychiatric diseases, but the mechanism of MIA for affecting on the fetal brain has not been elucidated. In this research, we focused on microglia, sole immune cell in central nervous system, and revealed the difference of motility and morphology of microglia between brain with MIA and wild type (WT) in live fetal mice, using *in vivo* two photon microscope. We furthermore showed the neuronal firing alteration in postnatal mice from MIA mice associated with the changes of fetal microglia. **Methods** Pregnant mice, of which fetal microglia were specifically labelled by GFP, were intraperitoneally injected with 10mg/kg of polyinosinic polycytidylic acid [poly (I : C)] at embryonic days 15 (E15) to cause MIA. GFP labelled microglia were visualized with two photon microscope, and their dynamic changes were analyzed at E17 in live fetuses. After image acquisition, fetal brains were fixed and sectioned to analyze distribution and morphology of microglia. **Results** The velocity of fetal microglia was increased after poly (I : C) injection *in vivo*. The cell body area ( $52.4 \pm 18.1 \mu m^2$ ) of microglia with MIA (n=155) was smaller ( $p=1.59 \times 10^{-40}$ ) than that ( $90.4 \pm 22.5 \mu m^2$ ) of WT (n=127). The process length ( $95.9 \pm 42.0 \mu m$ ) of microglia with MIA (n=23) was longer ( $p=0.0085$ ) than that ( $70.4 \pm 34.1 \mu m$ ) of WT (n=31). These data suggest microglia of MIA mice have more matured phenotype of their motility and morphology. **Conclusion** MIA may be causally associated with developmental disorders and psychiatric diseases through changes in function and morphology of fetal brain microglia.

### IS-WS-10-7

**Mesenchymal stem cell can induce offspring's immune tolerance against non-inherited antigens in murine Maternal-to-Fetal microchimeric model**  
Aiko Okada<sup>1</sup>, Masayuki Endo<sup>1</sup>, Kei Sasano<sup>1</sup>, Yoko Kawanishi<sup>1</sup>, Takao Owa<sup>1</sup>, Etsuko Kajimoto<sup>1</sup>, Hiroko Tanaka<sup>1</sup>, Aiko Kakigano<sup>1</sup>, Kazuya Mimura<sup>1</sup>, Takuji Tomimatsu<sup>1</sup>, Katsuto Tama<sup>2</sup>, Tadashi Kimura<sup>1</sup> *Osaka University<sup>1</sup>, Stem Cell Therapy Science, Osaka University<sup>2</sup>*

**Objective** Recent studies revealed that there are mutual cell migrations including hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) through the placenta between mother and fetus. In this study, we investigated allogeneic MSCs can induce immune tolerance *in utero* to proteins specifically expressed in MSCs and their lineages. **Methods** We evaluated immune reaction after syngeneic skin graft in three chimeric models. The recipient was C57BL/6 (WTB6) mice. As donor cells, we firstly used HSCs, MSCs and Lineage positive (Lin<sup>+</sup>) cells,

which are not stem cells, isolated from bone marrow cells (BMCs) of C57BL/6TgN (act-EGFP) (B6GFP) mice, which all express GFP. The second donor HSCs and MSCs were isolated from BMCs of PDGFR $\alpha$ -H2BGFP mice, which only express GFP in MSCs, but not in HSCs. These cells were injected intravenously into neonatal recipient mice. Finally, we applied a mouse F1 backcross bleeding model (B6 males x PDGFR $\alpha$ -H2BGFP females), as maternal-to-fetal microchimeric model. **Results** In B6GFP model, HSCs and MSCs transplantation induced both humoral and cell-mediated immune tolerance against GFP, but Lin<sup>+</sup> cells didn't. In PDGFR $\alpha$ -H2BGFP model, MSCs transplantation induced both humoral and cell-mediated immune tolerance against GFP, but HSCs didn't. In F1 model, successful engraftment was observed in 15% of the recipient mice until 20 weeks. **Conclusion** It is necessary to be exposed stem cells such as HSCs or MSCs, rather than non-stem cells to induce immune tolerance. Furthermore, MSCs rather than other stem cells should present to induce immune tolerance *in utero* to proteins specifically expressed in MSCs and their lineages.

### IS-WS-10-8

**The impact of the Great East Japan Earthquake on obstetric complications : results from the Fukushima Health Management Survey**  
Tsuyoshi Murata, Hyo Kyozyuka, Tsuyoshi Hiraiva, Shun Yasuda, Akiko Yamaguchi, Keiya Fujimori *Fukushima Medical University*

**Objective** This study aimed to assess the effects of the Great East Japan Earthquake on obstetric complications. **Methods** We used the results of the Fukushima Health Management Survey. Pregnant women were divided into three groups according to their residence during the disaster (affected area : n=2,207, middle area : n=5,183, and less-affected area : n=933). Adjusted odds ratios (aORs) for preterm birth (PTB) <37 weeks, threatened PTB, low birth weight <2,500g, pregnancy-induced hypertension (PIH), and gestational diabetes mellitus (GDM) were calculated using a logistic regression model. Leaving residence area and trimester at the time of the disaster were used as reference. **Results** The affected area was not a significant factor for any obstetric complications. However, the middle area was related to LBW <2,500g (aOR : 0.74,  $p < 0.05$ ) and GDM (aOR : 2.50,  $p < 0.05$ ) compared to the less-affected area, after accounting for several factors. With regard to maternal gestational age, being in the second trimester at the disaster was a significant risk factor for threatened PTB (aOR : 1.84,  $p < 0.05$ ) when compared to the pregnancies conceived after the disaster. Similarly, being in the third trimester at the disaster was a significant risk factor for PIH (aOR : 1.80,  $p < 0.05$ ). **Conclusion** Living in the affected area at the disaster was not a significant risk factor for obstetric complications. However, maternal gestational age at the time of the disaster may affect the occurrence of obstetric complications.

### IS-WS-10-9

**Efficacy of maternal screening and perinatal prevention program for hepatitis B**  
Tokuro Shirakawa<sup>1</sup>, Yuuki Sasagawa<sup>1</sup>, Masashi Deguchi<sup>1</sup>, Kenji Tanimura<sup>1</sup>, Mayumi Morizane<sup>1</sup>, Ichiro Morioka<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University<sup>1</sup>, Department of Pediatrics, Kobe University<sup>2</sup>*

**Objective** The aim of this study is to assess the effect of maternal screening for HBV and perinatal HBV prevention program. **Methods** With approvals from institutional ethics boards, this study was performed prospectively. 3,102 pregnant women delivered at our hospital between Jul. 1, 2008 and Jun. 30, 2015 and their neonates were participated in this study. HBs antigen (HBsAg) was measured during the first trimester as a maternal screening. HBe antigen (HBeAg) was measured for the HBsAg

positive patients. All neonates delivered from HBsAg-positive women were given HBIG and HB vaccine based on the Japanese HBV prevention program after birth. **Results** Of 3,102 pregnant women, 33 were positive for HBs antigen. 10 of the 33 were positive for HBe antigen. Two exacerbation cases were observed among the patient with positive for HBeAg, HBsAg and HBeAg. AST, ALT and HBV-DNA titers increased in both exacerbation cases. HBV prevention program was accomplished for all neonates, and consequently, vertical infection was not observed. **Conclusion** We find that perinatal HBV prevention program is so effective. HBsAg, HBeAg, AST, ALT and HBV-DNA titers seem useful for evaluating patients condition, but it seems difficult to predict exacerbation by these factors. Careful follow up is necessary to exclude exacerbation, for the women with HBeAg positive result.

### IS-WS-11-1

**Amenorrhea in female athletes deteriorates bone microarchitecture of cortex** Yuriko Kitajima<sup>1</sup>, Shizuka Ogawa<sup>2</sup>, Naoko Murakami<sup>1</sup>, Michio Kitajima<sup>1</sup>, Kiyonori Miura<sup>1</sup>, Hideaki Masuzaki<sup>1</sup> *Nagasaki University<sup>1</sup>, Marusan-Ai Co. LTD<sup>2</sup>*

**Objective** Young female athletes may suffer from disturbed energy availability, hypothalamic amenorrhea, lower bone density, which are designated as female athlete triad. In this study, we evaluated the microstructure of bone using HR-pQCT in female athletes. **Methods** Nineteen female long distance runners or rhythmic gymnastics athletes and 29 non-athlete (control) with comparable age (15–23y) were allocated for this study. We performed questionnaire survey to obtain menstrual history. Bone density of lumbar and femur was measured by dual energy x-ray absorptiometry (DXA). Bone microarchitecture of radius and tibia was measured by HR-pQCT. **Results** Although the height were not significantly different, BMI in athletes were significantly lower than control (18.4 vs. 20.6kg/m<sup>2</sup>, p<0.01). Age of menarche in athletes was significantly older than control (14.5 vs. 12.9y, p<0.01). In addition, 73.7% of athletes showed irregular menstrual cycles despite 6.9% in control (p<0.01). Bone density of lumbar and femur measured by DXA were not significantly different in each group. Cortical bone density in radius and in tibia were significantly lower in athletes than control (880.4 vs. 920.9mg/cm<sup>3</sup>, p<0.03; 935.2 vs. 956.5mg/cm<sup>3</sup>, p<0.01, respectively), but not trabecular bone density. Cortical porosity of athletes was significantly increased comparing to control in radius (0.34 vs. 0.2%, p=0.01). Cortical thickness of athletes was significantly thinner than control in radius (0.93 vs. 1.05mm, p<0.02). **Conclusion** Even the bone density measured by DXA may not show significant changes, bone microarchitecture of cortex can be deteriorated in amenorrheic athletes. HR-pQCT may be useful to evaluate the bone stiffness of female athletes.

### IS-WS-11-2

**Bone mineral density in premenopausal women is associated with antioxidant nutrient intake** Tamami Odai, Masakazu Terauchi, Asuka Hirose, Naoyuki Miyasaka *Tokyo Medical and Dental University*

**Objective** Although the intake of calcium, vitamins D, and K are known to be positively associated with bone mineral density (BMD), the effects of other nutrients on BMD are yet to be elucidated. The aim of the current study was to investigate the relationship between the consumption of a variety of nutrients and BMD in middle-aged women. **Methods** In 279 middle-aged women, lumbar spine BMD (L2-4) was measured with dual energy X-ray absorptiometry (DEXA), and the dietary habits were assessed with brief-type self-administered diet history questionnaire (B-DHQ) from 2009 to 2016. 117 women treated with estrogen or anti-osteoporosis drugs were excluded. Divid-

ing the remaining 162 women (204 DEXA measurements) into pre- and postmenopausal groups, the correlation between their BMD and the intake of 97 nutrients were investigated separately. **Results** 47 women (48 DEXA measurements) were premenopausal and 117 women (156 DEXA measurements) were postmenopausal. Their average age (years) was 49.3±2.8 and 58.5±7.6 (mean±SD), and the BMD (g/cm<sup>2</sup>) was 1.123±0.180 and 0.988±0.148, respectively. The daily intake amount of calcium,  $\alpha$ -tocopherol, and cryptoxanthin was positively correlated with BMD in premenopausal women (r=0.2958, 0.3136, 0.3826, p<0.05), but not in postmenopausal women. **Conclusion** Oxidative stress has been linked to bone loss through the increase in bone resorption and the formation of abnormal collagen cross-links. In the current study, we found that BMD in premenopausal women were associated with not only calcium but also antioxidant nutrients, namely  $\alpha$ -tocopherol and cryptoxanthin. This result suggests that the health diet rich in antioxidant nutrients may contribute to the preservation of bone mass in women before menopause.

### IS-WS-11-3

**The Evaluation of Efficiency of CRISPR/Cas9 System in Generating Fibulin-5 Knockout Mice** Kohei Kitada<sup>1</sup>, Masami Hayashi<sup>2</sup>, Aki Takase<sup>2</sup>, Natsuko Yokoi<sup>2</sup>, Hiroko Katayama<sup>2</sup>, Akihiro Hamuro<sup>2</sup>, Akemi Nakano<sup>2</sup>, Takuya Misugi<sup>2</sup>, Daisuke Tachibana<sup>2</sup>, Masayasu Koyama<sup>2</sup> *Izumitsu Municipal Hospital<sup>1</sup>, Osaka City University<sup>2</sup>*

**Objective** The aim of this study was to generate fibulin-5 knockout mice, which were known for the model of pelvic organ prolapse, by CRISPR/Cas9 system and to evaluate the efficiency of this method. **Methods** To design single guided RNA for CRISPR/Cas9 system, we selected Cas9 target sites in the fibulin-5 gene. We searched for 20-nucleotide sequences in fibulin-5 gene followed by the protospacer-adjacent motif (PAM) sequence (NGG) after the translational start site (ATG). C57BL/6 female mice were superovulated and mated with C57BL/6 males, and fertilized embryos were collected from the oviduct. The pronuclear stage embryos were injected with pX330 plasmid and single guided RNA. The embryos were cultivated then transferred into the oviducts of pseudopregnant ICR females. We extracted DNA from mouse tail and analyze genotype by DNA sequencing. **Results** We obtained 29 mice (16 male and 13 female), and gene mutation of fibulin-5 was introduced in 58.6% of mice (17/29, 8 male and 9 female). In the fibulin-5 gene mutation mice, homozygous mutation was found in 53% (9/17). We chose 2 female mice which had homozygous type fibulin-5 mutation and mated with C57BL/6 male mice. After delivery, rectal prolapse was found in all mice. **Conclusion** Fibulin-5 gene mutation mice were obtained efficiently by CRISPR/Cas9 system and almost half of mutation mice were homozygous mutation.

### IS-WS-11-4

**A genome-wide association study identifies 10 new susceptibility loci for uterine leiomyoma in Japanese population** Kensuke Sakai<sup>1</sup>, Akira Hirasawa<sup>2</sup>, Wataru Yamagami<sup>2</sup>, Nobuyuki Susumu<sup>3</sup>, Mamoru Tanaka<sup>2</sup>, Daisuke Aoki<sup>2</sup>, Koichi Matsuda<sup>1</sup> *The Institute of Medical Science, The University of Tokyo<sup>1</sup>, Keio University<sup>2</sup>, International University of Health and Welfare<sup>3</sup>*

**Objective** Uterine leiomyoma is a common benign gynecologic tumor occurring up to 30% of women population. Nevertheless, the pathogenesis of this tumor still stays unclear. We conducted a genome-wide association study to elucidate the pathogenesis. **Methods** In this study, we conducted a genome-wide association study in which 951,117 SNPs were analyzed in 5,720 indi-

viduals with clinically diagnosed uterine leiomyoma and 17,492 female controls in the screening stage. After the quality control of the genotyping data and the imputation using 1,000 Genome project phase 1 dataset, we further analyzed the association of 7,521,072 SNPs. A total of 3,830 SNPs with  $P < 1 \times 10^{-4}$  in the first screening were further analyzed using an independent case-control set consisting of 8,026 individuals with previous history of uterine leiomyoma and 52,824 controls those were genotyped with illumina Omni express exome BeadChip. A meta-analysis of the screening step and the replication step identified 13 genomic loci with P-value of  $< 5 \times 10^{-8}$  (genome-wide significance). **Results** Three genomic loci (chromosome 10, 11, 22) were previously reported, and we identified 10 novel loci: chromosome 1, 2, 3, 4, 5, 7, 8, 12 and 13. One SNP on ch 1 is located within the estrogen receptor (ER) binding site. Because estrogen is known to be the most critical regulator of leiomyoma, this SNP could potentially regulate target genes and play an important role in the pathogenesis of uterine leiomyoma. **Conclusion** These 13 genomic loci should contribute to elucidate the pathogenesis of uterine leiomyoma.

### IS-WS-11-5

**A novel approach to treat endometriosis via targeting epithelial-mesenchymal transition** Hirotaka Masuda<sup>1</sup>, Masataka Furuya<sup>2</sup>, Tetsuo Maruyama<sup>1</sup>, Fumie Miki<sup>1</sup>, Satomi Katakura<sup>1</sup>, Yushi Yoshimasa<sup>1</sup>, Sayaka Uchida<sup>1</sup>, Hiroshi Uchida<sup>1</sup>, Tomoka Takao<sup>1</sup>, Hidetaka Katabuchi<sup>3</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Rose Ladies Clinic<sup>2</sup>, Kumamoto University<sup>3</sup>*

**Objective** Endometriosis shares some malignant features such as invasion and metastasis despite its benignancy. These features are thought to be involved in epithelial-mesenchymal transition (EMT). This study sought to investigate EMT statuses in endometriosis and drug potency of an EMT inhibitor. **Methods** Ten endometriosis, nine adenomyosis and seventeen non-endometriosis patients undergoing surgery for benign indications were recruited. We examined the expression of E-cadherin, N-cadherin, vimentin and EMT-induced transcriptional factors (Snail and ZEB1) in epithelium of each type of endometriotic lesions and normal endometria by immunohistochemical scoring. The western blot analysis was employed to assess EMT induction of TNF $\alpha$  and TGF $\beta$  on cultured endometrial epithelial cells (cEECs). An inhibitory effect of an EMT inhibitor was evaluated by wound healing assay. **Results** N-cadherin and Snail were preferentially expressed in deep infiltrating endometriosis (DIE) and ovarian endometrioma (OVE). Vimentin expression level was significantly higher in eutopic endometria of endometriosis patients compared to non-endometriosis women. E-cadherin staining showed isolated/scattered pattern in DIE and adenomyosis. ZEB1 was only expressed in endometriotic lesions, especially DIE and adenomyosis, but not in eutopic endometria. Western blot analysis demonstrated cadherin switch in cEECs, which indicated EMT was easily provoked by TNF $\alpha$  and TGF $\beta$  in cEECs. Wound healing assay revealed that the EMT inhibitor reduced the migration ability of cEECs. **Conclusion** The differential EMT status of each endometriotic lesion may indicate different etiology or pathophysiology according to the type of lesions. The EMT inhibitor could be the first non-hormonal drug without anovulatory effect, which confers tremendous benefits to infertility women.

### IS-WS-11-6

**Intraoperative and postoperative clinical evaluation for hysteroscopic resection of submucosal uterine fibroids with a hysteroscopic morcellator system** Akira Tsuchiya, Yasunori Komatsu, Michiko Honda, Hiroko Tsuchiya, Reiko Matsuyama, Akihisa Fujimoto, Osamu Nishii *Teikyo University Hospital, Mi-*

*zonokuchi*

**Objective** To evaluate the use of a hysteroscopic morcellator system in terms of the operating time, surgeon's convenience, and effect on patients in comparison with the performance of conventional electrosurgical resection in the hysteroscopic resection of submucosal uterine fibroids. **Methods** Patients undergoing hysteroscopic resection of submucosal uterine fibroids were randomly allocated to undergo either hysteroscopic morcellation or electrosurgical resection after obtaining the approval from the institutional review board. The primary outcome was the operating time. Secondary outcomes were the removal success, fluid deficit, convenience associated with the technique, visibility of the operative field, recurrence of the patient's chief complaint, and adverse events. **Results** Ten women were randomly allocated to either the morcellation arm (n=5) or the electrosurgical resection arm (n=5) from November 2015 to November 2016. The fibroids were completely removed in all patients (100%) of the morcellation arm and in two patients (40%) of the electrosurgical resection arm. The average operating time (15.8 minutes vs. 27.7 minutes,  $P=0.149$ ) tended to be lower in the morcellation arm than in the electrosurgical resection arm. Surgeons' subjective evaluation measured on a 10-cm visual analog scale was higher in the morcellation arm than in the electrosurgical resection arm in terms of ease of removal (8.4 vs. 6.2,  $P=0.010$ ) and visibility of the operative field (8.8 vs. 5.7,  $P=0.010$ ). **Conclusion** In the resection of submucosal uterine fibroids, the use of a hysteroscopic morcellator system in comparison with electrosurgical resection received a higher evaluation score from surgeons, and may shorten operating time.

### IS-WS-11-7

**Expression of Müllerian inhibiting substance receptor and anti-proliferative effects of MIS on human adenomyosis tissue** Youn Jee Chung, Jae Yen Song, Young Sin Han, Soo Hyun Sim, Hyun Hee Cho, Hyejin Hwang, Mee Ran Kim, Jang Heub Kim *The Catholic University of Korea, Korea*

**Objective** Müllerian inhibiting Substance (MIS) is known to not only act as a regulator of female reproductive function but also inhibits the growth of Müllerian duct-derived tumors. But the role of MIS in adenomyosis is unclear. Therefore, this study is aimed to confirm the expression of MISR2 and effects of MIS on adenomyosis. **Methods** We gathered the tissues from the 30 patients who had hysterectomy for adenomyosis. We performed immunohistochemistry with rabbit polyclonal anti-human MISR2 antibody. The cultured cells were exposed to MIS and MTT assay. Induction of cell cycle and apoptosis was also observed in the cells treated with MIS as measured by using DNA PI staining and annexin V binding. The cells were analyzed on a flowcytometer. We evaluated the expression of proteins which is related apoptosis and cell cycle arrest in adenomyosis. **Results** MISR2 was stained in adenomyosis tissues and The expression level of MISR2 was in the order of weakly, mild, strong positive and negative. The cultured adenomyosis cells treated with MIS for 48 and 96 hours significantly exhibited growth inhibition 14.59%, 26.6% ( $P < 0.05$ ). It will perform experiments for the changes in cell cycle distribution and apoptosis related in a short time. **Conclusion** The expression of MISR2 has difference between myometrial tissue and adenomyosis. MIS induces G0G1 cellcycle arrest and apoptosis of adenomyosis. These finding suggest that MIS has a greater role on adenomyosis than myometrium in cellcycle inhibition and apoptosis. Therefore, MIS could be used as a biological modifier or therapeutic agent for the treatment of adenomyosis.

### ISP-1-1

**Compare the levels of IL-2, IL-6, IL-10 and IFN- $\gamma$  in cervical lesions tissues and serum of Uyghur and Han women** Mayinuer Niyazi, Gulan Tuohetumulati, Suray Husayin *The People's Hospital of Xinjiang Uighur Autonomous Region, China*

**Objective** To test the IL-2, IL-6, IL-10, IFN- $\gamma$  and (HPV) L1 in serum from Han and Uyghur screened with HPV (+). **Methods** The data gathered Uyghur at the People's Hospital of Xinjiang Uyghur Autonomous Region from August of 2013 to June of 2015, cervical erosion was determined by HC-2, HPV-DNA, and HPV typing technique, the factors analyzed by means of Logistic Regression Analysis, which were severed into several groups of cervicitis, CIN1, CIN2-3 and cervical carcinoma. The levels of IL-2, IL-6, IL-10 and IFN- $\gamma$  in serums and cervical tissues was measured. ELISA and Immunocytochemical and IHCA were applied to inspect 197 specimens with positive HPV. **Results** The IFN- $\gamma$  in cervical tissues was inversely proportional to the severity of cervical lesions while the IL-10 was in proportion to cervical lesions, which can be inferred that descended with an increase of severity of cervical lesions while the other climbed up with the severity of that, both had a statistical significance ( $P < 0.05$ ). The IL-2 and IFN- $\gamma$  with different grades of cervical lesions declined with an increase of the severity of cervical lesions while the IL-6 and IL-10 was opposite, which went up with the severity of cervical lesions, both showed a statistical significance ( $P < 0.05$ ). The comparison between Han and Uyghur no statistical differences ( $P > 0.05$ ). **Conclusion** The IL-2 and IFN- $\gamma$  with different grades of cervical lesions declined with an increase of the severity of cervical lesions, the IL-6 and IL-10 was opposite to this.

### ISP-1-2

**Selective cytotoxic effect of non-thermal micro-DBD plasma** Byung Su Kwon, Hyun Nyung Jo, Kim Yoon Hwa, Ka Yeong Yun, Sieun Han, Ki Hyung Kim, Dong Soo Suh *Pusan National University Hospital, Korea*

Non-thermal plasma has been extensively researched as a new cancer treatment technology. We investigated the selective cytotoxic effects of non-thermal micro-dielectric barrier discharge (micro-DBD) plasma in cervical cancer cells. Two human cervical cancer cell lines (HeLa and SiHa) and one human fibroblast (HFB) cell line were treated with micro-DBD plasma. All cells underwent apoptotic death induced by plasma in a dose-dependent manner. The plasma showed selective inhibition of cell proliferation in cervical cancer cells compared to HFBs. The selective effects of the plasma were also observed between the different cervical cancer cell lines. Plasma treatment significantly inhibited the proliferation of SiHa cells in comparison to HeLa cells. The changes in gene expression were significant in the cervical cancer cells in comparison to HFBs. Among the cancer cells, apoptosis-related genes were significantly enriched in SiHa cells. These changes were consistent with the differential cytotoxic effects observed in different cell lines.

### ISP-1-3

**Whole-genome analysis of human papillomavirus genotypes 52 and 58 isolated from Japanese women with cervical intraepithelial neoplasia and invasive cervical cancer** Yuri Tenjimabayashi<sup>1</sup>, Yusuke Hirose<sup>1</sup>, Mamiko Onuki<sup>1</sup>, Sari Nakao<sup>2</sup>, Takashi Iwata<sup>3</sup>, Koji Matsumoto<sup>1</sup>, Akihiko Sekizawa<sup>1</sup> *Showa University<sup>1</sup>, University of Tsukuba<sup>2</sup>, Keio University<sup>3</sup>*

**Objective** HPV52/58 are frequently detected in patients with CIN and invasive cervical cancer (ICC) in East Asian countries including Japan. As with other HPV genotypes, HPV52/58 consist of multiple lineages of genetic variants harboring less than

10% differences between complete genome sequences of the same HPV genotype. However, variations of viral genome sequences have not been fully examined for HPV52/58. The aim of this study was to investigate genetic variations of HPV52/58 prevalent among Japanese women by analyzing the viral whole-genome sequences. **Methods** The entire genomic region of HPV52/58 was amplified by long-range PCR with total cellular DNA extracted from cervical exfoliated cells isolated from Japanese patients with CIN or ICC. The amplified DNA was subjected to next generation sequencing to determine the complete viral genome sequences. Phylogenetic analyses were performed with the whole-genome sequences to assign variant lineages/sublineages to the HPV52/58 isolates. **Results** Among 52 isolates of HPV52, 50 isolates belonged to lineage B and two isolates belonged to lineage A. Among 48 isolates of HPV58, 47 isolates belonged to lineage A and one isolate belonged to lineage C. SNPs specific for individual variant lineages were determined throughout the viral genome based on multiple sequence alignments of the Japanese HPV52/58 isolates and reference HPV52/58 genomes. **Conclusion** Among the HPV52/58-positive specimens from Japanese women with CIN/ICC, the variant distributions were strongly biased toward lineage B for HPV52 and lineage A for HPV58 across histological categories.

### ISP-1-4

**Mieap induces cell death via non-canonical mitophagy in human cervical cancer** Makoto Yamamoto, Shizuka Yamada, Hideaki Tsuyoshi, Makoto Orisaka, Tetsuji Kurokawa, Yoshio Yoshida *University of Fukui*

**Objective** Canonical mitophagy plays a pivotal role in mitochondrial quality control, which is mediated by the Parkin/Pink1-mediated macroautophagy. Recently, we discovered non-canonical mitophagy that is induced by Mieap. Overexpression of Mieap induces large vacuole structures (designated MIV: Mieap-induced vacuole). MIV eats and degrades cancer specific unhealthy mitochondria. This non-canonical mitophagy leads to cancer cell death via the ROS production and caspase activation. To clarify the role of Mieap-mediated non-canonical mitophagy in cervical cancer, this study was carried out. **Methods** A total of 70 patients with cervical cancer underwent immunohistochemistry to assess Mieap protein expression. Using HeLa cells, Mieap was overexpressed by adenovirus infection, and cell death was examined by caspase assay and cytochrome c immunostaining. **Results** Immunohistochemistry of 70 cervical cancer patients indicated that high level of Mieap expression was frequently detected in premalignant lesions and early stage cancers, but not in advanced and invasion cancers. Enforced-expression of exogenous Mieap in HeLa cells induced MIVs and cell death. Activation of caspase 3 and 9 were observed, but not that of caspase 8. In immunofluorescence experiment, cytochrome c was released from the mitochondria throughout the cytoplasm and nucleus of the dying HeLa cell. **Conclusion** In cervical cancer clinical specimens, early stage cancer tends to Mieap positive. Mieap-mediated non-canonical mitophagy induces cell death of HeLa cells via mitochondrial apoptotic pathway. These results suggest that Mieap-mediated non-canonical mitophagy plays a critical role in cervical cancer tumor suppression via cell death.

### ISP-1-5

**Establishment of a patient-derived orthotopic Xenograft (PDOX) model of HER-2-positive cervical cancer expressing the clinical metastatic pattern** Takuya Murata<sup>1</sup>, Robert Hoffman<sup>2</sup>, Mitsuru Shiota<sup>1</sup>, Koichiro Shimoya<sup>1</sup> *Kawasaki Medical School<sup>1</sup>, US San Diego Medical Center, USA<sup>2</sup>*

**Objective** Patient-derived xenograft (PDX) mouse models of



cancer are emerging as an important potential aid to personalized cancer therapy. Subcutaneous transplantation (patient-derived subcutaneous xenograft ; PDSX) is often used because it is easy to transplant but rarely metastasize. Unlike PDSX, the patient-derived orthotopic xenograft (PDOX) model is known to metastasize and correlate with what it occurred to cancer patient. HER-2 positive uterine cervical carcinoma consisted of 42% of 136 uterine cervical carcinoma cases in the most recent report. Its biological feature is not well understood. **Methods** The PDSX and PDOX was performed to 10 and 8 nude mice respectively. Growth of primary tumor, tumor-take rate, sites and rate of metastasis, histological comparison of primary and metastatic tissue was performed. **Results** Metastasis was detected in 4 of 8 nude mice in case of PDOX but no metastasis was detected in case of PDSX. The sites of metastasis after surgical orthotopic implantation in nude mice included peritoneal dissemination, liver metastasis, lung metastasis as well as lymph node metastasis reflecting the metastatic pattern in the donor patient. Primary tumors and metastases in the nude mice had histological structures similar to the original tumor and were stained by an anti-HER-2 antibody in the same pattern as the patient's cancer. **Conclusion** PDOX model reflect well with cancer patient clinical feature and has a potential to be a good model to achieve personalized cancer therapy.

### ISP-1-6

**CDX2 expression and cancer progression in cervical cancer** Suguru Nosaka, Iemasa Koh, Eiji Hirata, Yoshiki Kudo *Hiroshima University*

**Objective** In cervical adenocarcinoma, detection at the stage of precancerous lesions is difficult, and invasion or metastasis is frequently detected even at the early stage. Patients with cervical adenocarcinoma have a poorer prognosis than dose with squamous cell carcinoma, because of resistance to chemotherapy and radiotherapy contributing to high recurrence rates. We previously reported that in ovarian mucinous adenocarcinoma, the transcription factor caudal type homeobox 2 (CDX2) expression is positive and it transcriptionally regulates multidrug resistance 1 (MDR1) expression, leading to drug resistance. We reported that CDX2 expression was observed in tissue specimens of adenocarcinoma in situ (AIS) and intestinal-type mucinous adenocarcinoma. We therefore have examined relation between CDX2 expression in cytologic specimen and tissue specimen in uterine cervical neoplasia. **Methods** We applied immunochemical staining to clinical specimens of cervical neoplasia, and examined the correlation between cytochemical staining and histochemical staining. **Results** In tissue specimens, CDX2 expression was positive at a high rate in AIS sample, and at half in intestinal-type mucinous adenocarcinoma sample. CDX2 expression was also positive in cytologic specimens from patients whose tissue samples are positive for CDX2. **Conclusion** Our data suggest that CDX2 expression may influence cancer progression in intestinal-type mucinous cervical adenocarcinoma and that expression of CDX2 in cytologic specimen can be a novel marker for the diagnosis of intestinal-type mucinous adenocarcinoma.

### ISP-1-7

**Tumor-derived G-CSF induces Tumor-associated neutrophils (TANs) and suppresses the activation of T cell in cervical cancer microenvironment** Naoko Komura, Seiji Mabuchi, Eriko Yokoi, Katsumi Kozasa, Michiko Kodama, Kae Hashimoto, Kenjiro Sawada, Tadashi Kimura *Osaka University*

**Objective** To investigate the mechanism by which tumor-associated neutrophils (TANs) are induced in cervical cancer microenvironment, we conducted in vitro and in vivo analyses.

**Methods** [1] The baseline characteristics of FIGO stages IB-IVB cervical cancer patients treated with definitive radiotherapy between January 1996 and December 2011 were collected. We evaluated the relationships between intratumoral CD66b<sup>+</sup> TAN density and tumor G-CSF expression by immunohistochemistry. [2] By inoculating G-CSF-expressing or Mock-expressing cervical cancer cells into nude mice, we investigated whether tumor-derived G-CSF induces TANs in cervical cancer microenvironment using flow cytometry. Finally, using TANs obtained from tumor-bearing mice, immunosuppressive activity of TANs was assessed by T cell suppression assay. **Results** Intratumoral TAN density was positively correlated with the intensity of tumor G-CSF expression in cervical cancer patients ( $p < 0.05$ ). In mice studies, TANs were more frequently observed in tumor and peripheral blood of G-CSF-expressing cells-bearing mice than in Mock-expressing cells-bearing mice ( $p < 0.05$ ). When co-incubated, TANs isolated from G-CSF-expressing cervical cancer-bearing mice significantly inhibited the proliferation of CD8<sup>+</sup>T cell in vitro. **Conclusion** Tumor-derived G-CSF induces TANs and suppresses the activation of T cell in cervical cancer microenvironment.

### ISP-1-8

**The clinicopathological characteristics and PD-L1 expression in neuroendocrine carcinoma of the cervix** Yukihiro Hirata<sup>1</sup>, Hirokazu Ozone<sup>1</sup>, Youko Nagayoshi<sup>2</sup>, Chikage Narui<sup>2</sup>, Hiromi Komazaki<sup>3</sup>, Noriko Yamaguchi<sup>1</sup>, Hirokuni Takano<sup>2</sup>, Aikou Okamoto<sup>2</sup> *The Jikei University Kashiwa Hospital<sup>1</sup>, The Jikei University Hospital<sup>2</sup>, The Jikei University Katsushika Medical Center<sup>3</sup>, The Jikei Daisan Hospital<sup>1</sup>*

**Objective** Neuroendocrine carcinomas of the cervix (NECC) are characterized by a high mitotic rate, necrosis, frequent lymphovascular space involvement and a more aggressive clinical course. Clinical treatment relies on operation, chemotherapy and radiotherapy ; relapses are frequent. The Programmed death-ligand 1 (PD-L1) pathway is a major target of anti-tumour immunotherapy. Aberrant PD-L1 expression may cause local immune-suppression in NECC. Here, we studied the clinicopathological characteristics and PD-L1 expression in NECC. **Methods** Tissue specimens were obtained from 15 patients with NECC who were diagnosed at our hospital from 2007 to 2016. PD-L1 protein expression were analyzed by immunohistochemistry using monoclonal antibodies (E1L3N). **Results** We identified a total of 942 patients in cervical cancer including 15 (1.5%) with NECC. FIGO staging was as follows : Stage IB1, n=5 ; stage IB2, n=2 ; stage IIB, n=3 ; stage IVB, n=5. 10 patients were pure neuroendocrine carcinoma, 5 patients were mixed adenoneurocrine carcinoma. The median survival duration was 15 months (range, 1-44), survival was worse for NECC compared to squamous cell carcinoma and adenocarcinoma. PD-L1 positivity was observed in 60% of the NECC. No correlations were observed between the clinical parameters and PD-L1 protein expression. The PFS and OS did not correlate significantly with PD-L1 expression. **Conclusion** We found that NECC is a rare and aggressive type of cervical cancer that is generally associated with poor survival. Further studies of PD-L1 may generate insights into the biological characteristics that drive the clinical behavior of NECC.

### ISP-2-1

**Research on early warning factors of cervical carcinomas and precancerous lesions** Suray Husayin, Gulan Tuohetamurat, Mayineur Niyazi *The People's Hospital of Xinjiang Uighur Autonomous Region, China*

**Objective** To evaluate the capsid protein in cells and exfoliated cells, the genetic load of HPV16 DNA L1, E6/E7 in cells, the ex-

pression of HPV16L1, HPV E6/E7 Protein, HPV E6/E7mRNA in the progress of cervical erosion between Han and Uyghur women. **Methods** Data gathered at our hospital from August of 2013 to June of 2015, the type and infection of cervical erosion was determined by HC-2HPV DNA. Patient were severed into cervicitis, CIN1, CIN2-3 and cervical carcinoma groups. Immunocytochemical and IHC were applied to inspect the capsid protein in cervical exfoliated cells and tissues towards 197 specimens with positive HPV, RT-PCR and western-blot were tested genes and protein of HPV16DNA L1, DNA E6, DNA E7. ELISA was tested the antibody HPV16L1 in serums. APTIMA was executed to have an HPV E6/E7 mRNA inspection upon cervical lesions. **Results** the positive rate of HPV L1 in tissues and exfoliated cell outlined a declining trend, which demonstrated statistical significance. ( $P < 0.05$ ). antibody HPV16L1 in serums ascending with the severity of cervical lesions, which have statistical significance ( $P < 0.05$ ). No statistical significance between Han and Uyghur ( $P < 0.05$ ). Both HPV16E6/E7 protein and HPV E6/E7mRNA in cervical upgraded with an aggregation the severity of cervical lesions, both conferred statistical significance ( $P < 0.05$ ). PPV was measured at 72.88% while NPV equaled to 81.02%. AP was 76.14%. **Conclusion** HPV L1 protein and HPV E6/E7mRNA expected a marker for predicting the severity of cervical lesions in Uyghur.

### ISP-2-2

**A neast case-control study on type-specific persistent HPV infection in Uyghur women** Gulan Tuohetumulati, Mayinuer Niyazi *The People's Hospital of Xinjiang Uighur Autonomous Region, China*

**Objective** To investigate the feature of type-specific persistent HPV infection and the associated risk factors in Uyghur women. **Methods** From September 2012 to August 2013, Uyghur women. Who underwent opportunistic screening for cervical cancer at the People's Hospital of Xinjiang Uighur Autonomous Region were recruited during the baseline investigation. After tasting for HPV infection and genotyping, 300 women with enrolled in the nested case-control study, information came from the sample subjects interviewed using questionnaires and follow-up associated risk factors in Uyghur women study. **Results** The type-specific persistent HPV infection rate was 25.50% (65/255). The top five most common HPV types were HPV16 (48.80%), HPV18 (31.03%), HPV58 (28.30%), HPV52 (23.40%), HPV45 (21.43%). The risk of type-specific persistent HPV infection was increased 4.81 fold for HPV16 compared with non HPV16. Compared with transient HPV infection, menopause and not using condoms were risk factors for persistent HPV infection. Having menopause and not using condoms. Regular scanning and close follow-up be carried out in the high risk population. **Conclusion** The risk factors for persistent HPV infection for Uyghur women included having HPV16 infection, having menopause and not using condoms. Regular scanning and close follow-up be carried out in this high risk population.

### ISP-2-3

**Chemoradiotherapy followed by consolidation chemotherapy involving paclitaxel and carboplatin and in FIGO stage IIIB/IVA cervical cancer patients** Hiroko Shimura, Seiji Mabuchi, Tsuyoshi Takiuchi, Yuri Matsumoto, Michiko Kodama, Eiji Kobayashi, Kae Hashimoto, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** To evaluate the efficacy and toxicity of paclitaxel plus carboplatin (TC)-based concurrent chemoradiotherapy (CCRT) followed by consolidation chemotherapy in the International Federation of Gynecology and Obstetrics (FIGO) stage

IIIB/IVA cervical cancer patients. **Methods** We reviewed the medical records of FIGO stage IIIB/IVA cervical cancer patients ( $n=30$ ) who had been intended to be treated with TC-based CCRT followed by consolidation chemotherapy (TC-CCRT-group) from April 2012 May 2016. Patients who had been treated with CCRT involving a single platinum agent (CCRT-group ;  $n=52$ ) or definitive radiotherapy alone (RT-group ;  $n=74$ ) from January 1997 September 2012 were also identified and used as historical controls. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. **Results** Of the 30 patients included in the TC-CCRT-group, 22 patients (73.3%) completed the planned TC-based CCRT. The most frequently observed acute grade 3/4 hematological toxicities were leukopenia and neutropenia, and diarrhea was the most common acute grade 3/4 non-hematological toxicity. After a median follow-up of 35 months, 9 patients (30.0%) had developed recurrent disease. The patients' estimated 3-year progression-free survival (PFS) and overall survival (OS) rates were 67.9% and 90.8%, respectively. In comparisons with historical control groups, the survival outcomes of TC-CCRT-group was significantly superior to CCRT-group in terms of OS ( $p=0.011$ ) and significantly superior to RT-group in terms of both PFS ( $p=0.009$ ) and OS ( $p < 0.001$ ). **Conclusion** TC-based CCRT followed by consolidation chemotherapy is safe and effective. A randomized controlled study needs to be conducted to further evaluate the efficacy of this multimodal approach in this patient population.

### ISP-2-4

**Phase I study of multiple epitope peptide vaccination in patients with recurrent or persistent cervical cancer** Yuji Ikeda, Akira Kurosaki, Yuichi Imai, Shoji Nagao, Daisuke Shintani, Akira Yabuno, Keiichi Fujiwara, Kosei Hasegawa *Saitama Medical University International Medical Center*

**Objective** Cancer immunotherapy is recently established as the "fourth cancer therapy". In this study, we conducted a phase I dose-escalation study trial using a mixture of five peptides to vaccinate cervical cancer patients with HLA-A\*2402. **Methods** The primary endpoints were safety and determination of a recommended vaccine dose, and the secondary endpoints were evaluations of immunological responses and clinical efficacy. All patients had recurrent or persistent disease and had failed to respond to or were intolerant to prior standard chemotherapy. Peptides derived from forkhead box protein M1 (FOXM1), maternal embryonic leucine zipper kinase (MELK), holliday junction-recognition protein, and vascular endothelial growth factor receptors 1 and 2 were administered to nine patients in a three patient-cohort design, with doses of 0.5, 1, or 2 mg of each of the individual peptides in a mixture with incomplete Freund's adjuvant. **Results** The major adverse events were anemia and injection site reactions, which were seen in 77.8% (7/9) and 66.7% (6/9) of patients, respectively. Grade 3 anemia was observed in one patient. No dose-limiting toxicity of the vaccine was observed. Seven (78%) patients achieved stable disease, and the median progression-free survival was 3 months. Interferon- $\gamma$  ELISPOT assays for each of the five antigens showed that eight (89%) and seven (78%) patients had high T cell responses to FOXM1 and MELK, respectively. **Conclusion** We demonstrated that this five-peptide vaccine was tolerable, and that FOXM1 and MELK could be promising targets for immunotherapy in patients with cervical cancer.

### ISP-2-5

**Neoadjuvant intraarterial chemotherapy using an original four-lumen double-balloon catheter for locally advanced uterine cervical cancer** Tomohito Tanaka, Hiromitsu

Tsuchihashi, Shinichi Terada, Misa Nunode, Hiromi Konishi, Natsuho Nakamura, Keisuke Ashihara, Kazuya Maeda, Saha Yoo, Hiroshi Sasaki, Yoshito Terai, Masahide Ohmichi *Osaka Medical College*

**Objective** We report the balloon-occluded arterial infusion therapy with original four-lumen double-balloon catheter (4L-DB), which enable to efficient injection of an anticancer agent at a high concentration to target spot, for patients with locally advanced uterine cervical cancer. **Methods** One hundred and forty-three patients with locally advanced cervical cancer treated with neoadjuvant intraarterial chemotherapy (NAIAC) or primary radical hysterectomy (PRH) were retrospectively assessed. The patients in NAIAC group were received irinotecan 70 mg/m<sup>2</sup> intravenously on day 1 and 8 and cisplatin 70 mg/m<sup>2</sup> intraarterially using 4L-DB on day 2 of a 21-day course, and two courses were performed in principle. Radical hysterectomy was performed within 6 weeks after NAIAC. **Results** Ninety-four patients were treated with NAIAC and 49 patients had PRH. In NAIAC group, 88 patients had 2 courses of NAIAC, 6 patients had 1 course of NAIAC and 88 had radical hysterectomy. The response rate of NAIAC was 92.6%. Fourteen patients (14.6%) had no evidence of cancer cells on pathologic diagnoses. The medium follow-up was 26 months and 25 months, respectively. NAIAC group had higher 2-year progression-free survival than PRH group (76.7% vs. 57.1%,  $p=0.03$ ), however, overall survival was not different significantly. The relative risk for recurrence was higher in patients with lymph node metastasis (4.31 ; 95% CI, 2.23-8.43) and lower in those with NAIAC (0.30 ; 95% CI, 0.14-0.68). **Conclusion** Our results with NAIAC using 4L-DB catheter in locally advanced cervical cancer indicates beneficial effects on primary lesions and improves progression-free survival.

## ISP-2-6

**Comparison of adjuvant therapy for node-positive clinical stage IB-IIIB cervical cancer : systemic chemotherapy versus pelvic irradiation** Hideki Tokunaga<sup>1</sup>, Muneaki Shimada<sup>1</sup>, Koji Matsuo<sup>2</sup>, Yoichi Aoki<sup>3</sup>, Masaru Sakamoto<sup>4</sup>, Nobuhiro Takeshima<sup>5</sup>, Hisaya Fujiwara<sup>6</sup>, Takashi Matsumoto<sup>7</sup>, Mikio Mikami<sup>8</sup>, Nobuo Yaegashi<sup>1</sup>, Toru Sugiyama<sup>9</sup> *Tohoku University<sup>1</sup>, University of Southern California, USA<sup>2</sup>, University of the Ryukyus<sup>3</sup>, Sasaki Foundation Kyoundo Hospital<sup>4</sup>, Japanese Foundation for Cancer Research<sup>5</sup>, Chugoku Rosai Hospital<sup>6</sup>, Ehime University<sup>7</sup>, Tokai University<sup>8</sup>, Iwate Medical University<sup>9</sup>*

**Objective** To examine survival outcomes and recurrence patterns of women with node-positive stage IB-IIIB cervical cancer who received only postoperative systemic chemotherapy after radical hysterectomy as compared to those women who received radiation-based therapy. **Methods** This was a nationwide retrospective study in Japan examining women who underwent radical hysterectomy for clinical stage IB-IIIB cervical cancer with pelvic and/or para-aortic lymph node metastasis between 2004 and 2008. Time to recurrence or death and patterns of disease recurrence were compared based upon the adjuvant treatment pattern : whole pelvic radiotherapy alone (n=253), concurrent chemo-radiotherapy (CCRT, n=502), and chemotherapy alone (n=319). **Results** Women who received chemotherapy alone had similar recurrence (5-year rates, 36.6% versus 34.1%) and mortality (24.7% versus 21.8%) compared to those who received CCRT on multivariate analysis. Chemotherapy treatment was independently associated with decreased risk of distant recurrence (5-year cumulative rates, 19.2% versus 24.6%) but increased risk of local recurrence (23.9% versus 14.3%) compared to CCRT. Non-squamous histology, parametrial involvement, and high lymph node ratio were independent predictors for local recurrence, and presence of multiple risk factors was associated with high 5-year cumulative local

recurrence rate in the chemotherapy group : no risk factor 3.9%, single factor 14.2-22.1%, and multiple risk factors 27.8-71.9% ( $P<0.001$ ). **Conclusion** Systemic chemotherapy may be as effective a postoperative treatment as radiation-based therapy in node-positive high-risk stage IB-IIIB cervical cancer. When tumor exhibits certain risk factors, chemotherapy alone is likely insufficient for local control and adding pelvic irradiation to systemic chemotherapy is recommended in this subgroup.

## ISP-2-7

**Effectiveness of adjuvant systemic chemotherapy for intermediate-risk stage IB cervical cancer** Takamichi Minato<sup>1</sup>, Muneaki Shimada<sup>1</sup>, Koji Matsuo<sup>2</sup>, Harushige Yokota<sup>3</sup>, Toyomi Satoh<sup>4</sup>, Hidetaka Katabuchi<sup>5</sup>, Shoji Komada<sup>6</sup>, Hiroshi Sasaki<sup>7</sup>, Noriomi Matsumura<sup>8</sup>, Mikio Mikami<sup>9</sup>, Nobuo Yaegashi<sup>1</sup>, Toru Sugiyama<sup>10</sup> *Tohoku University Hospital<sup>1</sup>, University of Southern California, USA<sup>2</sup>, Saitama Cancer Center<sup>3</sup>, University of Tsukuba<sup>4</sup>, Kumamoto University<sup>5</sup>, Niigata Cancer Center Hospital<sup>6</sup>, The Jikei University Kashiwa Hospital<sup>7</sup>, Kyoto University<sup>8</sup>, Tokai University<sup>9</sup>, Iwate Medical University<sup>10</sup>*

**Objective** To examine the effectiveness of systemic chemotherapy after radical hysterectomy for women with intermediate-risk stage IB cervical cancer. **Methods** This is a retrospective analysis of a previously organized nation-wide cohort study examining 6,003 women with stage IB-IIIB cervical cancer who underwent radical hysterectomy between 2004 and 2008 in Japan. Survival of 555 women with stage IB cervical cancer with intermediate-risk group (deep stromal invasion 50%, large tumor size 4cm, and lympho-vascular space invasion [LVSI]) were examined based on adjuvant therapy patterns : chemotherapy alone (n=223, 40.2%), concurrent chemo-radiotherapy (n=172, 31.0%), and radiotherapy alone (n=160, 28.8%). **Results** The most common intermediate-risk pattern was LVSI with deep stromal invasion (n=216, 38.5%). The most common chemotherapy choice was taxane/platinum doublet (52.2%). Women with adenocarcinoma/adenosquamous histology were more likely to receive chemotherapy ( $P=0.03$ ), and intermediate-risk pattern was not associated with chemotherapy use ( $P=0.11$ ). Women received systemic chemotherapy had disease-free survival (5-year rate, 88.1% versus 90.2%, adjusted-hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.52-1.83,  $P=0.94$ ) and cause-specific survival (95.4% versus 94.8%, adjusted-HR 0.85, 95%CI 0.34-2.07,  $P=0.71$ ) similar to those who received concurrent chemoradiotherapy on multivariable analysis. Similar results were seen among 329 women with multiple intermediate-risk factors (5-year rates for DFS, chemotherapy versus concurrent chemo-radiotherapy, 87.1% versus 90.2%,  $P=0.86$ ; and CSS 94.6% versus 93.4%,  $P=0.82$ ). Cumulative local-recurrence ( $P=0.77$ ) and distant-recurrence ( $P=0.94$ ) risks were similar across the adjuvant therapy types. **Conclusion** Our study suggests that systemic chemotherapy may be an alternative treatment choice for adjuvant therapy in stage IB cervical cancer with an intermediate-risk factor.

## ISP-2-8

**Paclitaxel plus cisplatin as adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIIB cervical cancer** Yuta Inoue, Takeshi Fukuda, Masahiro Shimomura, Hiroaki Matsubara, Mari Kasai, Yasunori Hashiguchi, Tomoyuki Ichimura, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

**Objective** The aim of the present study was to evaluate the efficacy and safety of paclitaxel plus cisplatin (TP) as adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIIB cervical cancer. **Methods** Thirty-eight patients with intermediate- and high-risk stage IB-IIIB cervical

cancer treated with radical hysterectomy received adjuvant TP (135mg/m<sup>2</sup> paclitaxel and 50mg/m<sup>2</sup> cisplatin, six courses for the patients who had lymph node metastasis and three courses for the others.) (TP group). Adverse events and disease-free survival were investigated. The outcome was compared with that for 40 patients who received adjuvant radiotherapy or concurrent chemoradiotherapy (RT group). This study was approved by the Ethics Committee in our facility. **Results** The completion rate of TP was 97.1%. One-year disease-free survival was 89.5% for the patients who received adjuvant chemotherapy. There was no significant difference in disease-free survival between two groups (P=0.873). Grade 3 and 4 adverse effects were identified as 15 neutropenia in TP group, 5 neutropenia, 4 diarrhea, 1 lymph edema, 3 ileus, 1 vesicovaginal fistula and 1 rectovaginal fistula in RT group. As for grade 3 and 4 adverse events, neutropenia was significantly more frequent in the TP group (P=0.004) and diarrhea was significantly more frequent in the RT group (P=0.045). **Conclusion** TP might be an effective and safe adjuvant therapy after radical hysterectomy for intermediate- and high-risk stage IB-IIB cervical cancer.

### ISP-2-9

**The comparison of CCRT protocols composed of different chemotherapy regimens for the patients with locally advanced cervical squamous cell carcinoma** Yoshifumi Nakao<sup>1</sup>, Asako Fukuda<sup>1</sup>, Takako Hikari<sup>1</sup>, Yukihiko Nakayama<sup>1</sup>, Satoshi Nishiyama<sup>1</sup>, Katsuyuki Hanashima<sup>2</sup>, Mariko Hashiguchi<sup>2</sup>, Masatoshi Yokoyama<sup>1</sup> *Saga University<sup>1</sup>, Saga University Graduate School of Medical Science<sup>2</sup>*

**Objective** To evaluate response and short time survival in patients with locally advanced squamous cell carcinoma of the uterine cervix who underwent historically different chemotherapy protocol with the same irradiation procedure. **Methods** A review of patients with locally advanced squamous cell cervical cancer who underwent definitive CCRT in the single institution. Chemotherapy included 2 monthly doses of intra-arterial infusion with cisplatin (50 mg/m<sup>2</sup>) and mitomycin C (10 mg/body) (MPia-CCRT) or weekly intra-venous infusions with cisplatin (40 mg/m<sup>2</sup>/week) (CDDPiv-CCRT). Both groups were irradiated to the whole pelvis and high-dose-rate brachytherapy in the same policy. From 2006 to 2012, 76 patients were treated with MPia-CCRT. From 2012 to 2015, 46 patients were treated with CDDPiv-CCRT. Patient distribution of each group according to the FIGO stage was as follows : 8 and 7 stage IB2, 6 and 13 stage IIA, 42 and 10 stage IIB, 3 and 2 stage IIIA, 16 and 12 stage IIIB and 1 and 2 stage IVA respectively. Radiological lymph node involvement except paraaortic nodes was present in 61.8% and 47.8%. The radiological response, pathological response, overall and disease-free survival were assessed. **Results** CR ratio and response rate showed 84.2% (64/76) and 98.7% (75/76) in MPia-CCRT group and 81.8% (36/44) 100% (44/44) in CDDPiv-CCRT group respectively. In the median follow-up duration (68.5 months and 30.5 months), the 2-year disease-free and overall survival 76.3% and 85.1%, and 70.3% and 86.7% respectively. **Conclusion** Different chemotherapy regimens administered with identical radiation protocol showed the statistically similar responses and short time survivals in patients with locally advanced cervical squamous cell carcinoma.

### ISP-3-1

**Posttreatment HPV genotyping for recurrent high grade cervical intraepithelial neoplasias** Chan Joo Kim<sup>1</sup>, SeoHye Won<sup>1</sup>, Keun Ho Lee<sup>2</sup>, TaeChul Park<sup>3</sup>, JongSup Park<sup>2</sup> *St. Paul's Hospital, The Catholic University of Korea, Korea<sup>1</sup>, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea<sup>2</sup>, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Medical Col-*

*lege, Korea<sup>3</sup>*

**Objective** Risk of recurrent CIN and CIS remains elevated for years following treatment of CIN3 and CIS. The role of HPV genotyping on subsequent risk of CIN2+ was evaluated. **Methods** This study was conducted on 66 patients with CIN3 and CIS after LEEP conization at the St Paul's Hospital of the Catholic University of Korea. Pathologic diagnosis of cervix were confirmed with colposcopic-guided biopsy or LEEP procedure. Pap smear and HPV genotyping were performed before surgery and every 3-6 month. We used HPV genotyping with Anyplex™ II HPV test. This test differentiates between 19 HPV-HR types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 26, 53, 69, 73, 82) and 9 low-risk HPV types. **Results** The mean age was 46.33 years. The most frequent HPV types were HPV-16 (17 cases, 25.8%), HPV-58 (9 cases ; 13.6%) and HPV-52/-33 (7 cases ; 10.6%). Women with single and multiple HPV type was 43 (65.2%) and 19 (28.8%). Median follow up was 16 month. Proportion of young women under 34 years old was 20 (30.3%) and nulliparity was 23 (34.8%). High risk HPV types during follow-up was found in 20 cases (30.3%). Among them, only one woman with persistent HPV-52 received total hysterectomy. Final pathology of cervix showed CIN-3 on one focus. **Conclusion** HPV infection is not completely eradicated by LEEP in patients with CIN3/CIS. HPV persistence using HPV genotyping after LEEP can identify women at greatest risk of posttreatment CIN 2+ lesions.

### ISP-3-2

**HPV subtyping according to the tissue biopsy of the cervix of the uterine at an institution** Eunseop Song, Hwa Yeon Choi, Haesun Joo, Eunye Jo, Hyungeun Choi, Shina Jang, Sukyung Jung *Inha University of Korea, Korea*

**Objective** To analyze the HPV typing according to the pathology of uterine cervix at an institution. **Methods** Medical records had been reviewed retrospectively at an institution. The result and time of the biopsies were reviewed. **Results** There were 441 biopsies from 2001 to 2016. There were 117 patients with CIN 1, 43 with CIN 2, 114 with CIN 3 and 167 with squamous cell carcinoma (SCC). At CIN 1, the frequency of HPV were 50%, and at CIN 2, 72%, and at CIN 3, 97%, and at SCC, 98%. The frequency of HPV 16, 18 and 16, 18, 31, 33, 45, 52, 58 at CIN 1 were 57% and 71%, at CIN 2 were 50% and 60%, at CIN 3 were 47% and 74% and at SCC, 72% and 94%. **Conclusion** The rate of High Risk HPV type according to the biopsy were 50% at CIN 1, 72% at CIN2, 97% at CIN 3 and 98 at squamous cell carcinoma. Among the patient with identified HPV type, the rate of 2 types (16 and/or 18) and 7 types (16, 18, 31, 33, 45, 52, and 58) were 57% and 71% at CIN 1 and 50% and 60 at CIN 2 and 47% and 74% at CIN 3, and 72% and 94% at squamous cell carcinoma. This data may helpful to prepare and expect the potency of the vaccination of HPV.

### ISP-3-3

**Outcomes of patients diagnosed with atypical glandular cells (AGC) in a single-institution experience** Mie Tanaka, Kiyoshi Yoshino, Akiko Okazawa, Tsuyoshi Takiuchi, Michiko Kodama, Kae Hashimoto, Eiji Kobayashi, Seiji Mabuchi, Yutaka Ueda, Takuji Tomimatsu, Kenjiro Sawada, Tadashi Kimura *Osaka University*

**Objective** This study aimed to investigate the outcomes of patients diagnosed with atypical glandular cells (AGC) and determine the clinical management for them. **Methods** We retrospectively reviewed the outcomes of patients with AGC from January 2010 to August 2017 in our institution. **Results** 195 patients were diagnosed with AGC during the study period. Among them, the final diagnosis was as follows : endometrial cancer 73 (37.4%), cervical cancer 41 (21.0%), cervical intraepithelial neo-



plasia 3 (CIN3) 13 (6.7%), adenocarcinoma in situ (AIS) 4 (2.1%), CIN3+ AIS 3 (1.5%), cervical intraepithelial neoplasia 1 (CIN1) or cervical intraepithelial neoplasia 2 (CIN2) 7 (3.6%), complex endometrial hyperplasia with atypia 2 (1.0%), ovarian cancer 7 (3.6%), peritoneal cancer+CIN2 1 (0.5%), other malignant lesions 3 (1.5%), and benign lesion 14 (7.2%). 24 patients (12.3%) had no lesions and the outcomes were unclear in 2 patients. Of all cases diagnosed as AGC, 64.1% had malignant lesions. **Conclusion** Patients diagnosed as AGC were high risk for malignancy. Most of them located in the uterus, biopsies of cervix under colposcopy, from endometrium and conization if necessary should be carried out. It was rare, but abdominal cancer coexisted with cervical AGC, so that careful imaging analysis of abdominal cavity such as with MRI can be considered if physician suspects malignancies.

### ISP-3-4

**The pathological investigation of parametrial invasion to diminish type III radical hysterectomy for stage IB-IIA cervical cancers** Fuminori Ito<sup>1</sup>, Atsushi Sugiura<sup>1</sup>, Kana Iwai<sup>2</sup>, Yuki Yamada<sup>2</sup>, Yasuhito Tanase<sup>2</sup>, Ryuji Kawaguchi<sup>2</sup>, Shinji Toyoda<sup>1</sup>, Yoshio Itani<sup>1</sup>, Hiroshi Kobayashi<sup>2</sup>, Tsunekazu Kita<sup>1</sup> *Nara Prefecture General Medical Center<sup>1</sup>, Nara Medical University<sup>2</sup>*

**Objective** To assess the adequate conditions of type II radical hysterectomy (RH-II) for stage IB1 to IIA2 cervical cancers in order to reduce postoperative complications by avoiding type III radical hysterectomy (RH-III). **Methods** The relationship between pathological parametrial invasion (PMI) and other prognostic factors was retrospectively investigated in cases performed with RH-III for stage IB1 to IIB cervical cancers in two tertiary institutions, from November 2006 to May 2017. Chi-square test was used as univariate analysis and multiple logistic regression analysis as multivariate analysis. **Results** One hundred forty cases were preoperatively diagnosed as stage IB1 in 54 cases, IB2 in 32, IIA in 17, IIB in 35 and IVB in 2. Thirty cases (21.4%) were revealed histologically with PMI. In univariate analysis, elder age (>50 yo), large tumor (>30mm) and common iliac lymph node metastasis were the significant risk factors for PMI. In multivariate analysis, all three factors were extracted as the significant risk factors for PMI with p-values 0.012, 0.020, 0.019, respectively. Combination of these three factors could estimate PMI with high sensitivity (90.9%) and negative predictive value (96.3%) in stage IB1 to IIA2 cases. These results mean RH-II might be enough for 26.2% of IB1 to IIA2 cases with an only 3.7% risk of pathological PMI. **Conclusion** RH-II nor RH-III could be enough for stage IB1 to IIA2 cervical cancers, with age younger than 50 years, with tumor size smaller than 30mm, and in addition, without metastasis to common iliac lymph nodes proved by intraoperative frozen section.

### ISP-3-5

**Lymph node metastasis of stage IA1 uterine cervical squamous cell carcinoma : case report** Kana Sekigawa<sup>1</sup>, Ichiro Ono<sup>2</sup>, Keijiro Sumori<sup>2</sup>, Hidenori Umeki<sup>3</sup>, Yoshiaki Somekawa<sup>3</sup>, Mikiko Tsugata<sup>3</sup>, Aya Osonoi<sup>2</sup>, Hironori Asada<sup>1</sup>, Shuji Takemoto<sup>1</sup>, Satoshi Asai<sup>1</sup> *Shin-yurigaoka General Hospital<sup>1</sup>, Ome Municipal General Hospital<sup>2</sup>, JA Toride Medical Center<sup>3</sup>*

Lymph node metastasis of stageIA1 uterine cervical squamous cell carcinoma (SCC) is very rare. In this report we will present two cases in which we detected post-surgical lymph node metastasis. In our first case was a 63 year-old women who was diagnosed with cervical microinvasive squamous cell carcinoma following a regular uterine cervical cancer check-up. We performed conization. The diagnosis was SCC stageIA1, the mass depth was 3mm, the length was 6mm and LVSI was negative. We added total abdominal hysterectomy (TAH) and bilateral

salpingectomy (BLS). Twenty-two months after the first surgery, increasing para-aortic lymph node was detected by CT, and she underwent pelvic lymphadenectomy and para-aortic lymphadenectomy. Second case was a 74 year-old woman. Hydrometra had been detected and the fluid had been suctioned, but soon reaccumulated. Since her abdominal pain had been worsening we preformed TLH and BLS. The diagnosis of the uterine cervix was SCC stageIA1, the mass depth was under 2mm and the length was 2mm and LVSI was negative. Fourteen months after the first operation inguinal lymph node had been palpated, and we removed it which was diagnosed with SCC. There were twenty-two SCC IA1 cases in two hospitals between 1996 and 2016, but only these two cases (9%) had relapsed. In both cases LVSI was negative even by immunostaining. Image testing for stage IA1 uterine cervical SCC is not standard during routine exam, but we must remember the potential for post-surgical metastasis and consider image testing logical addition to follow-up after initial surgery.

### ISP-3-6

**Leukocytosis as an initial sign of aggressive growth of granulocyte colony-stimulating factor-producing cervical cancer** Ai Yoshida, Kyousuke Takeuchi, Mamiko Sawada, Akiko Takeda, Makoto Sugimoto *Kobe Medical Center*

**Introduction** Granulocyte colony-stimulating factor (G-CSF)-induced leukemoid reaction is a rare paraneoplastic syndrome in cervical carcinoma, with rapid tumor progression and poor prognosis. We report three cases of G-CSF-producing squamous cell carcinoma of the cervix, where leukocytosis led to diagnosis and the disease and its recurrence. **Cases** A 57-year-old woman underwent radical hysterectomy for cervical carcinoma. No leukocytosis was noted. The patient was treated with concurrent chemoradiation therapy. One month after radiation therapy the patient developed fever without evidence of infection, and laboratory data showed leukocytosis (18,540/ $\mu$ L ; 90% neutrophils). Serum G-CSF was 125.2 pg/mL. The specimens found at surgery were focally positive for G-CSF. A 58-year-old woman had high fever. The biopsy specimens at cervix demonstrated a squamous cell carcinoma. The cytoplasm of the tumor cells was positive for G-CSF. Laboratory data showed severe leukocytosis (22,540/ $\mu$ L ; 93% neutrophils) and 58.2 pg/mL of G-CSF. Intensive irradiation and chemotherapy provided temporary remission. An 80-year-old woman had exploratory laparotomy under the diagnosis of colonic perforation, and perforated pyometra and advanced cervical carcinoma were diagnosed. Antibiotics therapy was performed. However, leukocytosis (31,300/ $\mu$ L ; 85% neutrophils) continued, regardless of improvement of other inflammatory findings. The cytoplasm of the tumor cells at cervix was positive for G-CSF. After radiation leukocyte count and G-CSF levels were decreased. **Discussion** The possible existence of G-CSF-producing carcinoma should be considered in cases of cervical carcinoma with remarkable leukocytosis and neutrophilia, but without obvious infection. White blood cell count should be closely followed as part of the monitoring of disease activity.

### ISP-3-7

**Retrospective study of metastatic size and recurrence pattern for lymph node positive cervical cancer patients** Tomoyuki Nagai, Hideki Tokunaga, Masafumi Toyoshima, Muneaki Shimada, Hitoshi Niikura, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** To evaluate the clinicopathological features in the lymph node positive cervical cancer patients. **Methods** FIGO IA 2-IIB cervical cancer patients who underwent surgery from 2012 to 2017 in our hospital and had histologically metastatic

positive lymph node were analyzed. We evaluated overall survival and progression free survival, recurrence pattern, size of metastatic lymph node, and operative procedure (with or without sentinel lymph node mapping). **Results** Thirty patients had positive lymph node metastases and 6 patients had recurrence. Four of six patients experienced lymph node recurrence. Four patients had only with micrometastases but 2/4 recurred. In patients using sentinel lymph node (SLN) mapping, 7/9 found lymph node metastases only in SLN. None with SLN mapping patients recurred. **Conclusion** Cervical cancer patients with micrometastases have a same risk compared with macrometastases patients. Using sentinel lymph node mapping may probably reduce the risk of lymph node recurrence.

### ISP-3-8

**Squamous cell carcinoma of the cervix with superficial spreading to the endometrium : A case report** Shuhei Abe, Kiyonori Miura, Noriko Miyashita, Toru Murakami, Yuri Hasegawa, Atsushi Yoshida, Hideaki Masuzaki *Nagasaki University*

Commonly, cervical squamous cell carcinoma (SCC) can directly invade the uterine wall with or without parametrial involvement and/or by lymphatic invasion. The superficial spreading to the endometrium replacing it without myometrial invasion is very uncommon, with fewer than 30 cases reported in the literature. The author reports a case of cervical SCC with superficial spread. A 69-year-old female (G 2-P 2) presented with abnormal cytological and histological finding of cervix (HSIL and CIN3) 7 years ago. However, she did not get cervical conisation. She admitted a local hospital with itching sensation of the vulva and atypical genital bleeding since the last three months and was introduced to our hospital because of further examination for abnormal cytology (ASC-H). Cervical cytology, endometrial cytology, cervical biopsy and endometrial curettage revealed SCC. There was CIN3 with gland involvement by cervical conisation and no mass lesion detected by imaging such as US/CT/MRI. The patient was diagnosed as cervical SCC (FIGO stage IA1 by endometrial curettage sample). A semi-radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection was performed. Microscopically, the cervical lesion revealed features of CIN3 (carcinoma in situ) extending up and lining the endometrial surface without myometrial invasion. In this case, the superficial spreading SCC of cervix involved the entire the endometrial surface without myometrial invasion. Although the FIGO staging system has ignored such a condition, as this case is rare phenomenon, more case studies are necessary to clarify the conclusion regarding treatment and prognosis of this condition.

### ISP-3-9

**Usefulness of diffusion-weighted MRI (DW-MRI) in the detection of lymph node metastases in patients with uterine cervical cancer** Yoshinori Takeda, Atsushi Sugiura, Shoichiro Yamanaka, Sayuri Morita, Hitomi Sugimoto, Satoko Ishibashi, Fuminori Ito, Hitoshi Hirano, Shinji Toyoda, Yoshio Itani, Tsunekazu Kita *Nara Prefecture General Medical Center*

**Objective** A high signal intensity on preoperative DW-MRI is widely relied upon for the diagnosis of malignant gynecological tumors. In this retrospective study, we investigated the effectiveness of this diagnostic method on detecting pelvic lymph node metastases in patients with uterine cervical cancer, who underwent pelvic lymph node dissections. **Methods** We studied 40 patients diagnosed with uterine cervical cancer, who underwent pelvic lymph node dissections between December 2013 and March 2017. We tried to clarify an association between a signal intensity on preoperative DW-MRI and the pathological

metastasis of the pelvic lymph node. **Results** Nineteen cases (47.5%) showed a high signal intensity on DW-MRI and only 5 cases (12.5%) showed metastasis-positive in pelvic lymph nodes. The sensitivity, specificity, positive-predictive value, and negative-predictive value of DW-MRI for pelvic lymph node metastases were 80.0%, 57.1%, 21.1%, and 95.2% (20/21), respectively. Of 21 cases with low signal intensity on DW-MRI, only 1 case was revealed with lymph node metastasis. The average sizes of metastasis-negative and metastasis-positive lymph nodes with high signal intensity on DW-MRI were 11.9 mm and 13.1 mm, respectively. The median tumor sizes of metastasis-negative and metastasis-positive were 28.1 mm and 33.7 mm, respectively. **Conclusion** Our findings suggest that we cannot predict a metastasis of pelvic lymph node with a high signal intensity on DW-MRI. But we can probably omit pelvic lymph node dissections in patients without high signal intensity on DW-MRI of the pelvic lymph node.

### ISP-3-10

**Clinical Features of High-grade Neuroendocrine Carcinoma of the Uterine Cervix : a single institute retrospective review of 21 cases** Yoko Furutake, Kaoru Abiko, Taito Miyamoto, Yoshimi Kitawaki, Ryusuke Murakami, Miyuki Ito, Akihito Horie, Junzo Hamanishi, Tsukasa Baba, Masaki Mandai *Kyoto University*

**Objective** High-grade neuroendocrine carcinoma (NEC) of the uterine cervix is aggressive, and its prognosis is extremely poor. Due to the rarity of the disease, the optimal treatment strategy is yet to be clear. In this study, we retrospectively investigated clinical features and treatment of NEC. **Methods** Patients with a diagnosis of NEC treated at our hospital between 2005 and 2016 were included. Clinical and pathological data were collected from the clinical records. **Results** The median age at the diagnosis was 45 (range, 27–83 years). 15 patients had small-cell and 6 had large-cell neuroendocrine carcinoma. FIGO stage was I in 12 patients, II in 1, III in 1, and IV in 7, respectively. 2-year and 5-year survival rates were 80.0% and 42.9% (FIGO I-II), 57.1% and 12.5% (FIGO III-IV). In 13 stage I-II patients, all but one underwent radical hysterectomy. 5 patients underwent neoadjuvant chemotherapy consisting of 2 courses of cisplatin/irinotecan (PI), and 4 of them obtained partial response, and 1 obtained stable disease. 10 patients received adjuvant therapy. 22% of stage IB1 patients and all stage IB2-II patients experienced relapse. Among stage IV patients, none obtained clinical response after 6 cycles of PI. In recurrent cases, 1 patient obtained partial response (PR) using abraxane, and 1 patient obtained PR using cisplatin/etoposide (PE)-CCRT followed by PE. No patient obtained clinical response with paclitaxel/carboplatin (TC). **Conclusion** The prognosis of NEC is dismal even in early stages. Some chemotherapy regimens other than standard TC showed clinical response. Specialized treatment strategy is required to improve outcomes.

### ISP-4-1

**Decreased expression of nuclear receptor coactivator-6 may correlate with the progression and less differentiation of human endometrioid adenocarcinoma** Norikazu Watanabe, Jun Kawagoe, Hizuru Yamatani, Seiji Tsutsumi, Satoru Nagase *Yamagata University Hospital*

**Objective** Nuclear receptor coactivator-6 (Nco6) is one of the coactivators that regulate transcriptional activities of estrogen receptor  $\alpha$  (ER $\alpha$ ). In mice, the knock-out of Nco6 facilitates the growth of endometrial carcinoma. However, the function of Nco6 in human endometrium and in endometrial cancer remains unclear. We therefore investigated the relationship between the expression levels of Nco6 and the clinical character-

istics of endometrial cancer. **Methods** Pathological samples of human endometrioid adenocarcinomas were obtained from patients who underwent surgery between 2009 and 2011. The expression of Nco6 in each sample was studied using immunohistochemistry, and classified into three groups: negative (0% Nco6-positive cells); weak (1% to 49% Nco6-positive cells); and positive (>50% Nco6-positive cells). Statistical analysis was performed to reveal the relationship between patient clinical status, including grade and staging of cancer, and Nco6 expression. Authorization was obtained from the appropriate ethics committee for this study. **Results** Ninety-eight patients were studied: 50 with Grade (G) 1, 35 with G2, and 13 with G3 cancer. Compared with 100% positive cells in the normal endometrium, the ratio of negative cells increased with cancer grade: specifically, 14% in G1, 17% in G2, and 38% in G3. The proportion of patients with advanced stage (stage III-IV) was significantly higher in the negative than in the positive group (odds ratio, 5.11; 95% CI, 1.13-23.1). **Conclusion** Expression of Nco6 is decreased in endometrioid carcinoma. Decreased expression of Nco6 may be associated with cancer progression.

#### ISP-4-2

**Estrogen-related receptor  $\alpha$  induces epithelial-mesenchymal transition through the cancer-stromal interaction in endometrial cancer** Kaori Yoriki, Taisuke Mori, Tetsuya Kokabu, Shiori Umemura, Hiroshi Matsushima, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** Estrogen-related receptor (ERR)  $\alpha$  shows structural similarities with estrogen receptors. We previously demonstrated the tumor promoting action of ERR $\alpha$  in endometrial cancer. However, little is known about the detailed underlying mechanism. In this study, we investigated whether ERR $\alpha$  in cooperation with peroxisome proliferator-activated receptor  $\gamma$  coactivator (PGC)-1 $\alpha$ , could participate in epithelial-mesenchymal transition (EMT) through the cancer-stromal interaction in endometrial cancer. **Methods** Endometrial cancer cell lines, Ishikawa and HEC-1A, transfected with ERR $\alpha$ /PGC-1 $\alpha$  or knocked down for ERR $\alpha$  using siRNA, were co-cultured with human endometrial stromal cells (T-HESCs) and mono-cultured with/without transforming growth factor (TGF)- $\beta$ . The expression of EMT-related factors including Snail, ZEB-1, and Vimentin, was measured by quantitative PCR and E-cadherin expression was examined by western blotting. Migration and invasion capabilities were evaluated by Matrigel invasion assay. **Results** The co-culture experiments showed that the expression of EMT-related factors was upregulated in cancer cells transfected with ERR $\alpha$ /PGC-1 $\alpha$  ( $P < 0.01$ ) and TGF- $\beta$  expression was significantly induced in T-HESCs ( $P < 0.01$ ). In the mono-culture system, ERR $\alpha$ /PGC-1 $\alpha$  overexpression significantly stimulated the expression of EMT-related factors after TGF- $\beta$  exposure ( $P < 0.01$ ); however, it decreased E-cadherin expression at the protein level. ERR $\alpha$  knockdown suppressed the expression of EMT-related factors in the presence of TGF- $\beta$  whereas E-cadherin expression remained unchanged. Invasion assay revealed that ERR $\alpha$  knockdown attenuated the migration and invasion abilities stimulated by TGF- $\beta$  ( $P < 0.01$ ). **Conclusion** These findings suggest that ERR $\alpha$  might be a potential target for inhibiting TGF- $\beta$ -induced EMT through the cancer-stromal interaction in endometrial cancer.

#### ISP-4-3

**There is a possibility that DUSP6 contributes to one of the stem-like cell phenotypes in uterine endometrial cancer** Masaya Kato, Ichiro Onoyama, Sachiko Yoshida, Natsuko Yokota, Teruhiko Kawamura, Keiko Kawamura, Keisuke Kodama, Hiroshi Yagi, Kazuo Asanoma, Kenzo Sonoda, Kiyoko

Kato *Kyushu University*

**Objective** Cancer stem cells (CSCs) are defined as a subset of tumor cells that can reconstitute cancer tissues and which are considered to be responsible for cancer progression, metastasis and therapeutic resistance. To clarify the molecular mechanism integrating the stemness of uterine endometrial cancer cells, we have focused on dual specificity phosphatase 6 (DUSP6), because our previous data showed that DUSP6 is specifically expressed in CSC-like cells although it is epigenetically silenced in differentiated tumor cells. **Methods** To analyze DUSP6 functions associated with the stemness of tumor cells, human DUSP6 was overexpressed in uterine endometrial cancer cell lines (Hec 1). We assessed the signaling pathways, ALDH1 (CSCs marker), the pluripotency associated factors and cell survival in hypoxic condition. **Results** DUSP6 suppressed Erk1/2 activity via dephosphorylation while it promoted Akt phosphorylation. DUSP6-overexpressed cells showed higher expression of ALDH1 and pluripotency associated factors compared with control cells. Although DUSP6 suppressed cell proliferation in normoxic condition, it did not inhibit cell growth in hypoxic condition. **Conclusion** There is a possibility that DUSP6 contributes to one of the stem-like cell phenotypes in uterine endometrial cancer by acquiring hypoxic resistance. DUSP6 might be a new target in therapeutic strategies for endometrial cancers.

#### ISP-4-4

**The high expression of claudin-6 is a poor prognostic factor in uterine endometrial cancer** Manabu Kojima<sup>1</sup>, Shu Soeda<sup>1</sup>, Shinji Nomura<sup>1</sup>, Takafumi Watanabe<sup>1</sup>, Toshifumi Takahashi<sup>1</sup>, Hideki Mizunuma<sup>1</sup>, Hideki Chiba<sup>2</sup>, Keiya Fujimori<sup>1</sup> *Fukushima Medical University Hospital<sup>1</sup>, Department of Basic Pathology, Fukushima Medical University Hospital<sup>2</sup>*

**Objective** Among the claudin (Cldn) family that are transmembrane protein of tight junctions, Cldn6 is expressed in various epithelial cells during fetal period, but not in any types of adult cells. Cldn6 is also detected in a part of lung, stomach, ovarian, and uterine endometrial adenocarcinomas, as well as in a significant part of germ cell tumors, but its functional relevance in cancers is largely unknown. Here, we demonstrated the clinicopathological significance of cldn6 expression in uterine endometrial cancers (UEC). **Methods** The Cldn6 expression was evaluated by immunohistochemistry in paraffin-embedded cancer tissues resected from 141 UEC cases, and semi-quantitatively scored Cldn6 expression by the immunoreactive scoring method (score 0, 1+, 2+, 3+). We next determined whether Cldn6 expression score was correlated with clinicopathological factors. And we produced a strain of CLDN6-overexpressing cells from the ECC-1 endometrial carcinoma cell line and compared their proliferation potential with those of the parent cell line in Brdu and scratch assay. **Results** Of 141 UEC cases, 105, 14, 12, 10 cases exhibited Cldn6 score 0, 1+, 2+, 3+, respectively. 5-year OS rates in Cldn6 score 3+ group were significantly lower than score 0/1+/2+ groups (5-year OS, 30.0% vs 89.3%,  $P < 0.001$ ). The frequencies of clinical stage III/IV, non-endometrioid adenocarcinoma, histological grade 3, lymphnode metastasis, distant metastasis were significantly higher in Cldn6 score 3+ group than those in score 0/1+/2+ groups. In Brdu and scratch assay, we found that the proliferation potential of the tumor cells was significantly elevated in the CLDN6-overexpressing cell strain. **Conclusion** In UEC, high Cldn6 expression is a very poor prognostic factor.

#### ISP-4-5

**Characterization of a cell line (NOMH-2) originating from a human uterine serous carcinoma** Takashi Yamada *Osaka Medical College*

**Objective** Cell lines are very useful for clinical and basic research. Due to the scarcity of information, the establishment of a uterine malignant tumor cell line with distinctive characteristics is particularly important to study this disease. Thus, this study was undertaken to establish and characterize a new human serous carcinoma of the uterine corpus. **Methods** The cell line NOMH-2 was established from a uterine tumor of a 65-year-old woman. Features of the cell line studied included morphology, chromosome analysis, heterotransplantation, tumor markers, and chemosensitivity. **Results** This cell line has grown well for 23 years and has been subcultured more than 50 times. Monolayer cultured cells are polygonal in shape and appeared to be epithelial showing a tendency to pile up without contact inhibition. The doubling time was 149 hours, the saturation density was  $2.4 \times 10^4/\text{cm}^2$ , the plating efficiency was 13.4% and the mitotic index was 0.5%. The chromosomal number shows aneuploidy and the modal chromosomal number was in the hypohexaploid range. The cells could be transplanted into the subcutis of nude mice and produced tumors resembling the original tumor. NOMH-2 cells ( $2 \times 10^6/5\text{ml}$ ) produced tissue polypeptide antigen (TPA), 1,500 U/mL; CA125; 100 U/mL; CA19-9, 86 U/mL during 5 days in culture media. The cells were sensitive to actinomycin D, cisplatin, carboplatin, mitomycin C by MTT assay. Point mutations were found in MLH-1 and TP53 gene. **Conclusion** NOMH-2 would be very useful for basic research of uterine serous carcinoma.

#### ISP-4-6

**The usefulness of transcervical needle biopsy in uterine body tumors** Shunpei Kato, Iemasa Koh, Satoshi Urabe, Norifumi Tanaka, Maki Hyodo, Eiji Hirata, Yoshiaki Kudo *Hiroshima University Hospital*

**Objective** It is important to assess malignant disease in the decision on a treatment strategy for uterine body tumors. However, myometrial tumors are often difficult to diagnose by means of endometrial cytology or histology. Therefore, we examined the usefulness of transcervical needle biopsy for histopathologic diagnosis. **Subjects and Methods** Of 104 patients who had undergone needle biopsy for uterine tumors, 58 underwent hysterectomy at our Hospital between 2006 and 2016. We compared preoperative needle biopsy and postoperative histopathology findings in these 58 patients. Eleven patients diagnosed with malignant uterine body tumors were further examined retrospectively. We also examined adverse events associated with all 104 needle biopsies. **Results** The diagnostic accuracy for detecting malignancy was 97% (56/58 patients). Of 11 patients diagnosed with malignant uterine body tumors, 9 underwent endometrial cytology. The results were negative for 6 of these patients. Histological types matched in 7 of 11 cases, when comparing needle biopsy and postoperative histopathological findings. Two cases were diagnosed as malignant out of the 4 cases in which histological types did not match. Adverse events associated with needle biopsy were pain and fever, which were observed in 26% (27/104) and 10% (10/104) cases, respectively. Almost all occurrences were mild and improved at follow-up. **Conclusion** Histopathology by needle biopsy may be useful based on its high diagnostic accuracy and safety in cases where malignant uterine body tumors are suspected and diagnosis via endometrial cytology or histology are difficult.

#### ISP-5-1

**Survival analyses based on tumor microenvironment profile in endometrial carcinoma** Shuang Zhang, Takeo Minaguchi, Ayumi Shikama, Shuling Liu, Bouchra Lachkar, Nobutaka Tasaka, Azusa Akiyama, Manabu Sakurai, Sari Nakao, Hiroyuki Ochi, Toyomi Satoh *University of Tsukuba*

**Objective** Tumor microenvironment (TME) including the immune checkpoint system reportedly contributes to prognosis in some kind of tumors. The aim of this study was to investigate the prognostic impact of TME profile in endometrial carcinoma. **Methods** We performed immunohistochemical evaluations of TME biomarkers, PD-L1, CD8, CD68, and VEGF, in 221 endometrial carcinomas. Overall survival (OS) was compared based on the evaluations. Univariate and multivariate analyses of prognostic factors for OS were conducted. **Results** High staining index of PD-L1 in tumor cells showed trends toward better OS ( $p=0.059$ ). High VEGF staining index in tumor cells was significantly associated with worse OS ( $p=0.019$ ). High PD-L1 in tumor-surrounding immune cells showed significant associations with CD8+ tumor-infiltrating lymphocyte count, CD68+ tumor-associated macrophage count, and microsatellite instability ( $p=0.0000003$ ,  $0.00001$ , and  $0.0056$ ), and showed trends towards shorter treatment-free interval after adjuvant chemotherapy ( $p=0.21$ ). Univariate analysis of prognostic factors showed that high PD-L1 in tumor cells was significant for better OS, and high PD-L1 in tumor-surrounding immune cells, older age, advanced FIGO stage, non-endometrioid histology, deep myometrial invasion, and positive lymphovascular space invasion (LVI) were significant for worse OS ( $p=0.007$ ,  $0.043$ ,  $0.000006$ ,  $0.00000002$ ,  $0.0000001$ ,  $0.000007$ , and  $0.0001$ ). Subsequent multivariate analysis revealed that high PD-L1 in tumor cells, older age, advanced stage, non-endometrioid histology, and positive LVI were significant and independent prognostic factors ( $p=0.017$ ,  $0.003$ ,  $0.0004$ ,  $0.001$ , and  $0.038$ ). **Conclusion** Our findings indicate that PD-L1-mediated immune checkpoint system may be contributing to prognosis through regulating TME in endometrial carcinoma, suggesting that inhibitors targeting this system may be efficacious for the subset of patients with the disease.

#### ISP-5-2

**Nanopore sequencing to uncover complex isoforms indicating lymph-node metastasis for endometrial cancer patients** Yosuke Ito, Yasuhisa Terao, Emiko Yoshida, Satoru Takeda *Junendo University Hospital*

**Objective** In a previous study, we found molecular biomarkers that enable prediction of lymph node metastasis of endometrial cancer by using CAGE (Cap Analysis Gene Expression). One of the markers is RNA molecules derived from TACC2 gene, a tumor suppressor. While eight isoforms are reported in TACC2 locus, we discovered that the maker RNAs are transcribed by a novel promoter. Our effort to identify its entire structure by using conventional cloning coupled with Sanger sequencing resulted in a series of distinct isoforms. While this unexpected complexity is quite interesting in terms of transcription and its regulation, it raises an important question in the aspect of application as clinical application: which isoform is the most strongly associated with lymph-node metastasis. **Methods** Oxford Nanopore technology (MinION) to sequence amplicons prepared from the TACC2 locus. The technology enables us to determine long nucleotide sequences (from 6 bases to over 100k bases) with single molecule, while a conventional Sanger sequencer determines 1kbp and a typical "next generation" sequencer in Illumina determines ~300 bases. **Results** We obtained 2,211,504 sequences from amplicons of the TACC2's novel isoform (i.e. starting from the novel 1st exon). The number of reads are 147,434 fold larger than the one of our previous sequencing by Sanger sequencer. **Conclusion** The data set provides us an unique opportunity to confirm the isoforms identified previously, and to explore further novel isoforms.



## ISP-5-3

**Dysadherin regulates cell invasion and might be an independent prognostic factor in uterine endometrial cancer** Kyoko Akashi, Taisuke Mori, Hiroshi Matsushima, Kaori Yoriki, Tetsuya Kokabu, Haruo Kuroboshi, Morio Sawada, Hiroshi Tatsumi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** Dysadherin, one of membrane glycoproteins, is inversely correlated with the expression of E-cadherin and an unfavorable prognostic factor and in some kinds of cancer. However, the significance of dysadherin in uterine endometrial cancer still remains unexamined. The aim of this study is to examine the expression and the function of dysadherin in uterine endometrial cancer. **Methods** Specimens from patients with endometrial cancer were immunohistochemically stained with E-cadherin and dysadherin. A quantitative PCR, Matrigel invasion/migration assay, and scratch assay were performed in endometrial cancer cell lines, Ishikawa less expressing dysadherin, and KLE cells higher expressing dysadherin, transfected with dysadherin plasmid and knocked-down for dysadherin for siRNA. **Results** The research protocol was approved by the Institutional Review Board. Eighty-five specimens from patients with endometrial cancer were examined. Dysadherin was highly expressed in 22.4% (19/85 cases), while E-cadherin was in 54.1% (46/85). There was no inverse association in the expression of dysadherin with E-cadherin. Dysadherin expression was significantly associated with lymphatic metastasis and vascular invasion. Kaplan-Meier analysis revealed dysadherin expression was inversely correlated with progression free survival. In vitro experiment, dysadherin overexpression stimulated invasion and migration in Ishikawa cells, regardless of the proliferative capacity. On the hand, dysadherin knockdown reduced invasiveness and cell motility of KLE cells. **Conclusion** Dysadherin could regulate invasiveness and cell motility leading to be an unfavorable prognosis factor in uterine endometrial cancer.

## ISP-5-4

**The role of myeloid-derived suppressor cells (MDSC) in the induction of endometrial cancer stem cells (CSC)** Eriko Yokoi, Seiji Mabuchi, Naoko Komura, Katsumi Kozasa, Hiromasa Kuroda, Yuri Matsumoto, Michiko Kodama, Kae Hashimoto, Kenjiro Sawada, Tadashi Kimura *Osaka University*

**Objective** To investigate the role of MDSC and 17 $\beta$ -estradiol (E<sub>2</sub>) in the induction of CSC in endometrial cancer. **Methods** CSC was defined as cells with high aldehyde dehydrogenase (ALDH) 1 activity. 1) Tumor samples and clinical data from surgically-treated endometrial carcinoma cases treated from January 2000 to March 2016 were collected. Then, the relationship between the immunoreactivities for G-CSF, CD33, or ALDH1 in tumor, pretreatment white blood cell (WBC) counts, and their prognosis were examined. 2) G-CSF-expressing and Mock-expressing endometrial carcinoma cell lines were established. Cells were subcutaneously inoculated into nude mice. The frequencies of MDSC and CSC in tumors were examined by flow cytometry. 3) MDSC isolated from tumor-bearing mice were co-cultured with endometrial carcinoma cell line in the presence or absence of E<sub>2</sub>. Then the frequencies of CSC were examined. **Results** 1) A positive correlation was demonstrated between the immunoreactivities for G-CSF, ALDH1, CD33 (MDSC marker), and pretreatment WBC count. 2) Increased MDSC and CSC were observed in G-CSF-expressing endometrial cancer cell derived tumors. 3) MDSC induces CSC through the production of PGE<sub>2</sub>. E<sub>2</sub> enhanced the activity of MDSC to induce CSC. **Conclusion** MDSC induced by tumor derived G-CSF, together with E<sub>2</sub>, promote CSC expansion via the production of PGE<sub>2</sub>.

## ISP-5-5

**Over expression of Carbonyl reductase 1 induces MET by suppressing transforming growth factor-beta signaling in uterine leiomyosarcoma cells** Takuya Kajimura, Shun Sato, Kengo Nakashima, Toshiaki Taketani, Koutarou Sueoka, Norihiro Sugino *Yamaguchi University*

**Objective** Carbonyl reductase 1 (CBR1) is an NADPH-dependent, mostly monomeric, cytosolic enzyme. We reported that CBR1 suppresses epithelial-mesenchymal transition (EMT) in uterine cervical squamous cell carcinoma. Uterine sarcoma is one of high grade malignancy tumor. This study investigated whether CBR1 induces mesenchymal to epithelial transition (MET) in uterine sarcoma and inhibits sarcoma's malignant behaviors. **Methods** (1) We established the clone of uterine leiomyosarcoma cell line, SKN, in which CBR1 was over-expressed, and expressions of EMT-related markers and TGF $\beta$  which is well known to induce EMT were analyzed by Western blot and RT-PCR. (2) To investigate whether TGF $\beta$  actually induces EMT in the CBR1-overexpression cells, the cells were treated with TGF $\beta$  (10 ng/ml) for 4 days. Furthermore, to investigate whether suppression of TGF $\beta$  signaling induces MET, SKN cells were treated with TGF $\beta$  receptor blocker (SB431542, 10  $\mu$ M) for 24 h. **Results** (1) In the CBR1-overexpression cells, expressions of epithelial markers of EMT (E-cadherin, cytokeratin) were increased while mesenchymal markers (N-cadherin, fibronectin) were decreased, and also TGF $\beta$  was decreased, indicating that CBR1 induces MET with the decrease in TGF $\beta$ . (2) TGF $\beta$  decreased E-cadherin expression with the increase in snail, a transcription factor to suppress E-cadherin. TGF $\beta$  receptor blocker increased E-cadherin expression with the decrease in snail expression of the TGF $\beta$  signaling induces MET. **Conclusion** CBR1 induces MET by suppressing the TGF $\beta$  signaling, which may inhibit the malignant behaviors in uterine leiomyosarcoma. This study provides a novel therapeutic strategy targeting CBR1 for uterine leiomyosarcoma.

## ISP-5-6

**Prolactin contributes to the cell proliferation of type I endometrial cancer by the regulation of prolactin receptor and estrogen receptor via MAPK signaling pathway** Erdenebaatar Chimeddulam<sup>1</sup>, Munekage Yamaguchi<sup>1</sup>, Fumitaka Saito<sup>1</sup>, Hironori Tashiro<sup>2</sup>, Hidetaka Katabuchi<sup>1</sup> *Kumamoto University<sup>1</sup>, School of Health Science, Kumamoto University<sup>2</sup>*

**Objective** Elevated levels of serum prolactin have been reported to contribute to the tumorigenesis of organs expressing prolactin receptor (PRLR). We previously reported that the expressions of PRLR and pJAK2 in cancer cells were significantly increased in hyperprolactinemic patients with type I endometrial cancer (EC) in the 69th annual congress of Japan Society of Obstetrics and Gynecology. This study aims to elucidate the effect of prolactin on type I EC cell lines. **Methods** Prolactin and/or estradiol (E<sub>2</sub>) were added in culture mediums of EC cell lines (Ishikawa cells and HEC-1). The proliferative ability of cell lines was assessed using MTS assay. The expressions of PRLR, pJak2, pERK1/2, pMEK1/2, and estrogen receptor alpha (ER- $\alpha$ ) were evaluated using western blotting. AG490 (JAK2 inhibitor) or U0126 (MEK1/2 inhibitor) were administered to assess the effect of prolactin on the downstream pathway of PRLR. **Results** MTS assay showed that the proliferative ability of EC cell lines was significantly increased after adding prolactin and/or E<sub>2</sub>. The administration of both prolactin and E<sub>2</sub> was most effective on the proliferative ability. Western blotting revealed that the expressions of PRLR, pJAK2, pERK1/2, pMEK1/2, and ER- $\alpha$  in cell lines were increased after adding prolactin. The concomitant administration of AG490 or U0126 inhibited the increased expressions of those proteins. **Conclusion** Prolactin

modulates the expression of PRLR and ER- $\alpha$  in type 1 EC cells via MAPK signaling. This mechanism may contribute to enhancing their proliferation particularly after adding both prolactin and E<sub>2</sub>. Anti-prolactin drug may be a treatment option for premenopausal women with type 1 EC especially who desire preserving fertility.

### ISP-5-7

**Genetic and epigenetic characterization of young-onset endometrial cancer** Takeshi Makabe<sup>1</sup>, Eri Arai<sup>2</sup>, Akira Hirasawa<sup>1</sup>, Wataru Yamagami<sup>1</sup>, Nobuyuki Susumu<sup>3</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup>, Yae Kanai<sup>2</sup> *Keio University<sup>1</sup>, Department of Pathology, Keio University<sup>2</sup>, International University of Health and Welfare<sup>3</sup>*

**Objective** This study aimed to clarify the genetic and epigenetic features of young-onset endometrial cancer. **Methods** Targeted sequencing of 50 tumor-related genes and single-CpG-resolution genome-wide DNA methylation analysis were performed using the Ion AmpliSeq Cancer HotSpot Panel v2 and the Infinium MethylationEPIC BeadChip, respectively, for 31 samples of normal control endometrium (C) from patients without endometrial cancer, 34 samples of endometrial cancer from patients aged 40 years or less (YE), and 40 samples of endometrial cancer from patients elder than 40 years of age (OE). **Results** There were distinct differences in non-synonymous driver mutations between the YE and OE samples. Principal component analysis revealed distinct DNA methylation profiles of endometrial cancers that differed from those of C samples. There were significant differences in the levels of DNA methylation at 1,034 CpG sites between YE and OE samples, and these were considered to potentially create differences in the expression levels of tumor-related genes, such as those participating in the cell cycle and autophagy. Unsupervised hierarchical clustering analysis of YE-specific DNA methylation profiles clustered the YE samples into Clusters YA (n=22) and YB (n=12). Clinically less aggressive tumors tended to be accumulated in Cluster YB. Eleven marker CpG sites discriminated YB samples from YA samples with 100% sensitivity and specificity. **Conclusion** Genetically and epigenetically different pathways may participate in the development of YEs and OEs. During treatment of YE patients, 11 CpG sites act as biomarkers for predicting patients amenable to fertility preservation.

### ISP-6-1

**A long non-coding RNA "LUCAT1" mediates taxane-resistance acquisition in ovarian cancer** Satoshi Tamauchi, Hiroaki Kajiyama, Nobuhisa Yoshikawa, Fumi Utsumi, Shiro Suzuki, Fumitaka Kikkawa *Nagoya University*

**Objective** Recently, long non-coding RNAs (lncRNAs) have been recognized as key factors of several malignancies. In addition, anticancer drug resistance including taxane is one of the biggest problems in cancer treatment. However, the relationship between lncRNA and taxane resistance has not been reported so far. In this study, we aimed to clarify the relation between lncRNAs and taxane resistance acquisition. **Methods** A microarray was used to identify lncRNA candidates relating taxane resistance, which analyzed gene expression changes in 3 couples of paclitaxel-resistant cell lines and control cell lines. For lncRNAs whose expression changed more than 2-fold, functional analysis was performed. **Results** The microarray revealed that expression of three lncRNAs were increased, and one was decreased more than 2-fold. Of these, knockdown of a lncRNA "LUCAT1" significantly reduced taxane resistance in ovarian cancer cell lines *in vitro* (p<0.05). LUCAT1 might not only promote drug excretion, but also induce microtubule instability and promote taxane resistance. LUCAT1 knockdown also reduced

ability of cell proliferation (p<0.05). **Conclusion** We identified the novel lncRNA "LUCAT1" involved in taxane resistance in ovarian cancer. Taxane resistance is also a serious problem in other malignancies, and further investigation is required.

### ISP-6-2

**CXCL10 works as a tumor promoter in tumor microenvironment in ovarian cancer** Juri Ogishima<sup>1</sup>, Ayumi Taguchi<sup>1</sup>, Kei Kawana<sup>2</sup>, Mitsuyo Yoshida<sup>1</sup>, Akira Kawata<sup>1</sup>, Masakazu Sato<sup>1</sup>, Kensuke Tomio<sup>1</sup>, Katsuyuki Adachi<sup>1</sup>, Takeshi Nagamatsu<sup>1</sup>, Katsutoshi Oda<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Nihon University<sup>2</sup>*

**Objective** CXCL10 is a chemokine which attracts activated T cells into inflammatory environment, however the relationship between its expression and tumor progression remains unclear. We investigated prognostic impact and effects on tumor microenvironment (TME) of CXCL10 in ovarian cancer. **Methods** Ovarian cancer specimens (RNA and paraffin sections) were obtained from 50 patients under informed consent and approval of our ethics committee, for cDNA microarray analysis and immunohistochemical staining of CXCL10. Correlation between CXCL10 expression and clinicopathological findings was assessed with focus on neutrophil-to-lymphocyte ratio. Mice were intraperitoneally injected with KRAS-transfected murine ovarian cancer cell line, ID8-KRAS. Concentration of CXCL10 in ascites was assessed by specific ELISA. DC and T cell subsets were assessed by flow cytometry. **Results** The level of CXCL10 in tumor was significantly higher in serous carcinomas, compared to endometrioid or clear cell carcinomas (serous : 746.7  $\pm$  219.6, endometrioid : 582.0  $\pm$  479.4, clear cell : 360.6  $\pm$  135.9, Wilcoxon-test, p<0.05). Immunohistochemistry revealed CXCL10 was mainly expressed in cancer cells, not in stromal cells. Overall and progression free survival were significantly lower in CXCL10-high group, compared to CXCL10-low group (log-rank test : p=0.02, p=0.01, respectively). Neutrophil-to-lymphocyte ratio was significantly higher in CXCL10-high group, compared to CXCL10-low group. *In vivo*, expression of CXCL10 in ascites was significantly increased accompanied with decreased number of cDCs and Tim-3+PD-1+CD8+-exhausted T cells along with tumor progression. **Conclusion** Higher level of CXCL10 was associated with poor prognosis in ovarian cancer. CXCL10 might modulate TME and promote tumor progression.

### ISP-6-3

**CXCL17, as a key regulator of microenvironment, promotes peritoneal dissemination in ovarian cancer** Akira Kawata<sup>1</sup>, Ayumi Taguchi<sup>1</sup>, Juri Ogishima<sup>1</sup>, Mitsuyo Yoshida<sup>1</sup>, Hiroe Nakamura<sup>1</sup>, Masakazu Sato<sup>1</sup>, Kensuke Tomio<sup>1</sup>, Katsuyuki Adachi<sup>1</sup>, Katsutoshi Oda<sup>1</sup>, Kei Kawana<sup>2</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Nihon University<sup>2</sup>*

**Objective** Tumor Associated Macrophage (TAM) and Myeloid-derived suppressor cell (MDSC) are known to promote anchorage-independent proliferation of cancer cells via activation of EGF/FGF signaling. In ovarian cancer, spheroid formation of cancer cells is essential for progression of peritoneal dissemination. We herein investigated the association of CXCL17, a chemokine, with TAM and MDSC, and its role on spheroid formation in ovarian cancer progression. **Methods** Mice were intraperitoneally injected with a KRAS-transfected mouse ovarian cancer cell line, ID8-KRAS, under approval of institutional ethics committees. Spheroid formation was assessed *in vitro* under EGF/FGF treatment. cDNA microarray was analyzed for 2 D-cultured or 3D-cultured tumor cells *in vitro*. *In vivo* time course analysis of tumor microenvironment (TME) such as TAM and MDSC, was investigated using flow cytometry. We

evaluated effects of CXCL17 level on tumor progression and alteration of TME with a CXCL17 knockdown cell line (shCXCL17-ID8KRAS) established by shRNA technique. **Results** EGF/FGF treatment markedly promoted spheroid formation *in vitro*. In 3D condition, 1,653 genes were upregulated, compared to 2D condition. Especially, CXCL17 expression was increased by 8 times. CXCL17 was also upregulated in peritoneal floating cancer cells *in vivo*. MDSC fraction was significantly increased along with the tumor progression (control vs ID8-KRAS : 0.3% vs 8.6%). shCXCL17-ID8KRAS significantly suppressed tumor progression, accompanied with decreased number of MDSCs in ascites. **Conclusion** Our findings suggest that transformation-induced chemokine, CXCL17, may promote peritoneal dissemination in ovarian cancer, mainly through spheroid formation via CXCL17-attracted MDSCs and EGF/FGF signaling.

#### ISP-6-4

**Antisense oligo nucleotide of Annexin A4 improves platinum resistance in ovarian clear cell carcinoma** Reisa Kakubari, Satoshi Nakagawa, Eiji Kobayashi, Shinya Matsuzaki, Yutaka Ueda, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** Annexin A4 is overexpressed in ovarian clear cell carcinoma (OCC) and contributes to chemoresistance. Our object is to develop the antisense oligonucleotides (ASOs) targeting Annexin A4 to improve chemosensitivity in OCC. **Methods** We used ASO targeting mRNA of Annexin A4 with 2,4-bridged nucleic acid. Gene suppression efficiency of Annexin A4 in ASO-transfected cell line was analyzed by real time PCR *in vitro*. In 16 types of ASOs targeting Annexin A4, 2 ASOs had strong gene suppression effect. We analyzed suppression of Annexin A4 in ASO-transfected RMG-I, OVISE cell lines (CCC) *in vitro*. Drug resistance for platinum was analyzed with IC50 values and intracellular accumulation of platinum. We used ICR nu/nu mice subcutaneously xenografted with CCC cell lines to assess the improvement of platinum resistance *in vivo* and also determined the adverse event of ASO against the tumor-infiltrated macrophages and NK cells by FACS analysis. Intraperitoneal injection of cisplatin 3mg/kg after intratumoral administration of ASO 1mg/kg each twice a week were given to xenografted mice and tumor volumes were monitored. **Results** Annexin A4 ASO effectively suppressed Annexin A4 expression *in vitro*. As we expected, Annexin A4 ASO-transfected cells were significantly resistant to cisplatin (IC50=3.3 $\mu$ M) compared control (IC50=5.2 $\mu$ M) in RMG-1 cell line. Intracellular platinum accumulation increased in Annexin A4 ASO transfection cell. Intratumoral administration of Annexin A4 ASO significantly improved platinum sensitivity *in vivo*. **Conclusion** Annexin A4 ASO improved chemosensitivity by suppressing Annexin A4 expression both *in vitro* and *in vivo*. Targeting Annexin A4 by ASO would be a promising therapeutic option for chemoresistant OCC.

#### ISP-6-5

**Histone methyltransferases are the candidate therapeutic targets in high-grade serous ovarian carcinoma (HGSC)** Asako Kukita, Kenbun Sone, Katsutoshi Oda, Hidenori Machino, Machiko Kojima, Shinya Oki, Michihiro Tanikawa, Kazunori Nagasaka, Yoko Matsumoto, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Dysregulation of histone methylation could be involved in human carcinogenesis. Several histone methyltransferases have been reported to be overexpressed in various types of cancers. However, there have been no reports of comprehensive analysis of histone methyltransferases in HGSC. The aim of this study is to elucidate the dysregulation of methyltransferases in HGSC. **Methods** We screened 9 methyltransferases,

which are reported as overexpressed in other human cancers. We analyzed the expression of these genes by quantitative real-time PCR (q-PCR) with 39 clinical specimens of HGSC. Written informed consent was obtained from all participants and this study was approved by our ethics committee. We performed knockdown experiments using siRNA against histone methyltransferases and control siRNA (siNC) in HGSC cell lines. The anti-tumor effects were examined with immunoblotting, MTT assay, cell cycle analysis, and Annexin V-FITC. **Results** Q-PCR revealed that 6 out of 9 methyltransferases (including) were overexpressed in clinical HGSC specimens ( $P < 0.01$ ), compared with a normal ovarian tissue specimen. In addition, knockdown of several histone methyltransferases using specific siRNAs resulted in growth suppression and apoptosis induction of HGSC cells, accompanied by attenuation of histone methylation. **Conclusion** The present findings highlight that overexpressed histone methyltransferases are involved in HGSC tumorigenesis and that several histone methyltransferases might be novel candidates for treating HGSC.

#### ISP-6-6

**Clinicopathological characteristics of clear cell ovarian carcinomas without any mutations in ARID1A and PIK3CA** Akira Nishijima<sup>1</sup>, Katsutoshi Oda<sup>1</sup>, Kosei Hasegawa<sup>2</sup>, Kayo Asada<sup>1</sup>, Akira Kurosaki<sup>2</sup>, Takahiro Koso<sup>1</sup>, Aki Miyasaka<sup>2</sup>, Yuji Ikeda<sup>2</sup>, Keiichi Fujiwara<sup>2</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Saitama Medical University International Medical Center<sup>2</sup>*

**Objective** Approximately 50% of clear cell ovarian carcinomas (CCOC) harbor mutations of ARID1A and PIK3CA, and coexistence of these mutations is frequent. However, the biological characteristics of CCOC which lacks mutations in ARID1A and PIK3CA ("double-negative" genotype) have not been fully understood. We aimed to clarify the clinicopathological characteristics of "double-negative" CCOC. **Methods** We performed whole-exome sequencing in 78 CCOC surgical specimens under informed consent and approval of our ethics committee. We analyzed the clinicopathological characteristics of "double-negative" group, and pathologically reviewed all the "double-negative" CCOC samples. **Results** We identified ARID1A and/or PIK3CA mutations in 57 CCOC samples, which classified 21 tumors as "double-negative" group. The "double-negative" group showed significantly poor progression-free survival ( $p=0.0052$  by Log-rank test), with higher ratio of TP53 mutations (29%), compared with the other group (1.8%) ( $p=0.0012$  by Fisher's exact test). Pathological review revealed that six out of 21 (28%) "double-negative" group partially contained components which are suspicious of high-grade serous carcinomas ("SC like" group). TP53 was mutated in 3 of 6 "SC like" group (50%) and in 2 of 15 (13%) in the remaining 15 samples ("non-SC like" group) ( $p=0.11$ ). High-grade nuclear atypia (Grade 3) was more common in "SC-like" group, compared with the "non-SC like" group (83% vs 33%,  $p=0.063$ ). **Conclusion** Genotyping by mutational status of ARID1A and PIK3CA may be useful to identify CCOC with more aggressive biology. Our data suggest that "double-negative" CCOC includes certain tumors with biological similarity to high-grade serous carcinomas with TP53 mutations.

#### ISP-6-7

**Ultrasound-based logistic regression model LR2 versus magnetic resonance imaging for discriminating between benign and malignant adnexal masses : a prospective study** Kanae Shimada<sup>1</sup>, Koji Matsumoto<sup>1</sup>, Takashi Mimura<sup>1</sup>, Chiaki Iitsuka<sup>1</sup>, Shingo Miyamoto<sup>1</sup>, Tetsuya Ishikawa<sup>1</sup>, Mamiko Onuki<sup>1</sup>, Kiyotake Ichizuka<sup>1</sup>, Hajime Tsunoda<sup>2</sup>, Akihiko Sekizawa<sup>1</sup> *Showa*

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**Objective** The diagnostic performances of the International Ovarian Tumor Analysis (IOTA) ultrasound-based logistic regression model (LR2) and magnetic resonance imaging (MRI) in discriminating between benign and malignant adnexal masses have not been directly compared in a single study. **Methods** Using IOTA LR2 model and subjective interpretation of MRI findings by experienced radiologists, 265 consecutive patients with adnexal masses were preoperatively evaluated in two hospitals between February 2014 and December 2015. Definitive histologic diagnosis of excised tissues was used as a gold standard. **Results** From the 265 study subjects, 54 (20.4%) tumors were histologically diagnosed as malignant (including 11 borderline and 3 metastatic tumors). Preoperative diagnoses of malignant tumors showed 91.7% total agreement between IOTA LR2 and MRI, with a kappa value of 0.77 (95% confidence interval [CI] : 0.68–0.86). Sensitivity of IOTA LR2 (0.94, 95% CI : 0.85–0.98) for predicting malignant tumors was similar to that of MRI (0.96, 95% CI : 0.87–0.99;  $P=0.99$ ), while specificity of IOTA LR2 (0.98, 95% CI : 0.95–0.99) was significantly higher than that of MRI (0.91, 95% CI : 0.87–0.95;  $P=0.002$ ). Combined IOTA LR2 and MRI results gave the greatest sensitivity (1.00, 95% CI 0.93–1.00) and had similar specificity (0.91, 95% CI 0.86–0.94) to MRI. **Conclusion** The IOTA LR2 model had a similar sensitivity to MRI for discriminating between benign and malignant tumors and a higher specificity compared with MRI. Our findings suggest that IOTA LR2 model, either alone or in conjunction with MRI, should be included in preoperative evaluation of adnexal masses.

### ISP-6-8

**Combination of MDM2 inhibitor, DS-3032b, and mTOR inhibitor, everolimus, exerts antitumor effect in ovarian and renal clear cell carcinomas** Yoshiko Kawata, Kazunori Nagasaka, Katsutoshi Oda, Shinya Oki, Makoto Takeuchi, Chinami Makii, Michihiro Tanikawa, Kenbun Sone, Yoko Matsumoto, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Both MDM2 overexpression and activation of mTOR pathway are frequent in clear cell carcinomas of the ovary and kidney. We aimed to clarify anti-tumor effect of inhibition of MDM2 and mTOR in ovarian and renal clear cell carcinomas with wild-type p53. **Methods** We investigated the effect of either MDM2 inhibitor (DS-3032b) or mTOR inhibitor (everolimus) in 8 ovarian (OVISe, OVTOKO, RMG-1, JHOC7, OVMANA, JHOC9, ES2, SKOV3) and 2 renal (Caki-1, Caki-2) cell clear cell carcinoma lines. The cell viability was evaluated by MTT assay and flow cytometry. In vivo anti-tumor effect was investigated by oral administration of (i) DS-3032b at 50 mg/kg/day, (ii) everolimus at 5 mg/kg/day, or (iii) combination of these two drugs for 3 weeks in mouse xenograft models. **Results** Dose-dependent suppression of cell proliferation by DS-3032b was observed only in cells with wild-type p53 (Median  $IC_{50}$  : 181.8 nM), while sensitivity to everolimus was generally observed in clear cell carcinoma cells, regardless of p53 mutational status (Median  $IC_{50}$  : 728.6 nM). The  $IC_{50}$  values of DS-3032b were drastically decreased when combined with 1 nM of everolimus. Combination of DS-3032b and everolimus increased the ratio of apoptotic cells in wild-type p53 cancer cells. In mouse xenograft models, oral administration of combination DS-3032b and everolimus significantly suppressed the tumor growth, compared with each single agent alone ( $p<0.05$ ). **Conclusion** Our data suggest that co-targeting MDM2 and mTOR signaling might be a promising novel therapy for wt-p53 clear cell carcinomas of both ovary and kidney.

### ISP-6-9

**The impact of UGT1A1 genotype upon prognoses of the patients with ovarian clear cell carcinomas—a historically controlled study**— Masashi Takano<sup>1</sup>, Tomoyuki Yoshikawa<sup>1</sup>, Morikazu Miyamoto<sup>2</sup>, Tadashi Aoyama<sup>2</sup>, Hiroaki Soyama<sup>2</sup>, Kento Kato<sup>2</sup>, Takahiro Sakamoto<sup>2</sup>, Kazuki Takasaki<sup>2</sup>, Mika Kuwahara<sup>2</sup>, Tomoko Goto<sup>2</sup>, Hidenori Sasa<sup>2</sup>, Kenichi Furuya<sup>2</sup> *Department of Tumor Chemotherapy, National Defense Medical College Hospital<sup>1</sup>, National Defense Medical College Hospital<sup>2</sup>*

**Objective** Genotyping of UGT1A1\*28 and \*6 was supported by national insurances since 2008 in Japan, however, there still exists argument over clinical application of the genotyping. The aim of the study was to evaluate the clinical significance of UGT1A1 upon prognoses of the patients with ovarian clear cell carcinomas. **Methods** Medical records of the patients with ovarian clear cell carcinoma that met inclusion criteria were reviewed (UGT group) : (a) those whose UGT1A1 genotype were available, (b) those treated with irinotecan-based therapy. For historical-control group (Non-UGT group), the patients treated with irinotecan-based therapy without UGT1A1 genotyping were evaluated. The study protocol was approved by the IRB of our hospital. **Results** A total of 17 cases with UGT-group and 37 cases with non-UGT group patients were analyzed. There were no significant difference clinical parameters including age, stage distribution. UGT-group included 8 cases with wild-type, 8 cases with hetero-type, and one case with homo-type genotype. There was no significant difference of progression-free survival in stage I patients between UGT group and non-UGT group. Among UGT-group Stage I patients, recurrence was observed in 67% (2/3) in wild-type cases, and 14% (1/7) in hetero/homo-type patients ( $p=0.097$ ). Additionally, G4 hematologic toxicities were frequently observed in hetero/homo-type patients. **Conclusion** Although significance was not observed, recurrence was frequently observed in the patients with UGT1A1 wild-type patients compared with UGT1A1 hetero/homo-type patients. The doses of irinotecan-based therapy might be lower for the UGT1A1 wild-type patients with ovarian clear cell carcinomas, although further studies are needed to confirm the results.

### ISP-7-1

**CRISPR/Cas9-mediated genome editing and efficient PD-L1 disruption on tumor cells promote antitumor immunity and suppress ovarian cancer progression in a mouse model** Tamaki Yahata, Naoyuki Iwahashi, Mika Mizoguchi, Madoka Yamamoto, Noriyuki Sasaki, Michihisa Shiro, Yasushi Mabuchi, Shigetaka Yagi, Sawako Minami, Kazuhiko Ino *Wakayama Medical University*

**Objective** Programmed cell death ligand 1 (PD-L1) on tumor cells unfavorably impacts patient prognosis. However, the functional roles of PD-L1 in ovarian cancer progression remain unclear. In this study, we examined the pathophysiological roles of PD-L1 in ovarian cancer. **Methods** Under the approval of institutional committee, PD-L1 was genetically disrupted in murine ovarian cancer cell lines, ID8 and HM-1, using CRISPR/Cas9-mediated genome editing. The generated PD-L1 knockout (KO) ovarian cancer cells and control cells were intraperitoneally inoculated into syngeneic mice, and survival time and tumor dissemination were evaluated. Moreover, intratumoral lymphocyte recruitment and cytokine levels were analyzed by immunohistochemistry and RT-PCR. **Results** The survival time was significantly longer in PD-L1 KO ID8 inoculated group compared with control group. The tumor weight and ascites volume were significantly reduced in PD-L1 KO ID8 and PD-L1 KO HM-1 groups compared with control groups. Immunohistochemically, the number of intratumoral CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, and NK cells was significantly increased in PDL1 KO ID8 and HM-1



groups compared with in control groups. In contrast, the number of regulatory T cells was significantly reduced in PDL1 KO groups. The intratumoral gene expression of IFN- $\gamma$ , TNF- $\alpha$ , IL-2, and IL-12a was significantly higher, whereas IL-10, VEGFa, and MMP9 were significantly reduced in PDL1 KO ID8 group compared with control. **Conclusion** CRISPR/Cas9-mediated PD-L1 disruption promoted antitumor immunity by increasing tumor-infiltrating lymphocytes and modulating cytokine production, thereby suppressing ovarian cancer progression. This suggests that PD-L1-targeted therapy by genome editing may be a novel therapeutic strategy for ovarian cancer.

### ISP-7-2

**Exosomal miR-99a-5p is upregulated in ovarian cancer patients' sera and enhance PAI-1 expression in neighboring peritoneal mesothelial cells to facilitate cancer invasion** Akihiko Yoshimura, Kenjiro Sawada, Koji Nakamura, Aasa Shimizu, Masaki Kobayashi, Mayuko Miyamoto, Erika Nakatsuka, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Tadashi Kimura *Osaka University*

**Objective** RNA-containing exosomes in circulating blood are emerging as potential target for disease diagnosis. The purpose of this study was to identify which miRNAs are highly produced from ovarian cancer (OC), to analyze whether serum miRNA can detect OC, and to examine the functional role of these miRNAs. **Methods** Using miRNA microarray, we found that several miRNAs including miR-99a-5p were specifically elevated in exosomes derived from OC. Expression level of serum miR-99a-5p of 58 patients with OC, 26 patients with benign ovarian tumor and 20 healthy controls were determined by miRNA qRT-PCR. To examine the role of miR-99a-5p in peritoneal dissemination, human peritoneal mesothelial cells (HPMCs) were transfected with miR-99a-5p mimic and the effect of cell invasion and proliferation was analyzed. Proteomic analysis with transfected HPMC was performed using tandem mass tag method. **Results** Serum miR-99a-5p levels were significantly increased in OC patients compared with those with benign tumor and healthy controls (2.1-fold and 4.0-fold, respectively). ROC analysis showed that using a cut-off of 1.57, the sensitivity and specificity were 78% and 68% respectively for detecting OC (AUC 0.78). The cell invasion was significantly increased through HPMC transfected with miR-99a-5p compared with negative control. Plasminogen activator inhibitor-1 (PAI-1) expression was increased in HPMC transfected with miR-99a-5p. **Conclusion** Serum miR-99a-5p was increased in OC patients and has the potential to predict OC. Exosomal miR-99a-5p promotes cell invasion by affecting HPMC through PAI-1 upregulation.

### ISP-7-3

**Induction of anti-VEGF therapy resistance by upregulated expression of microseminoprotein (MSMP)** Takashi Mitamura *Hokkaido University Hospital*

**Objective** Anti-VEGF therapy has demonstrated efficacy in treating human metastatic cancers, but therapeutic resistance is a practical limitation and most tumors eventually become unresponsive. **Methods** To identify microenvironmental factors underlying the resistance of cancer to anti-angiogenesis therapy, we conducted genomic analyses of intraperitoneal ovarian tumors in which adaptive resistance to anti-VEGF therapy (B20 antibody) developed. **Results** We found that expression of the microseminoprotein, prostate-associated (MSMP) gene was substantially upregulated in resistant compared to control tumors. MSMP secretion from cancer cells was induced by hypoxia, triggering MAPK signaling in endothelial cells to promote tube formation in vitro. Recruitment of the transcriptional repressor CTCF to the MSMP enhancer region was decreased by histone

acetylation under hypoxic conditions in cancer cells. MSMP siRNA, delivered in vivo using the DOPC nanoliposomes restored tumor sensitivity to anti-VEGF therapy. In ovarian cancer patients treated with bevacizumab, increased expression of MSMP was associated with significantly reduced disease-free survival in ovarian cancer patients given bevacizumab. **Conclusion** These findings imply that MSMP inhibition combined with the use of anti-angiogenesis drugs may be a new strategy to overcome resistance to anti-angiogenesis therapy.

### ISP-7-4

**Genomic alterations of tumor-related pathways suppresses a mitochondrial function through the activation of PDK2 in ovarian clear cell carcinoma** Sachiko Kitamura, Ken Yamaguchi, Ryusuke Murakami, Kaoru Abiko, Junzo Hamanishi, Tsukasa Baba, Noriomi Matsumura, Masaki Mandai *Kyoto University*

**Objective** Although various molecular targeting therapies have been developed, cancer cells can survive for escaping from targeting the specific pathway. Targeting metabolism is an attractive strategy to overcome this problem because tumor-related pathways regulate metabolism. We previously reported cancer-specific metabolism regulated by HNF1B pathway and the activation of KRAS-PIK3CA-AKT1-PTEN and MYC-CDK2/4-RB1 pathways in ovarian clear cell carcinoma (OCCC). The aim of this study is to identify universal metabolic targets induced by genomic alterations which render chemoresistance in OCCC. **Methods** 39 OCCC clinical samples and 13 OCCC cell lines were analyzed by whole exome sequencing and gene expression microarray. Immunohistochemistry, cell viability assay, apoptosis assay and in vivo a mouse xenograft model experiments were conducted. **Results** Chromosome (chr) 17q21-24 was significantly amplified in recurrent cases and the genes associated with mitochondrion were significantly enriched in chr17q21-24 amplified cases. Cell viability assay revealed chr17q21-24 amplification correlated with resistance to cisplatin. Pyruvate dehydrogenase kinase 2 (PDK2) located on chr17q21 regulates pyruvate entering into TCA cycle in mitochondrion. Inhibitors targeting the pathway in PIK3CA-AKT, MDM2-TP53 or MYC-RB1 reduced PDK2 expression. Immunohistochemistry showed high PDK2 expression was associated with poor prognosis. Knock down of PDK2 by short hairpin targeting PDK2 and the inhibitor, dichloroacetate (DCA), increased cisplatin sensitivity by upregulation of mitochondrial ROS production. A mouse xenograft model showed DCA synergistically inhibited tumor growth with cisplatin. **Conclusion** Genomic alterations of tumor-related pathways leading to upregulation of PDK2 expression rendered OCCC platinum-resistance. Targeting metabolism such as PDK2 is a new therapeutic strategy for OCCC.

### ISP-7-5

**Role of RNA chaperones in ovarian cancer metastasis** Mahy Egiz<sup>1</sup>, Kazuyuki Kitatani<sup>2</sup>, Masafumi Toyoshima<sup>1</sup>, Masumi Ishibashi<sup>1</sup>, Shogo Shigeta<sup>1</sup>, Junko Minato<sup>1</sup>, Nobuo Yaegashi<sup>1</sup> *Tohoku University<sup>1</sup>, Tohoku Medical Megabank Organization<sup>2</sup>*

**Objective** The lethality of ovarian carcinoma primarily stems from the inability to detect the disease at an early, organ-confined stage, and the lack of effective therapies for advanced-stage disease. Ovarian cancer metastasis requires many cellular processes such as cellular ability to form lamellipodia, to migrate from the primary site and to invade surrounding tissues. La related protein (LARP) 4 was described as one of the novel regulators for cytoskeletal organization, cell morphology and migration. Here, we report on LARP4 role in epithelial ovarian cancer progression. **Methods** SKOV3 cells were transfected with siRNA directed against LARP4, lamellipodia determined

with confocal microscopy, cell migration assessed by transwell assay. Rho proteins expression was detected by western blotting. Furthermore, metastatic potential in xenograft model was determined by counting metastatic nodules in the peritoneum. **Results** LARP4 knockdown significantly increased lamellipodia formation and cell migration. LARP4 knockdown upregulated Rho family proteins expression. Furthermore, in a LARP4 depleted xenograft model there was a significant increase in metastatic nodules number. **Conclusion** LARP4 is proposed to serve as a metastasis-suppressor protein in ovarian cancer. Rho family is a possible target for LARP4.

### ISP-7-6

**CD141<sup>+</sup> Dendritic cells in ovarian cancer microenvironment**  
Rin Mizuno, Kaoru Abiko, Tsukasa Baba, Junzo Hamanishi, Ryusuke Murakami, Masaki Mandai *Kyoto University*

**Objective** Patients with higher CD8<sup>+</sup> T cell numbers in the ovarian tumor exhibit better prognosis, but the functions of CD8<sup>+</sup> T cells are inhibited in the tumor environment by various factors. Dendritic cell (DC)-mediated cross-presentation of exogenous antigens to CD8<sup>+</sup> T cells is necessary for inducing antitumor immunity. The aim of this study is to investigate the function of DCs, especially CD141<sup>+</sup> DCs reported to traffic tumor antigens. **Methods** The immunostaining of anti-CD141 and anti-CD8 in paraffin-embedded sections of ovarian cancer clinical samples was performed to evaluate CD141<sup>+</sup> DC and CD8<sup>+</sup> T cells. The number of cells was counted at x400 magnification and the average number of five areas was determined. We evaluated the CD141<sup>+</sup> DC in relations with CD8<sup>+</sup> T cells and clinical background. **Results** The numbers of CD141<sup>+</sup> DC was significantly high in advanced cases (clinical stage I/II vs III/IV,  $p < 0.05$ ). Progression-free survival of the patients with higher number of CD141<sup>+</sup> DC tended to be longer than that of the patients with lower numbers ( $p = 0.13$ ). Patients with higher number of CD141<sup>+</sup> DC tended to have more CD8<sup>+</sup> T cells in stroma of the ovarian tumor ( $p = 0.08$ ). **Conclusion** Tumor-infiltrating CD141<sup>+</sup> DC in ovarian cancer may play important role in uprising anti-tumor immunity by CD8<sup>+</sup> T cells.

### ISP-7-7

**A Machine Learning Algorithm Using Blood Biomarkers for Diagnostic and Prognostic Prediction in Epithelial Ovarian Cancer**  
Junya Tabata<sup>1</sup>, Nozomu Yanaiharu<sup>1</sup>, Chihiro Goto<sup>1</sup>, Yuka Akiyama<sup>1</sup>, Ryosuke Saito<sup>1</sup>, Hiromi Komazaki<sup>1</sup>, Yasushi Iida<sup>1</sup>, Motoaki Saito<sup>1</sup>, Hirokuni Takano<sup>1</sup>, Seiji Isonishi<sup>1</sup>, Eiryo Kawakami<sup>2</sup>, Aikou Okamoto<sup>3</sup> *The Jikei University School of Medicine<sup>1</sup>, RIKEN<sup>2</sup>*

**Objective** We aimed to develop an ovarian cancer specific predictive algorithm for the pretreatment estimation of clinical stage, histotypes, and prognosis of patients with epithelial ovarian cancer (EOC) based on machine learning from multiple biomarkers available from peripheral blood tests. **Methods** We analyzed 334 patients with EOC and 101 patients with benign ovarian tumors who were treated between 2010 and 2017. We retrospectively investigated 38 parameters from pretreatment peripheral blood tests. Either one of four supervised machine learning classifiers including Bayesian, Neural networks, Random forests, and support vector machines was subjected to a "training and test" approach. **Results** Machine learning based classification could distinguish EOC from benign tumors at a precision of 91% predictive value. However, the preciseness of predicted staging and histotypes were 77% and 58%, respectively. Values for platelet, fibrinogen, and hemoglobin, in addition to tumor markers, were central factors for classifying histotype. Furthermore, using Random Survival Forests analysis, we identified factors (total protein, C-reactive protein, carbohy-

drate antigen 125, lactate dehydrogenase, blood urea nitrogen, and albumin) strongly associated with prognosis in patients with EOC. Supervised clustering analysis based on these factors identified two distinct clusters in which patients survival statistically differed. **Conclusion** It may be possible to select personalized treatment options by stratifying the prognosis of pretreatment patients with EOC using machine learning based predictive algorithms.

### ISP-7-8

**Diagnosis of early stage ovarian clear cell carcinoma (CCC) and endometrioid carcinoma (EMC) - the combination assay of A2160 (Alpha-chain of Complement 4-Binding Protein with Fully-Sialylated Glycans) and C4BP with all types of glycans (ALL-C4BP) - Masaru Hayashi, Hiroko Machida, Tetsuji Iida, Masae Ikeda, Masako Shida, Takeshi Hirasawa, Mikio Mikami *Tokai University Hospital***

**Objective** For detecting early stage CCC, we developed the novel marker A2160, which can be potentially applied for the monitoring of endometrioma patients (*Gynecol Oncol*, 2015; 139: 520-8). To upgrade the diagnostic utility of A2160 between endometrioma, early stage CCC and EMC, we tried to examine the combination assay of A2160 and ALL-C4BP (COMB). **Methods** A total of 62 patients who had CCC (n=38) or EMC (n=14) or endometrioma (n=10) were enrolled in the study from 2009 to 2014. Serum A2160 was measured by LC-MS (Liquid chromatography mass spectrometry), and ALL-C4BP values were measured by ELISA. Diagnostic accuracy of the combination of A2160 and ALL-C4BP (COMB) was compared by AUC. The COMB value was statistically calculated by the formula, COMB = [A2160] × 2.0 - [All-C4BP]. **Results** COMB was significantly higher in early stage of CCC and EMC than in endometrioma ( $p < 4.8 \times 10^{-5}$  and  $p < 0.003$ ). Diagnostic accuracy of COMB to distinguish early stage CCC from endometrioma was higher than that of A2160 or ALL-C4BP only: AUC for ALL-C4BP, A2160 only versus COMB, 82, 90, versus 92%. Diagnostic accuracy of COMB to distinguish early stage EMC from endometrioma was higher than that of A2160 or ALL-C4BP only: AUC for ALL-C4BP, A2160 only versus COMB, 81, 80, versus 86%. **Conclusion** This combination assay can potentially be applied for monitoring of endometrioma patients and make the early diagnosis of CCC and EMC possible.

### ISP-7-9

**Ex vivo chemosensitivity assay using patient-derived spheroids of ovarian cancer**  
Yu Ito<sup>1</sup>, Satoshi Kubota<sup>2</sup>, Yumiko Kiyohara<sup>3</sup>, Shinya Matsuzaki<sup>1</sup>, Eiji Kobayashi<sup>1</sup>, Toshihiro Kimura<sup>3</sup>, Yutaka Ueda<sup>1</sup>, Kiyoshi Yoshino<sup>1</sup>, Shoji Kamiura<sup>3</sup>, Tadashi Kimura<sup>1</sup>, Masahiro Inoue<sup>3</sup> *Osaka University<sup>1</sup>, Research Center, Osaka Medical Center for Cancer and Cardiovascular Diseases<sup>2</sup>, Osaka Medical Center for Cancer and Cardiovascular Diseases<sup>3</sup>*

**Objective** The aim of this study is to evaluate the clinical relevance of a newly developed chemosensitivity assay in ovarian cancer. **Methods** We previously developed cancer tissue-originated spheroid (CTOS) method, a primary 3D culture system to prepare cancer cells from patient tumors. In this study, we conducted sensitivity assay for paclitaxel and carboplatin using CTOSs from ovarian cancer. Single CTOS was placed in one well of a 96-well plate, and five CTOS were examined for one dose of each drug. After 7 days of culture, CTOS viability was evaluated by measuring intracellular ATP levels, corrected by the CTOS size at day 0. **Results** We prepared CTOSs from 45 ovarian cancer. The overall success rate of CTOS formation and culture was 100% (45 out of 45). Characteristics of the original tumors were well retained in CTOS. Among these 45 cases, pa-

tients diagnosed with FIGO Stage IC–IV and underwent TC chemotherapy were 32 cases. The overall success rate of sensitivity assay was 90.6% (29 out of 32). The success of the sensitivity assay depended on the amount of specimen. There were substantial differences in sensitivity among the CTOSs from different patients. These results might reflect the clinical diversity in chemosensitivity to paclitaxel and carboplatin among patients. In some cases, the assay results corresponded with their clinical courses. **Conclusion** We are assessing the correlation between *ex vivo* sensitivity assay and clinical patient response. Sensitivity assays using CTOS from ovarian cancer might be useful in precision medicine.

### ISP-8-1

**Lysosomal function estimated through the autophagic features in ovarian carcinoma** Koji Kumagai, Masahiro Sakai, Takayoshi Maeda *Osaka Railway Hospital*

**Objective** Many cancer cells increase the number of lysosomes to maintain homeostasis by the degradation and recycling of essential nutrients. Ovarian cancer has 2 major distinct subtypes: high-grade serous carcinoma (HGSC) and clear cell carcinoma (CCC). Recent reports demonstrate that autophagic tumor stroma provide recycled nutrients for cancer cell metabolism. In this study, we estimated the lysosomal function through the autophagic features in ovarian HGSC and CCC. **Methods** This study was approved by the institutional ethics committee. We evaluated the expression of microtubule-associated protein 1 light chain 3 (LC3) and pan cathepsin (panCat), 2 representative proteins of early- and late-stage autophagy (i.e. autophagosome and autolysosome), respectively, by immunohistochemical analysis of paraffin-embedded HGSC and CCC tissue sections. Then we speculated the lysosomal function in those carcinomas. **Results** The average age of the patients with HGSC (n=6) and CCC (n=6) was 73 and 60 years, respectively, and the number of cases of FIGO clinical stage I, II, III, and IV tumors was 0, 0, 6, 0 and 4, 0, 2, 0, respectively. Consequently, 2 patients with HGSC and 2 with CCC died of the disease. Strong LC3 and panCat expression was detected in the tumor stromal cells of 83% (5/6) and 100% (6/6) of patients with HGSC and 66% (4/6) and 50% (3/6) of patients with CCC. These data suggested the lysosomal involvement between the early- and late-stage autophagy both in HGSC and in CCC. **Conclusion** We estimate the lysosomal involvement between the early- and late-stage autophagy in HGSC and CCC.

### ISP-8-2

**Overexpression of histone methyltransferases is involved in the proliferation of ovarian clear cell carcinomas** Machiko Kojima, Kenbun Sone, Katsutoshi Oda, Asako Kukita, Hidenori Machino, Shinya Oki, Michihiro Tanikawa, Kazunori Nagasaka, Yoko Matsumoto, Osamu Hiraike, Yuta Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Dysregulation of histone methylation is involved in the development and progression of cancer. Several histone methyltransferases have been reported to be overexpressed in various types of cancers. Meanwhile, there are no reports of comprehensive analysis of histone methyltransferases in ovarian clear cell carcinomas (OCCC). We investigated the involvement of histone methyltransferases in OCCC and evaluated their therapeutic potential. **Methods** We screened 9 histone methyltransferases, which were reported to be overexpressed in human cancer. We analyzed expression of these genes by quantitative real-time PCR (q-PCR), in 23 clinical OCCC specimens under informed consent and approval of our ethics committee. Anti-tumor effect of histone methyltransferases was evaluated by knockdown experiments using siRNAs against

these histone methyltransferases in OCCC cell lines. **Results** Q-PCR revealed that 2 histone methyltransferases (SMYD2 and WHSC1) were significantly overexpressed in clinical OCCC specimens, compared with normal ovarian tissues ( $p < 0.05$ ). Knockdown of either SMYD2 or WHSC1 induces growth suppression and apoptosis in OCCC cell lines through attenuation of histone methylation of H3K4, H3K36. **Conclusion** Our results suggest that overexpression of SMYD2 and WHSC1 is involved in the cell growth of OCCC. Further functional studies may affirm the importance of SMYD2 and WHSC1 as a promising therapeutic target for OCCC.

### ISP-8-3

**The mechanism of ceramide nanoliposomes-induced necroptosis in ovarian cancer** Xuewei Zhang<sup>1</sup>, Kazuyuki Kitatani<sup>2</sup>, Masafumi Toyoshima<sup>1</sup>, Masumi Ishibashi<sup>1</sup>, Shogo Shigeta<sup>1</sup>, Junko Minato<sup>1</sup>, Nobuo Yaegashi<sup>1</sup> *Tohoku University<sup>1</sup>, Tohoku Medical Megabank Organization<sup>2</sup>*

**Objective** Ceramides are bioactive lipids that mediate cell death in cancer and ceramide-based therapy has been proposed for cancer treatment. The most representative ceramide formulation is ceramide nanoliposomes (CNL) that have been preclinically studied. However, the effect of CNL in ovarian cancer is still unclear. Thus, we investigated the therapeutic efficacy and signaling mechanisms of the CNL in refractory ovarian cancer. **Methods** Cell viability was measured by Cell-Titer Glo Kit. Cell death was determined by Annexin-V/7-amino-actinomycin D assay. The proteins involved in apoptosis and necroptosis were detected by immunostaining. **Results** Treatment of ovarian cancer cells with CNL decreased the number of living cells. Surprisingly, CNL treatment predominantly induced necrosis, but not apoptosis. Necrosis is also programmed like apoptosis. Necroptosis, the best-characterized form of regulated necrosis, is mediated with regulatory proteins such as protein kinase receptor-interacting protein kinase (RIPK) 1, RIPK3 and pseudokinase mixed lineage kinase domain-like (MLKL). Importantly, dying cells exhibit activation of MLKL as evidenced by oligomerization and relocation to the blebbing membranes. Knock-down of MLKL with siRNA abolished CNL-induced cell death. Mechanistically, ceramide was revealed to interact with MLKL in a binding assay, suggesting MLKL as a novel pro-necroptotic target for ceramide. **Conclusion** CNL is suggested to serve as a therapeutic reagent that inducing MLKL-dependent necroptosis in ovarian cancer.

### ISP-8-4

**GEP oncogene induces epithelial-mesenchymal transition through LATS1 down-regulation in ovarian cancer** Hiroshi Yagi, Ichiro Onoyama, Kazuo Asanoma, Keisuke Kodama, Masafumi Yasunaga, Tatsuhiro Ohgami, Kenzo Sonoda, Kiyoko Kato *Kyushu University*

**Objective**  $G\alpha_{12/13}$ , heterotrimeric G-proteins, encoded by GEP oncogene, are implicated in the progression of several human cancers. However, the underlying mechanisms by which GEP oncogene promote cancer progression has not been fully elucidated. We herein evaluated downstream targets of GEP oncogene that are implicated in ovarian cancer progression. **Methods** To examine the effect of  $G\alpha_{13}$  activation on ovarian cancer cells, we employed constitutively active mutant of  $G\alpha_{13}$  ( $G\alpha_{13}QL$ ) or synthetic biology approach using a GPCR activated solely by artificial ligands (RASSL). Morphological change, protein expression profiles and intracellular signaling pathways were analyzed. **Results** Regarding both in cell morphology and protein expression profile,  $G\alpha_{13}$  activation induced epithelial-mesenchymal transition (EMT)-like phenotypes. Cycloheximide chase assay revealed that LATS1 degradation mediated by  $G\alpha_{13}$  was involved

in EMT-like phenotype of ovarian cancer cells. **Conclusion**  $G\alpha_{13}$  activation may contribute to EMT-like phenotypical change through LATS1 degradation in ovarian cancer.

### ISP-8-5

**Regulation of Reg IV expression and prediction of response to 5-fluorouracil by CDX2 in ovarian mucinous carcinoma** Iemasa Koh, Eiji Hirata, Suguru Nosaka, Yoshiki Kudo *Hiroshima University*

**Objective** Ovarian mucinous carcinoma is a disease with a poor prognosis and a low response rate to chemotherapy. *REG4*, which encodes the Reg IV protein, is a potent activator of the epidermal growth factor receptor (EGFR)/AKT/activator protein 1 (AP-1) signaling pathway. Reg IV is overexpressed in several human cancers, and is involved in apoptosis inhibition, as well as in resistance to 5-fluorouracil (5-FU). Ovarian mucinous carcinoma has also been found to be associated with the overexpression of Reg IV, and we have confirmed the regulation of Reg IV expression by CDX2. Therefore, we have examined the effect of 5-FU and anti-EGFR treatment by profiling CDX2 and Reg IV expression. **Methods** We examined the changes in Reg IV expression in response to CDX2 overexpression in OMC-3 cells, which display relatively low endogenous CDX2 among ovarian mucinous carcinoma cell lines. In addition, using this cell line, we confirmed an effect of 5-FU and anti-EGFR treatment (cetuximab) by cytotoxicity assay (MTS assay). **Results** CDX2 overexpression in OMC-3 cells resulted in upregulation of Reg IV expression. OMC-3 cells ectopically expressing CDX2 displayed 5-FU sensitivity through overactive apoptosis, but sensitivity to 5-FU in combination with cetuximab was not increased. **Conclusion** CDX2 regulates the expression of Reg IV, but any combined effect involving an anti-EGFR antibody is poor. However, the sensitivity to 5-FU is high in ovarian mucinous carcinoma cells expressing CDX2. Therefore, our study suggests the potential of novel chemotherapy regimens using 5-FU in the treatment of ovarian mucinous carcinoma.

### ISP-8-6

**Expression of epithelial cell adhesion molecule and CD44 variant 6 is a predictive biomarker of chemoresistance and prognosis in epithelial ovarian cancer** Yashiro Motooka<sup>1</sup>, Takeshi Motohara<sup>1</sup>, Kiyomi Takaishi<sup>1</sup>, Fumitaka Saito<sup>1</sup>, Isao Sakaguchi<sup>1</sup>, Ritsuo Honda<sup>1</sup>, Takashi Ohba<sup>1</sup>, Hironori Tashiro<sup>2</sup>, Hidetaka Katabuchi<sup>1</sup> *Kumamoto University<sup>1</sup>, School of Health Science, Kumamoto University<sup>2</sup>*

**Objective** Cancer stem cell (CSC) are associated with chemoresistance and poor prognosis. Epithelial cell adhesion molecule (EpCAM) or CD44 variant 6 (CD44v6) are over-expressed in some epithelial cancers. We examined the involvement of EpCAM and CD44v6 in clinical outcomes of epithelial ovarian cancer patients. **Methods** The expression of EpCAM and CD44v6 was examined by immunohistochemical analysis using primary ovarian cancer specimens from 167 patients. The relationship between expression level of EpCAM and/or CD44v6 and prognosis of patients was assessed. In addition, we studied the association between the expression patterns of EpCAM and CD44v6 and the resistance to platinum agents in *in vitro* assays. **Results** We found that EpCAM/CD44v6 double positive epithelial ovarian cancer patients had poorer survival than single positive or double negative counterparts. We also found that EpCAM/CD44v6 double positive patients have a lower probability of achieving overall responsive rate after first line adjuvant chemotherapy than the EpCAM negative patients, and also that EpCAM/CD44v6 positive patients have the worst overall responsive rate than single positive or double negative counterparts. Consistent with clinical findings, in *in vitro* assays, the subpopulation of Ep-

CAM/CD44v6 double positive cells showed higher viability in response to platinum agents in comparison with single positive or double negative cells. **Conclusion** We demonstrated that expression of EpCAM and CD44v6 is a predictive biomarker of chemotherapeutic response and unfavorable prognosis in ovarian cancer patients.

### ISP-8-7

**Ferroptosis induced by erastin in RAS mutant ovarian cancer cells** Motoki Takenaka, Minako Mori, Yoko Ueda, Kyoko Kikuno, Kenichiro Morishige *Gifu University Hospital*

**Objective** Although apoptosis has been thought as the principal mechanism of cell death in chemotherapy, other forms of non-apoptotic death also has been noted. The oncogenic RAS-selective lethal small molecule erastin triggers a unique iron-dependent form of cell death termed ferroptosis. This mechanism is expected to induce eradication of chemotherapeutic resistant cancer cells. In this study we demonstrate this new form of cell death in ovarian cancer cells. **Methods** The clear cell epithelial ovarian cancer cell lines, TOV21G (RAS mutant type) and KOC (RAS wild type) were treated with erastin and deferoxamine (DFO). The results of cell proliferation were measured by using Premix WST-1 Cell Proliferation Assay System (Takara). The glutathione (GSH) concentrations were determined with the GSSG/GSH Quantification Kit (Dojindo) and the expression of glutathione peroxidase (GPx4) was identified by using a western blot. **Results** Erastin dose-dependently inhibited growth in TOV21G cells, but not KOC cells. DFO rescued growth inhibition induced by erastin in TOV21G cells. The GSH level was reduced by erastin and this reduction was not rescued by DFO. In addition, the basal level of GSH in TOV21G cells was lower than KOC cells. The expression of GPx4 was reduced by erastin and this reduction was not rescued by DFO. **Conclusion** Ferroptosis was induced by erastin in RAS mutant ovarian cancer cells. Although erastin induced cell death by reducing the level of GSH, DFO rescued this cell death by another pathway. The sensitivity to erastin might depends on the basal level of GSH in cells.

### ISP-8-8

**Efficacy and toxicity of PEGylated liposomal doxorubicin for recurrent ovarian cancer according to number of previous chemotherapy regimens : Comparison with gemcitabine** Yoshifumi Takahashi, Yuji Takei, Shizuo Machida, Akiyo Taneichi, Suzuyo Takahashi, Takahiro Yoshida, Hiroyuki Morisawa, Chikako Yoshida, Kouhei Tamura, Yasushi Saga, Hiroyuki Fujiwara, Shigeki Matsubara *Jichi Medical University*

**Objective** PEGylated liposomal doxorubicin (PLD) is one of the second-line chemotherapy regimens for platinum-resistant recurrent ovarian cancer, but in clinical practice, PLD is often selected for third-line or higher regimens. We previously reported that the disease control rate of gemcitabine (GEM) tended to decrease as the number of previous chemotherapy regimens increased, without an increase in toxicity. However, there is no report on the efficacy and toxicity of PLD based on the number of previous chemotherapy regimens. The purpose of this study was to clarify this point in comparison with GEM. **Methods** We retrospectively reviewed the medical records of patients at our institution with epithelial ovarian cancer who underwent two or more cycles of single-agent PLD therapy between July 2009 and March 2017. We used our reported data on GEM for the comparison analysis. **Results** Seventy-eight patients were enrolled in this study. The overall response rate was 19%, and the disease control rate (DCR) was 54%. The DCR of one, two, three, and >three previous chemotherapy regimens were 54%, 49%, 64%, and 67%, respectively. Grade 3/4 neutropenia and anemia occurred in 59% and 13%, respectively. When



the number of previous regimens was limited to 3 or more, the DCR for PLD was significantly higher than that for GEM (65% vs 31%,  $p=0.038$ ). **Conclusion** The DCR did not decrease with an increase in the number of previous chemotherapy regimens. When the number of previous regimens was high, the DCR of PLD was higher than that for GEM. Adverse events were tolerated with both regimens.

### ISP-8-9

**Interleukin-34 is a promising prognostic biomarker in ovarian cancers** Hiraku Endo<sup>1</sup>, Nao Suzuki<sup>1</sup>, Akiko Tozawa<sup>1</sup>, Hidemichi Watari<sup>2</sup>, Tatsuya Kato<sup>2</sup>, Yosuke Konno<sup>2</sup>, Daisuke Endo<sup>2</sup>, Hiroshi Asano<sup>2</sup>, Hisamori Kato<sup>4</sup>, Ken-ichiro Seino<sup>3</sup>. *St. Marianna University School of Medicine<sup>1</sup>, Hokkaido University<sup>2</sup>, Hokkaido University Institute for Genetic Medicine<sup>3</sup>, Kanagawa Cancer Center<sup>4</sup>*

**Objective** Despite several advances in the treatment of ovarian cancers, most patients suffer recurrence even after full remission following first-line therapy, which significantly impact patient's prognosis. Prognostic assessment depends clinically on few biomarkers, which still have many disadvantages regarding sensitivity, specificity and reliability. Thus, it is of great importance to identify new biomarkers that help to monitor response to cancer therapy and predict recurrence in ovarian cancer patients. Interleukin-34 (IL-34) has been suggested previously to act as an important factor that contributes to resistance against cytotoxic chemotherapy. Also, it correlates with poor prognosis when highly expressed in lung cancers, based on our previous report. In present study, we examined the possible involvement of IL-34 in chemoresistance and recurrence in ovarian cancers.

**Methods** We checked expression of IL-34 in several ovarian cancer cell lines and clinical samples from chemotherapy-untreated or treated ovarian cancer patients using RT-PCR, IHC and Ion AmpliSeq targeted sequencing analysis. And present study is performed under approval of multicenter research ethics committees. **Results** IL-34 was found to be expressed in ovarian cancer cell lines, in addition to a subset of ovarian cancer patients. IL-34 expression was enhanced by cytotoxic chemotherapy in ovarian cancer cell lines in addition to clinical samples from chemotherapy-treated ovarian cancer patients. Importantly, high IL-34 expression correlated with worse progression-free survival (PFS) in ovarian cancer patients ( $P=0.0421$ ). **Conclusion** These findings suggest a high usefulness of IL-34 as a prognostic biomarker that helps to predict and monitor disease recurrence.

### ISP-9-1

**SPIO method for the diagnosis of pelvic lymph node metastasis** Kosuke Murakami, Ayako Suzuki, Hanako Sato, Risa Fujishima, Masato Aoki, Shiro Takamatsu, Yoshie Yo, Akiko Kanto, Hisamitsu Takaya, Takako Tobiume, Hidekatsu Nakai, Noriomi Matsumura *Kindai University*

**Objective** Lymph node (LN) metastasis in uterine cervical and endometrial cancer is a significant risk factor of recurrence. To determine appropriate therapeutic strategy, precise evaluation of LN metastasis is important. The aim of this study is to develop more accurate imaging and pathological methods for pelvic LN metastasis. **Methods** We studied cervical and endometrial cancer cases which were planned pelvic LN dissection from February 2016. We injected Super Paramagnetic Iron Oxide (SPIO) into uterine cervix, and took T2\* weighted image of MRI. Normal LN takes SPIO and is enhanced, but metastatic LN does not. After surgery, we pathologically examined thinly sliced LNs which reacted strongly to iron staining. This study was approved by institutional review board, and we got informed consent from all patients. **Results** All of 27 patients did

not have adverse events. For patient base, accuracy was 89% (24/27 cases), sensitivity was 80%, specificity was 91%, positive predictive value was 67%, negative predictive value was 95%. There was a 10mm short-axis diameter LN, but it could be diagnosed no metastasis accurately. For 5-9mm short-axis diameter but easy to notice, accuracy was 85% (23/27 nodes), and 6mm and 8mm LN metastasis could be diagnosed. We could detect iron staining-positive LNs, and evaluate them retrospectively as sentinel LNs. **Conclusion** Local injection of SPIO in uterine cervix were performed safely. SPIO-enhanced MRI and immunopathological investigation by iron staining may be useful for diagnosis of pelvic LN metastasis of uterine cervical and endometrial cancer.

### ISP-9-2

**Discrimination of malignant transformation from benign endometriosis using near-infrared approach** Yuki Yamada, Chiharu Yoshimoto, Kenji Ogawa, Naoki Kawahara, Ryuji Kawaguchi, Toshiyuki Sado, Hiroshi Kobayashi *Nara Medical University*

**Objective** Endometriosis is known to increase the risk of ovarian cancer. Iron and hemoglobin (Hb) species in the cyst fluid can be used as markers of malignant transformation in benign ovarian endometriosis (OE). The aim of this study was to investigate the discrimination of malignant transformation from OE using near-infrared approach in the ex vivo study. **Methods** In a single center retrospective study, we collected the cyst fluid samples from patients with OE (n=34) and endometriosis-associated ovarian cancer (EAOC) (n=12) between February 2013 and January 2015. The light reflected from each cyst fluid (a change in luminance,  $\delta L$  (cd/m<sup>2</sup>)) was spectrally measured by a near-infrared CCD camera with band-pass filter (800 nm). Cyst fluid level of Hb (g/dL) was converted from heme levels in all patients. The value of  $\delta L$  and Hb for the diagnosis of malignant transformation was assessed by receiver operating characteristic (ROC) curve analysis. **Results** The  $\delta L$  in EAOC is significantly lower than that in OE ( $14.4 \pm 10.8$  versus  $29.6 \pm 5.0$  [mean  $\pm$  SD],  $p < 0.001$ ). A positive correlation between the  $\delta L$  and Hb level in cyst fluid was observed from regression analysis results. The diagnosis sensitivity and specificity for  $\delta L$  were 83.3% and 94.1% at the cutoff value of 21.5 cd/m<sup>2</sup> with the area under the ROC of 0.897. **Conclusion** This ex vivo study potentially provides a powerful near infrared approach for quantitative discrimination between EAOC and benign OE with high sensitivity and specificity. Our study lays a foundation for future clinical approaches.

### ISP-9-3

**Pathogenic KRAS mutation was frequently found in endometrial polyp with whole exome sequencing** Takashi Takeda<sup>1</sup>, Kouji Banno<sup>1</sup>, Masataka Adachi<sup>1</sup>, Megumi Yanokura<sup>1</sup>, Arata Kobayashi<sup>1</sup>, Mayuka Anko<sup>1</sup>, Asako Sera<sup>1</sup>, Yusuke Kobayashi<sup>1</sup>, Eiichiro Tominaga<sup>1</sup>, Kenjiro Kosaki<sup>2</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Center for Medical Genetics, Keio University<sup>2</sup>*

**Objective** Endometrial polyp is a common disease for women in reproductive age, however a molecular mechanism of endometrial polyp is still unclear. Next-generation sequencer makes whole exome analysis and detection of gene mutation easier. We analyzed endometrial polyp by next-generation sequencer with the goal to reveal a driver gene of endometrial polyp. **Methods** After an approval of ethics committee and written informed consent, 4 cases of endometrial polyp who were premenopausal, did not take medicine and had transcervical resection of endometrium were recruited. DNA was extracted from endometrial polyp as a tumor tissue and peripheral blood

lymphocytes as a normal tissue. Whole exome was analyzed by next-generation sequencer and derived candidate gene by the subtraction of gene mutation in tumor and normal samples. Then, we recruited totally 21 cases of endometrial polyp and additionally analyzed the extracted candidate gene by PCR-rSSO (reverse sequence specific oligonucleotide) method. **Results** Among 4 cases who were analyzed subtraction of whole exome, 2 cases had pathogenic mutation in exon2 of *KRAS* (p.G12V, p.G13C). Additional *KRAS* analysis revealed 7 of 21 cases (33.3%) had mutation in exon2 of *KRAS* (p.G12V, p.G12D, p.G13C). These mutation cases tended to have more endometrial polyps which were preoperatively checked in outpatient hysteroscopy ( $4.1 \pm 3.4$  vs  $1.7 \pm 0.9$ ,  $p=0.088$ ). **Conclusion** Endometrial polyp is a benign tumor, however it had pathogenic mutation in exon2 (codon 12,13) of *KRAS* with the similar frequency to that of endometrial cancer. This result indicates that *KRAS* may be a driver gene of endometrial polyp.

### ISP-9-4

**Evaluation of safety and diagnostic concordance for flexible hysteroscopy in 1,591 outpatient cases** Kosuke Tsuji, Yusuke Kobayashi, Kouji Banno, Kanako Nakamura, Arata Kobayashi, Takayuki Takahashi, Takuro Hirano, Haruko Kunitomi, Wataru Yamagami, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** There have been few large studies concerning the safety and diagnostic concordance rates of outpatient flexible hysteroscopy. In our institution, outpatient hysteroscopy has been routinely and educationally applied to intrauterine lesions; thus, we retrospectively investigated outpatient flexible hysteroscopy cases at our institution. **Methods** Fifteen hundred ninety-one cases of outpatient flexible hysteroscopy conducted at our institution during the previous 5 years (2012-2016) were retrospectively analyzed considering the clinical background, complications, and diagnostic concordance rates. **Results** The diagnosis before outpatient flexible hysteroscopy included 540 cases of benign disorders (317 endometrial polyps, 168 myomas, and 55 endometrial hyperplasia), 355 atypical endometrial hyperplasia, 570 endometrial cancers, and 126 others. There were no major complications including uterine perforation. Only one case (0.06%) was diagnosed as septic shock derived from intrauterine infection, in which the patient had been receiving immunosuppressive drugs. Three hundred eighty-two cases diagnosed as benign disorders through outpatient flexible hysteroscopy underwent operation, and the diagnostic concordance rate was 70.4% (269 cases). However, this included 14 cases (3.7%) which were diagnosed as malignant disorders postoperatively. In preoperative endometrial cancer cases, the sensitivity and specificity for diagnosis of cervical invasion was 39.4% and 90.8%, and positive intraoperative ascites cytology possibly caused by outpatient hysteroscopy was seen in only one patient. **Conclusion** Outpatient flexible hysteroscopy had high safety and almost negligible effect on ascites cytology. Although outpatient hysteroscopy had a high diagnostic rate, there were limitations in diagnosing malignancies by this procedure alone, so it is important that the diagnosis is determined by multidisciplinary approaches.

### ISP-9-5

**Influence of adverse effects on quality of life of survivors of gynecologic cancer** Keiichiro Nakamura, Naoyuki Ida, Masayuki Saijo, Junko Haraga, Takeshi Nishida, Chikako Ogawa, Tomoyuki Kusumoto, Hisashi Masuyama *Okayama University*

**Objective** The objective of this observational study was to investigate correlations between adverse effects (lower extremity

lymphedema [LEL], dysuria, severe gastrointestinal symptoms [SGS], and Peripheral motor neuropathy [PMN]/Peripheral sensory neuropathy [PSN]) and quality of life (QOL) (physical well-being [PWB], social well-being [SWB], emotional well-being [EWB], and functional well-being [FWB]) at least 3 year after treatment (post-treatment 1), over 3 years post-treatment (post-treatment 2) of with patients with gynecologic cancer (GC). **Methods** From January to August 2017, questionnaire responses and clinical data of 215 patients with GC were collected and assessed by treatment received. The  $\chi^2$  test was used to determine the significance of correlations. **Results** Participants with LEL had significantly poorer QOL than those without it in the domains of PWB at post-treatment1 ( $p=0.006$ ). SGS had significantly poorer QOL than those without it in the domains of PWB at post-treatment1 ( $p=0.034$ ) and post-treatment 2 ( $p=0.009$ ), and FWB at post-treatment1 ( $p=0.038$ ). Moreover, patients with PMN/PSN had significantly poorer QOL than those without it in the domains of EWB at post-treatment1 ( $p=0.046$ ). **Conclusion** Poorer QOL in emotional, physical and functional domains is associated with adverse effects of treatment in patients with GC. It is important to consider the effects of radical therapy not only on survival but also on the QOL of survivors.

### ISP-9-6

**Application of hysteroscopic transcervical resection for cervical proliferative disorder diagnostic method** Kensuke Hamamura, Yayoi Sugimori, Youko Fujiura, Sumire Ishii, Asako Kumagai, Kanako Murata, Yukari Kitagawa, Yota Shimanuki, Syozo Matsuoka, Daiki Ogishima *Juntendo University Nerima Hospital*

**Objective** Cervical conization has been widely performed to diagnose of cervical proliferative disorders presenting with multiple cysts, however, this method might not provide enough tissue to diagnose because the tumor lesion is often located at the internal os. We applied hysteroscopic transcervical resection (TCR) for a cervical biopsy method. This study aimed to compare the clinical/histological results of TCR with conization and to confirm usefulness of TCR biopsy for diagnosis of cervical cystic tumor. **Methods** We retrospectively studied 11 patients with large amount of vaginal discharge and cervical multicystic lesions in MRI who visited our hospital between April 2007 and August 2017. These patients underwent conization, TCR, (or both) for diagnosis. Conization was selected including the cases regarded as suspicious of malignancy and TCR was selected for lobularendocervical glandular hyperplasia (LEGH) suspected cases by endocervical cytology. **Results** Conization or TCR method was performed for 5 or 7 patients respectively. Both were done for one case. There was no statistical difference in two methods (conization : TCR) about operative duration (average : 22.8min : 25.4min) and amount of blood loss (average, 21g : 15.5g). Postoperative complication did not occurred in any cases. Conization provided appropriate diagnosis for malignancy, but provided insufficient tissue to detected tumor pathologically in two benign cases. All TCR cases obtained enough tissue for pathological diagnosis, and three of them were revealed LEGH after hysterectomy. **Conclusion** Cervical biopsy using TCR was applicable for cervical tumor diagnosis with high safety and accuracy. It may useful for the case which could not be diagnosed with conization.

### ISP-9-7

**Relation between intracardiac thrombus and advanced cancer : Report of two cases** Yasuka Miyakuni, Wakako Mouri, Yasuho Yanagihara, Ryosuke Shibui, Kyoko Oshina, Atsuko Yamada, Aya Otsuka, Akari Koizumi, Izumi Suzuki, Takafumi Ujihira, Michio Nojima, Koyo Yoshida *Juntendo University*

*Urayasu Hospital*

Cancer-associated thrombosis is a significant cause of death in patients with cancer. Although deep venous thrombosis and pulmonary embolism (PE) are commonly encountered, little has been reported on intracardiac thrombus. We report two cancer patients who died after suffering intracardiac thrombus. Case 1 : 50-year-old woman presented with dyspnea and chest pain, and was diagnosed with PE and sick sinus syndrome, and she was suspected of ovarian cancer. She got cardiac pacemaker implantation and started treatment with anticoagulant. She underwent bilateral salpingo-oophorectomy and was diagnosed with ovarian cancer, stage IIIC, and received adjuvant chemotherapy. After 1 year and 2 months, thrombosis of left subclavian vein and left internal jugular vein and progression of cancer were found. Then she chose to take only palliative care and anticoagulant. Two months later, right atrial thrombi was detected and she passed away three months later. Case 2 : 84-year-old female was diagnosed cervical cancer, stage IIB, and went through concurrent chemoradiotherapy. She had been taken novel oral anticoagulant (NOAC) for paroxysmal atrial fibrillation, but genital bleeding made her stop to take NOAC. After three years, the cancer spread to the lungs and liver, and she was admitted with complains of dyspnea and diagnosed left ventricular thrombus and renal infarction. She died before one month had passed since the diagnosis. Thrombotic events are reported to be the second cause of death in cancer patients and aggressiveness of cancer reflects on thrombotic events. When we recognize the progression of cancer, we should be careful with thrombosis.

## ISP-9-8

**Consideration of outpatient mammary gland at our hospital** Takako Kawakita, Yuri Kadota, Kana Kasai, Kanako Yoshida, Takeshi Kato, Masato Nishimura, Minoru Irahara *Tokushima University*

**Objective** It has been reported that HRT affects breast cancer although its risk is low, and breast cancer screening in HRT, LEP is recommended. In this issue, we examined breast cancer screening examinees in our department retrospectively and examined the usefulness of breast cancer screening for gynecologic disease patients. **Methods** We studied breast cancer examinees in our department from August 2016 to July 2017 retrospectively. **Results** There were 89 examinees, 44 check-ups during HRT, and 45 other screenings during gynecological treatment. Median age was 54 years old (29-81 years old), medical examiners in their thirties were undergoing HRT therapy after cancer surgery (4 cases), oral administration of LEP (5 cases). At 40 years of age or older, it was medical examination during HRT therapy or during treatment of other diseases. 20.4% during HRT administration showed increased mammary gland concentration. Two out of 44 patients undergoing HRT admitted fibroadenoma of breast, but one patient did not show any significant change in continuing HRT. In one case there was a tendency to reduction. We also admitted a case of breast cancer discovery in a screening before HRT. In this study, no onset of breast cancer was observed during HRT. **Conclusion** In women's lifestyle, HRT is an important treatment option. Periodical health examination during HRT is thought to be a trigger for breast cancer screening examination.

## ISP-9-9

**A retrospective study for the effectiveness and the safety of chemotherapy for elderly gynecologic cancer patients** Mihoko Aoki<sup>1</sup>, Yukihide Ota<sup>1</sup>, Mikiko Sato<sup>1</sup>, Natsuko Kamiya<sup>1</sup>, Yukio Suzuki<sup>1</sup>, Yuichi Imai<sup>1</sup>, Tae Mogami<sup>2</sup>, Naho Ruiz Yokota<sup>1</sup>, Tatsuya Matsunaga<sup>1</sup>, Etsuko Miyagi<sup>1</sup> *Yokohama City University*

*Hospital<sup>1</sup>, Kanagawa Cancer Center<sup>2</sup>*

**Objective** The purposes of this study were to evaluate the effectiveness and safety of chemotherapy and to identify pre-treatment risk factors in elderly gynecologic cancer patients. **Methods** We assessed the medical courses of the patients with the age over 74 years who were diagnosed gynecologic cancer in our department between 2011 and 2015. The correlation between variety of clinicopathological factors and overall survival of the patients were analyzed using Log-rank test. **Results** The number of the study subjects were 105 (range : 75-92 years old). Chemotherapy was considered for 70 patients (73%). Only 30 patients (39%) received chemotherapy. Among them, 9 (30%) patients accomplished the planned therapy, 11 (36%) needed anticancer-agent reduction and 10 (33%) stopped the chemotherapy. The disease control rates were 100%, 81%, 40%, respectively. A few life-threatening events occurred, but the chemotherapy was feasible for most of cases. Twenty-six (37%) patients who decided not to receive chemotherapy had no particular reason other than the elderly. The log-rank test of the 70 patients revealed significant correlations between the overall survival and pre-treatment performance status, falls risk assessment score, nourishment status and high CRP. **Conclusion** Chemotherapy was beneficial for appropriately selected elderly gynecologic cancer patients. Considering that significant number of the patients did not receive chemotherapy with no convincing reason, proper pre-treatment assessment is required to select the patients who would benefit chemotherapy.

## ISP-10-1

**Primary vaginal gestational trophoblastic neoplasia treated with uterine angiographic embolization and chemotherapy** Maria Concepcion Cenizal<sup>1</sup>, Angelica Anne Chua<sup>1,2</sup>, Leo Francis Aquilizan<sup>1,2</sup> *St. Luke's Medical Center, Philippines<sup>1</sup>, St. Luke's Medical Center Global City, Philippines<sup>2</sup>*

Gestational trophoblastic neoplasia in general is a rare condition, much so is primary extrauterine gestational trophoblastic neoplasia. The incidence of gestational trophoblastic neoplasia varies in different regions of the world. In the Philippines, local data showed that incidence of gestational trophoblastic neoplasia remained to be almost constant at 22.4 per 40,000 pregnancies. However, incidence of primary extrauterine gestational trophoblastic neoplasia was not mentioned. To date, there are only 2 cases of primary vaginal choriocarcinoma and 1 case of primary vulvar choriocarcinoma reported in literature. This is a case of a 26-year old gravida 1 para 0 (0-0-1-0) who came in for profuse vaginal bleeding. Serum beta human chorionic gonadotropin was elevated and ultrasonographic study showed a hypervascular vaginal mass and an empty uterus. Patient was diagnosed with primary vaginal gestational trophoblastic neoplasia and was started with combination chemotherapy. However, during the course of chemotherapy, profuse vaginal bleeding was noted which was controlled by angiographic embolization of the uterine arteries. The patient tolerated the procedure and completed cycles of Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine (EMACO). She had a complete remission of the tumor and had two successful subsequent pregnancies. Primary vaginal gestational trophoblastic neoplasia is a rare condition that warrants high index of suspicion. Combined chemotherapy with EMACO is the cornerstone of treatment. Angiographic embolization is a minimally invasive procedure that is safe and effective in managing acute hemorrhage among patients with gestational trophoblastic neoplasia.

## ISP-10-2

**The Mole that Created a Hole : A Case of an Invasive Mole with Uterine Perforation in a Primigravid** Lugie

Testado-Ouano, Angelita Teotico *Manila Central University-Ultrasound Services Incorporated, Philippines*

Invasive mole is a condition where molar pregnancy – partial or complete hydatidiform mole invades the myometrium. The occurrence of an invasive mole following a nonmolar pregnancy is very rare and most rare is an invasive mole without antecedent pregnancy. Presented here is a case of a 29 years old, primigravid, who was admitted for hypogastric pain with a positive pregnancy test. Transvaginal ultrasound revealed an enlarged uterus with a complex mass at the fundal area without visible intact myometrium and massive hemoperitoneum suggestive of a gestational trophoblastic tumor with suspicious uterine perforation versus ruptured interstitial pregnancy. Serum B-hCG was elevated – 311, 413 mIU/ml. Patient then underwent exploratory laparotomy. Intraoperatively, the uterus was symmetrically enlarged with smooth serosa. There was 1–2 cm rupture with active bleeding noted at the fundal area with a spongy mass. On cut section of the uterus, a poorly circumscribed mass was seen infiltrating the myometrium. The endometrium was smooth. Both fallopian tubes and ovaries were grossly normal, and there was hemoperitoneum of 2 liters. Total abdominal hysterectomy and bilateral salpingectomy were done. Repeat serum B-hCG was 44,660 mIU/ml. Histopathology result revealed chorionic villi invading the myometrium suggestive of an invasive mole. Patient was discharged improved with final diagnosis of gestational trophoblastic neoplasia (invasive mole) stage I, low risk (WHO score of 4). The case aims to emphasize the sonographic appearance of the different trophoblastic neoplasias as well as the difficulty surrounding the management of invasive mole with complication in a primigravid.

### ISP-10-3

**Prognostic effect of ABO blood groups in patients with androgenetic complete hydatidiform moles** Asuka Sato<sup>1</sup>, Hirokazu Usui<sup>1</sup>, Yuji Habu<sup>1</sup>, Ayumu Matsuoka<sup>2</sup>, Kyoko Nishikimi<sup>2</sup>, Shinichi Tate<sup>2</sup>, Akira Mitsuhashi<sup>1</sup>, Makio Shozu<sup>1</sup> *Chiba University<sup>1</sup>, Chiba University Hospital<sup>2</sup>*

**Objective** The association between ABO blood groups and gestational trophoblastic disease is still unclear, although it has been discussed since the 1970s. This study aimed to evaluate the effect of ABO blood groups on the prognosis of molar pregnancy by enrolling only subjects with genetically diagnosed complete hydatidiform moles (CHMs). **Methods** This was an observational cohort study of 206 patients who primarily underwent an operation for suspected molar pregnancy between January 2007 and February 2016. Among the patients, 132 were diagnosed as having CHMs according to multiplex short tandem repeat polymorphism analysis. The ABO blood groups of patients were determined serologically. The incidence of gestational trophoblastic neoplasia (GTN) was compared based on ABO blood groups. **Results** Of the patients, 54 (41%), 28 (21%), 11 (8%), and 39 (30%) were classified as types A, B, AB, and O, respectively. The distribution was approximately equal to that of the general Japanese population. The overall incidence of GTN was 17.4% (23/132). GTN occurred in 15% (8/54), 21% (6/28), 36% (4/11), and 13% (5/39) of the type A, B, AB, and O patients, respectively. The incidence of GTN in patients with A and B antigens tended to be higher ( $p=0.062$ , Cochran-Armitage trend test). **Conclusion** Patients with blood type O had a tendency not to develop GTN. The hypothesis is that immunological rejection against A and B antigens could play an important role in eliminating the trophoblastic cells after a molar pregnancy. Further study is needed to prove the relationship between ABO compatibility and the occurrence of GTN.

### ISP-10-4

**Primary choriocarcinoma of the mesentery in a pregnancy woman : A case report** Misaki Ozawa<sup>1</sup>, Masakazu Kitagawa<sup>1</sup>, Tamina Kino<sup>2</sup>, Ayasa Hashimoto<sup>1</sup>, Eri Uchida<sup>1</sup>, Asuna Yumori<sup>1</sup>, Kimiko Enomoto<sup>2</sup>, Yukiko Okada<sup>1</sup>, Shigeru Aoki<sup>2</sup>, Etsuko Miyagi<sup>1</sup>, Hideya Sakakibara<sup>1</sup> *Yokohama City University Medical Center<sup>1</sup>, Department of Obstetrics, Yokohama City University Medical Center<sup>2</sup>, Yokohama City University<sup>3</sup>*

Choriocarcinoma usually develops subsequently after pregnancy and cases developing during pregnancy are very few. As our knowledge, this is the first report of primary choriocarcinoma of the mesentery in a pregnant woman. She was 40-year-old woman, gravida 2 (induced abortion), para 0 and had been diagnosed with schizophrenia. She had been pregnant spontaneously and health checkups started in another hospital. From 1st trimester, 6 cm mass in adnexal area was detected and had been observed as an ovarian tumor or a uterine subserosal myoma. MRI scan at 31 weeks of pregnancy revealed that the mass enlarged to 10 cm, showing high signal intensity on T1-weighted images and heterogeneous signal intensity on T2-weighted images. Because of exacerbation of schizophrenia, she was referred to our hospital at 35 weeks. A cesarean section was performed at 37 weeks due to poor control of preeclampsia and schizophrenia. Observing intra-abdominal cavity, bilateral adnexae were normal. The origin of the tumor existed in sigmoidal mesentery and severe adhesion was seen between the tumor and sigmoid colon, and tumor resection with colectomy was performed subsequently. By immunohistochemical analysis, it was diagnosed as choriocarcinoma of the mesentery. No cancer cells could be found in her placenta. Final diagnosis was primary choriocarcinoma of the mesentery, stage IV, and FIGO scoring was 15 points. Preoperative serum hCG level was 1,445,000 mIU/mL. We have been performing chemotherapy comprised of methotrexate, actinomycin D and etoposide after operation, so serum hCG level has decreased and finally been unable to be detected.

### ISP-10-5

**Treatment of choriocarcinoma with 4-day methotrexate, etoposide and actinomycin D regimen : a single center experience** Eiko Yamamoto<sup>1</sup>, Shizuka Sato<sup>2</sup>, Kaoru Niimi<sup>3</sup>, Kimihiro Nishino<sup>3</sup>, Kenichi Nakamura<sup>2</sup>, Yoshiki Ikeda<sup>2</sup>, Fumitaka Kikkawa<sup>3</sup> *Department of Medical Adminst, Nagoya University<sup>1</sup>, Nagoya Memorial Hospital<sup>2</sup>, Nagoya University<sup>3</sup>*

**Objective** The aim of this study was to examine the efficacy and safety of 4-day methotrexate, etoposide and actinomycin D (MEA) regimen for treatment of choriocarcinoma. **Methods** Thirty patients of choriocarcinoma had treatment with 4-day MEA regimen between January 1999 and December 2015. Retrospective analysis was performed on the outcomes and adverse effects. This study was approved by the ethics committee of the hospital. **Results** The mean age was 35.8 years old. The diagnoses of 30 patients were pathological choriocarcinoma in 12, clinical choriocarcinoma in 17 and non-gestational choriocarcinoma in one. Twenty-five patients (83.3%) had 4-day MEA as the first-line regimen and five patients had other regimens previously. Twenty-four patients (80.0%) achieved complete remission and 3 patients (10%) relapsed followed by cured by 4-day MEA. Of 6 patients who developed drug resistance, three patients were completely cured by surgery, radiotherapy and the other regimen, and three patients died of choriocarcinoma. The remission rate as the first and the secondary therapies were 88.0% and 44.0%, respectively. The adverse effects were nausea (64.2%), stomatitis (61.5%), leukocytopenia (G3-4, 49.7%), anemia (G2-3, 24.0%), and hepatotoxicity (G2-3, 13.6%). Among patients in the reproductive age, 15 patients recovered natural cy-



cles after hormone treatment. Eleven patients hoped for child-bearing, and five patients had nine conceptions with the results of two spontaneous abortion and seven term live births with no anomaly. **Conclusion** The total remission ratio of 4-day MEA was almost the same as those of 5-day MEA and EMA/CO. Adverse effects, including reproductive status, were acceptable by using supportive therapy.

### ISP-10-6

**The Usefulness of genetic analysis for differential diagnosis between complete and partial hydatidiform moles** Noriko Miyashita, Yuri Hasegawa, Ai Higashijima, Shuhei Abe, Atsushi Yoshida, Kiyonori Miura, Hideaki Masuzaki *Nagasaki University*

**Objective** It is difficult to differentiate complete and partial hydatidiform moles by image findings. Hydatidiform moles have been diagnosed by pathological examination. We performed genetic diagnosis for hydatidiform moles to clarify if hydatidiform mole is complete or partial. **Methods** From 2013 to 2017, we diagnosed 10 cases of complete hydatidiform moles and 4 cases of partial moles by pathological examination. In 14 cases, 4 cases were obtained after receiving written informed consent to get patient's and their husband's blood samples and the tissues of hydatidiform moles. We performed genetic analysis of cystic villi and patient's and their husband's blood samples by short tandem repeat PCR. **Results** One case was diagnosed partial hydatidiform mole by pathological examination. In this case, p57 (Kip2) immunohistochemistry was found at the partial nuclei of trophoblast and stromal cells of the villi. However, as genetic analysis of cystic villi showed that the cystic villi had paternal homozygosity. Finally, we diagnosed this case as complete hydatidiform mole. Three cases were diagnosed as complete hydatidiform moles by both pathological examination and genetic analysis. **Conclusion** Genetic analysis of hydatidiform mole is useful technique for the differential diagnosis between complete and partial hydatidiform mole.

### ISP-10-7

**Three cases of complete hydatidiform mole coexistent with a live twin fetus** Hikari Yoshizawa, Yasuhiko Ebina, Hitomi Imafuku, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Masashi Deguchi, Hideto Yamada *Kobe University*

Complete hydatidiform mole coexisting with a live twin fetus (CHMCF) is very rare, occurring in 1/20,000 - 1/100,000 pregnancy. We report 3 cases of NHMCF. The median age was 24 years (range 24-39). Diagnosis of complete hydatidiform mole was obtained by histopathology and immunohistochemistry. The gestational weeks at diagnosis were 12-14 weeks gestation. Two of three women became pregnant after administration of ovulation inducer. Maternal complications were severe hyperemesis gravidarum (n=1) and genital bleeding (n=2). Pregnancies were terminated in 14 and 15 weeks in 2 women because of the patient's request. One woman was diagnosed as clinical invasive mole 20 days after termination and received methotrexate/actinomycin-D therapy. The other woman intended to continue the pregnancy, but pregnancy was terminated at 21 weeks gestation due to lung metastasis. Her serum hCG decreased rapidly after methotrexate treatment and metastasis to lung disappeared. The overall rate of GTD was 67%. In the cases with CHMCF we experienced, the incidence of GTD was considerably high. Even if pregnancy was terminated in the first trimester, strict check for GTD is crucial.

### ISP-11-1

**The change of maternal cardiac function in twin pregnant women** Mayu Ukai, Eiji Yoshida, Takuji Ueno, Takuma

Yamada, Takehiko Takeda, Sho Tano, Kaname Uno, Teppei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi *TOYOTA Memorial Hospital*

**Objective** Twin pregnant women have 20% higher cardiac output and 10 to 20% greater increase in plasma volume than singleton pregnant women. These physiological changes impose considerable stress. The aim of this study was to reveal the changes in cardiac function in twin pregnant women compared with singleton pregnant women. **Methods** This study was a prospective cohort study from January 2010 to February 2016. Echocardiography and BNP levels were examined at early, middle, and late pregnancy, within 5 days after delivery, and at one month postpartum. Left ventricular ejection fraction (LVEF) < 55% was defined as systolic dysfunction. Early transmitral velocity/early diastolic velocity of the mitral annulus (E/Ea) > 15 was defined diastolic dysfunction. **Results** A total of 142 twin pregnant women and 44 singleton pregnant women were enrolled. Twenty one twin pregnant women were excluded due to preeclampsia or cardiovascular disease. LVEF were not significantly different in both twin and singleton pregnant women. E/Ea and BNP did not deteriorate in singleton pregnant women. In twin pregnant women, E/Ea elevation was observed at late pregnancy ( $9.6 \pm 2.8, p < 0.01$ ) and within 5 days after delivery ( $9.7 \pm 2.2, p < 0.01$ ) compared with early and middle pregnancy. BNP elevation was much higher in twin pregnant women than singleton pregnant women in late pregnancy ( $43.4 \pm 8.8, p < 0.01$ ) and early postpartum ( $46.9 \pm 8.0, p < 0.05$ ). **Conclusion** Twin pregnant women have a risk of cardiac functional deterioration. Late pregnancy and early postpartum should be considered as high risk periods for maternal cardiac dysfunction.

### ISP-11-2

**Pregnancy outcomes of MD twins** Miki Nishizawa, Koichiro Kido, Rina Sakurai, Takayuki Ichinose, Shigenari Namai, Rintaro Kishimoto, Yasuhiro Matsumoto, Haruko Hiraike, Masahiro Shiba, Yukifumi Sasamori, Eiji Ryo, Takuya Ayabe *Teikyo University*

**Objective** FLP is effective for twin to twin transfusion syndrome (TTTS). In MD twins, however, poor pregnancy outcomes are also caused by similar situations such as twin anemia-polycythemia sequence, twin amniotic fluid discordance, and selective fetal growth restriction, which are not eligible for FLP. We analyzed medical records, and tried to draw some suggestions to expand FLP indications. **Methods** Forty-three MD pregnancies from 2013 through 2016 at our hospital were analyzed retrospectively based on the medical records. **Results** There were 27 MD twins of normal amnion without FGR (control group : CG), and 16 cases which are suspected of TTTS and similar situations (suspected group : SG). The mean delivery week were 33.7 vs 35.9 (SG vs CG) ( $p < 0.01$ ). The mean Apgar scores of the first twin at 1 min were 6.5 vs 7.7 (SG vs CG) ( $p < 0.01$ ), and that of the second twin were 6.7 vs 7.9 (SG vs CG) ( $p < 0.01$ ). There were two cases of TTTS in the SG group, one occurred at 28 weeks of gestation and the other deteriorated from TAPS at 31 weeks of gestation, both of them yielded low APSS. **Conclusion** Pregnancy ended earlier in SG than in CG. Babies in SG showed lower APSS, but have shown no neurological complications at the latest follow-up. The current management for MD twins seemed effective to prevent neurological complications. Some TTTS, however, occurred after the present deadline of FLP, or 26 weeks. Study to expand FLP indication is expected.

### ISP-11-3

**Clinical significance of pregnancy in Japanese women aged 15 years** Asako Watanabe, Asako Saso, Naofumi Okuda, Sayuri Kondo, Marie Ito, Miwa Miyazaki, Yoshie Shibata, Zuisai

Hayashi, Shunji Suzuki *Japanese Red Cross Katsushika Maternity Hospital*

**Objective** We examined the clinical characteristics and obstetric outcomes in pregnancies in Japanese women aged 15 years. **Methods** The present study was a retrospective investigation of all Japanese women with singleton pregnancies who gave birth beyond 22 weeks' gestation aged 15 years old between 2002 and 2016 at our institute (n=56). **Results** Of the 56 women, 7 (13%) gave birth without visiting prenatal care. Adverse obstetric outcomes were not observed in the pregnancies in women aged 15 years; however various social and economic problems regarding pregnancy in these women were observed. In addition, the rate of more serious social problems such as insulted state with their parents and unknown pregnant partners was higher significantly in women without prenatal care than that in women received prenatal care. **Conclusion** Adequate social support is needed for the young pregnant women.

### ISP-11-4

**Pregnancy after fertility preservation with high-dose medroxyprogesterone acetate : Three cases of obstetric complications** Karin Imaizumi, Hyo Kyoizuka, Satoshi Suzuki, Daisuke Suzuki, Akiko Yamaguchi, Shu Soeda, Takafumi Watanabe, Keiya Fujimori *Fukushima Medical University*

High-dose medroxyprogesterone acetate (MPA) therapy is a fertility-preserving treatment for early-stage endometrial cancer or atypical endometrial hyperplasia. However, obstetric complications after MPA therapy are not well known. Here, we report 3 cases of obstetric complications after fertility preservation therapy using MPA. Case 1 : A 35-year-old woman was referred to our hospital for the management of threatened preterm birth at 23 weeks. The patient had preterm premature rupture of membrane (pPROM) at 29 weeks despite use of several tocolytic agents. Caesarean section (CS) was performed after a course of antenatal corticosteroids. Severe inflammation of the placenta and umbilical cord was histologically confirmed. Case 2 : A 41-year-old woman underwent CS because of arrest of labor at 41 weeks in our hospital. The placenta was difficult to remove. Because of postpartum hemorrhage, abdominal total hysterectomy was performed soon after the delivery. Histological examination revealed placenta increta and intrauterine inflammation. Case 3 : A 35-year-old woman was referred to our hospital for the management of pPROM at 26 weeks. CS was performed after a course of antenatal corticosteroids. An attempt was made to remove the placenta; however, manual removal was unsuccessful because the partial placenta adhered to the uterine wall at the fundus. Placenta accreta was clinically diagnosed. Conservative management for placenta accreta was selected as the course of action.

### ISP-11-5

**Pregnancy outcome of extremely advanced maternal age** Tomoyuki Sekizuka, Masayuki Yamaguchi, Kazufumi Haino, Ryo Tamura, Kunihiro Yoshida, Mina Itsukaichi, Taro Nonaka, Koichi Takakuwa, Takayuki Enomoto *Niigata University Medical and Dental Hospital*

**Objective** To evaluate pregnancy outcome in women of extremely advanced maternal age (>45 years) in our hospital. **Methods** This is a retrospective study of all women delivering singletons births in our hospital from 2006 to 2015. Data were extracted from maternal registry of our hospital. Women with multiple gestation, stillbirth and whose records lacked were excluded. We compared non-advanced maternal age women (non-AMA women; age 20-34 years, reference group) to advanced maternal age women (AMA women; age 35-39, 40-44 and >45 years). The primary outcome was route of delivery (cesarean vs

vaginal). Incidences of maternal and fetal adverse outcomes were also analyzed. The Fisher's test was used to analyze categorical variables. Findings were considered statistically significant if  $p < 0.05$  for all outcomes. **Results** There were 3,781 women who met criteria, which included 17 (0.45%) women who were age >45 years at the time of delivery. Rates of cesarean delivery differed by age group (31.1%, 20-34 years; 39.1%, 35-39 years; 42.4%, 40-44 years; 58.8%, >45 years). Compared to the reference group, women age >45 years were significantly more likely to undergo a cesarean delivery (OR 3.17; 95% CI 1.20-8.36,  $p < 0.02$ ), experience severe maternal morbidity (11.76% vs 1.82%; OR=7.18; 95% CI, 1.59-32.41,  $p < 0.05$ ) and blood transfusion (11.76% vs 1.61%; OR=8.17; 95% CI, 1.80-37.03,  $p < 0.05$ ). **Conclusion** Compared to non-AMA women, extremely AMA women experience significantly increased rates of cesarean delivery and maternal risks. Extremely AMA women should be informed about these risks.

### ISP-11-6

**Ultrasound study of fetal movements in singleton and twin pregnancies at 12 to 19 weeks** Mohamed Aboellail<sup>1</sup>, Kenji Kanenishi<sup>1</sup>, Nobuhiro Mori<sup>1</sup>, Junko Noguchi<sup>2</sup>, Toshiyuki Hata<sup>1</sup> *Kagawa University<sup>1</sup>, Kagawa Prefectural College of Health Sciences<sup>2</sup>*

**Objective** To evaluate fetal behavioral differences between singleton and twin fetuses before 20 weeks of gestation using four dimensional (4D) ultrasound. **Methods** 4D ultrasound was used to examine fetal movements in 58 singleton and 48 twin normal fetuses at 12 to 19 weeks. The frequencies of eight fetal movements were assessed through 15 minutes recordings. The fetuses were divided into two gestational age groups (12 to 13 and 14 to 19 weeks) to evaluate the changes with advancing gestation in twin versus singleton fetuses. **Results** Arm and general movements were the most frequent movements in singleton fetuses, whereas only general movement was significantly more frequent than the other seven fetal movements in twin fetuses at 12 to 13 weeks. At 14 to 19 weeks, frequencies of arm and leg movements were significantly higher than those of the other six movements in singleton fetuses, while only arm movement was significantly more frequent than the other fetal movements in twin fetuses. Comparisons of fetal movements between singleton and twin fetuses revealed that only arm movement showed a significant difference at 12 to 13 weeks, while the frequencies of all movements in singleton fetuses were significantly higher than those in twin fetuses at 14 to 19 weeks. **Conclusion** Our results suggest that the limitation of available space and crowding of twin fetuses with advancing gestation may have a marked impact on twin fetal movements compared with singleton fetuses, even in the first half of pregnancy.

### ISP-11-7

**The effect of trimester-specific gestational weight gain on the risk of light for date in Japanese women stratified by the methods to calculate trimester-specific gestational weight gain** Takuhiro Yamada<sup>1</sup>, Tadahiko Uesato<sup>1</sup>, Tadashi Uesato<sup>1</sup>, Eiji Imaizumi<sup>1</sup>, Kazuhiro Fujita<sup>1</sup>, Jutarō Fujita<sup>1</sup>, Chisato Mori<sup>2</sup> *Aiwa Hospital<sup>1</sup>, Department of Bioenvironmental Medicine, Chiba University<sup>2</sup>*

**Objective** To investigate associations between trimester-specific gestational weight gain (GWG) and fetal birth weight. **Methods** The term singleton 24,517 births were analyzed retrospectively. We calculated the odds ratio of light for date (LFD) among women who were low weight gain in each trimester. We also calculated the adjusted odds ratio with maternal age, parity, height, body mass index (BMI), infant sex and weight gain in other trimesters using multivariate logistic re-

gression. Then we calculated the adjusted odds ratio of LFD by BMI category. **Results** The mean (standard deviation) 1st trimester-specific GWG rate was 50.1 (161.5) g/w, and the 2nd was 367.9 (123.4) g/w, and the 3rd was 356.5 (151.3) g/w. Low weight gain both in the 2nd and in the 3rd trimester significantly increased the risk of LFD. In the crude model low weight gain in the 1st trimester did not increase the risk of LFD, but in the adjusted model, low weight gain in the 1st trimester significantly increased the risk of LFD. In low and normal BMI groups low weight gain in the 2nd and in the 3rd trimester significantly increased the risk of LFD. In high BMI group low weight gain only in the 2nd trimester increased the risk of LFD. **Conclusion** Low weight gain in the 2nd trimester affected the risk of LFD the most. Low weight gain in the 3rd trimester had higher risk of LFD than the 1st trimester. The effects of trimester-specific GWG on the risk of LFD differed by BMI groups.

### ISP-11-8

**The client's attitude survey after invasive or non-invasive prenatal testing** Mie Tahara, Hiroaki Nakamura, Atsushi Matsuki, Maya Komori, Takako Matsuki, Sachiyo Nishimoto, Kazuharu Tanaka, Osamu Nakamoto *Osaka City General Hospital*

**Objective** In Japan, Non-Invasive Prenatal Testing (NIPT) has been performed for many pregnant women from April, 2013. The differences about client's attitude between invasive and non-invasive testing are unknown. Therefore, we report here using the questionnaires. **Methods** Under the permission of ethics committee, we asked 1,352 clients after prenatal testing using questionnaire from March, 2015 to August, 2017. Four questions are 1. Did you understand about your results? 2. Did you feel your anxiety was resolved? 3. In future, if you get pregnant again, do you want to receive same prenatal testing? 4. If possible, please let us know your opinion. Data were analyzed using Fishers' exact test. **Results** We collected 1,337 answers (411 of amniocentesis, AC and 926 of NIPT). 1. 89% of AC and 95% of NIPT clients answered "understood very well". 2. 75% of AC and 68% of NIPT clients answered "extremely resolved". 3. 65% of AC and 70% of NIPT client answered "agree". 4. Of the 345 described clients, 70% of AC and 65% NIPT clients were satisfied, but 20% and 30% clients were dissatisfied, respectively. **Conclusion** From this attitude survey, although same genetic counseling, the attitude of clients after invasive or non-invasive study were different. NIPT is safe but expensive, and the information of the test is limited more than invasive tests.

### ISP-11-9

**An investigation of the benefits of first trimester ultrasound screening combined with second trimester maternal serum screening** Yumi Araki, Maki Hyodo, Norifumi Tanaka, Tomomi Yamazaki, Yoshiki Kudo *Hiroshima University*

**Objective** Maternal serum screening (MSS) is used for trisomy 21 and 18. However, many women who have false-positive results feel anxiety and undergo invasive procedures unnecessarily. In our hospital, first trimester ultrasound screening is also performed in all cases of MSS. We investigated the benefits of combining these exams. **Methods** From 2015 to 2016, 192 pregnant women underwent first trimester ultrasound screening and second trimester MSS. On ultrasound screening, fetal nuchal translucency thickness  $>3$  mm and/or hypoplasia (including absence) of nasal bone were considered positive findings. We studied the correlation of these screening results and outcomes. **Results** Six (3.1%) cases were positive in both exams, with 3 cases diagnosed as chromosomal abnormalities. One of the 3 cases was trisomy 18 and the other 2 were trisomy 21. In 33 (17.2%) positive cases only on MSS, 16 women who underwent

non-invasive prenatal testing (NIPT) or amniocentesis had negative or normal findings. The other 17 women and the 131 who had negative results in both exams were satisfied by these results and decided to continue their pregnancies without further examination. In 22 (11.5%) positive cases only on ultrasound screening, 5 cases were diagnosed with fetal abnormalities such as trisomy 13, Noonan syndrome, polycystic kidney disease, cleidocranial dysplasia, and multiple congenital malformation syndrome. **Conclusion** Using first trimester ultrasound screening, trisomy 21 and 18 can be screened more precisely than only MSS, and more fetal abnormalities can be screened. Additionally, ultrasound screening before MSS could reduce the number of women who feel anxiety and undergo invasive procedures unnecessarily.

### ISP-12-1

**Immunoglobulin fetal therapy for symptomatic congenital cytomegalovirus infection** Yutoku Shi<sup>1</sup>, Kenji Tanimura<sup>1</sup>, Akiko Uchida<sup>1</sup>, Mizuki Uenaka<sup>1</sup>, Mayumi Morizane<sup>1</sup>, Masashi Deguchi<sup>1</sup>, Yasuhiko Ebina<sup>1</sup>, Ichiro Morioka<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University<sup>1</sup>, Department of Pediatrics, Kobe University<sup>2</sup>*

**Objective** Approximately 90% of the surviving infants with symptomatic congenital cytomegalovirus (CMV) infection (CCI) have severe neurological sequelae. We aimed to assess the efficacy of fetal therapy with immunoglobulin (Ig) of a high titer anti-CMV antibody for symptomatic CCI. **Methods** This study was approved by the institutional ethic boards, and written informed consent was obtained from all participants. Mothers with fetuses of symptomatic CCI received Ig injection into the fetal peritoneal cavity (Fip) or intravenous Ig injection into maternal blood (Miv). **Results** Twelve fetuses received fetal therapy (Fip 1, Miv 5, and Fip+Miv 6) from 2009 to 2017. After Ig fetal therapy, ultrasound examinations and CMV-DNA PCR tests demonstrated the following changes: ascites disappearance of 8.3% (1/12), improvement in fetal growth restriction of 33.3% (4/12), and the disappearance of CMV-DNA in fetal ascites of 8.3% (1/12). The survival rate was 83% (10/12). In the 7 surviving infants whose neurological outcomes were evaluated at age of 12 months or later, 2 (28.5%) developed severe or mild sequelae, 2 (28.5%) had unilateral hearing difficulty only, and 3 (42.9%) developed normally. **Conclusion** Ig fetal therapy may be effective for reducing the incidence and severity of sequelae in symptomatic CCI infants.

### ISP-12-2

**Anti-cytomegalovirus IgM titer for congenital infection in first-trimester pregnancy with primary infection** Kuniaki Toriyabe<sup>1</sup>, Fumihiko Morikawa<sup>2</sup>, Toshio Minematsu<sup>3</sup>, Asa Kitamura<sup>1</sup>, Kyoko Shimada<sup>1</sup>, Michiko Kubo<sup>1</sup>, Masafumi Nii<sup>1</sup>, Kayo Tanaka<sup>1</sup>, Hiroaki Tanaka<sup>1</sup>, Kazuhiro Osato<sup>1</sup>, Yuki Kamimoto<sup>1</sup>, Tomoaki Ikeda<sup>1</sup> *Mie University Hospital<sup>1</sup>, Mie Association of Obstetricians and Gynecologists<sup>2</sup>, Aisenkai Nichinan Hospital<sup>3</sup>*

**Objective** We evaluated cytomegalovirus (CMV) immunoglobulin M (IgM) titer in first-trimester pregnant women with primary infection as a predictive factor for congenital infection in a multi-center prospective cohort study. **Methods** Maternal CMV antibody screening during the first trimester was conducted prospectively at 16 centers in Japan between September 2013 and September 2015. Pregnant women with primary infection underwent testing for fetal congenital infection by real-time polymerase chain reaction on CMV DNA. We investigated the positive predictive value of CMV IgM titer levels for congenital infection in first-trimester pregnant women with a positive/borderline IgG, positive IgM, and low IgG avidity (IgG avidity index of 35.0% or less) result. **Results** We identified six (8.6%)

cases of congenital infection among 70 pregnant women with positive/borderline IgG, positive IgM, and IgG avidity index of 35.0% or less and eleven (39.3%) among 28 women with IgG and/or IgM seroconversion after an initial negative IgG and negative IgM result. Keeping 100% sensitivity for the former six congenital infection cases, positive predictive values of IgM titer level for congenital infection were 8.6% (IgM titer of 1.21 or more), 11.8% (2.00 or more), 15.0% (4.00 or more), 17.1% (6.00 or more), respectively. An IgM titer level of 6.00 or more showed the highest positive predictive value for congenital infection in first-trimester pregnant women with a positive/borderline IgG, positive IgM, and low IgG avidity result. **Conclusion** High titer of CMV IgM during the first trimester in pregnant women with primary infection is a predictive factor for congenital infection.

### ISP-12-3

**Biphasic MCA-PSV elevation in a case of congenital cytomegalovirus infection** Sho Tano, Eiji Yoshida, Hatsuo Isogai, Takuji Ueno, Takuma Yamada, Takehiko Takeda, Kaname Uno, Mayu Ukai, Teppei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi *Perinatal Medical Center, TOYOTA Memorial Hospital*

**Introduction** Congenital cytomegalovirus (CMV) infection is the leading cause of nonhereditary sensorineural hearing loss and neurodevelopmental impairment. The nervous system is one of the main targets of congenital CMV infection, but the infectious dynamics of CMV in vivo brain has not been sufficiently studied. Although it is difficult to evaluate inflammation of the fetus in uterus, it is reported that the middle cerebral arterial peak systolic velocity (MCA-PSV) correlates with the inflammatory response. We reported a case of congenital CMV infection without fetal anemia, in which MCA-PSV was elevated to biphasic in uterus. **Case** A 28-year-old pregnant woman, gravida 2, para 1, had no infectious episodes. At 26 week of pregnancy, fetus MCA-PSV increased to 77.7 cm/sec, but there was no other abnormality. After that, once the MCA-PSV remained in the normal range, the ventricular enlargement was recognized from 30 weeks of gestation, and MCA-PSV increased after 34 weeks of pregnancy. She has labor in 39 weeks of pregnancy, delivering 2,590 g of boy without anemia. He was diagnosed as congenital CMV infection and took valganciclovir. Now 2 years old, there are no abnormalities except for speech developmental disorder due to sensorineural hearing loss. **Discussion** The biphasic increase in MCA-PSV in our case may have been affected by the biological properties of CMV. CMV is a member of the herpes virus family, and has latency and reactivation properties. CMV shifts to the latent phase within one month after infection and reactivates later. This characteristic is useful for ultrasound diagnosis.

### ISP-12-4

**Prediction of functional pulmonary hypoplasia using MRI** Junya Sakuma, Mayumi Takano, Sadanori Kasai, Sumito Nagasaki, Eijiro Hayata, Ayako Oji, Toshimitsu Maemura, Yukiko Katagiri, Masahiko Nakata, Mineto Morita *Toho University Omori Medical Center*

**Objective** The aim of this study was to investigate the utility of fetal lung to liver signal intensity ratio calculated by MRI for the prediction of functional pulmonary hypoplasia. **Methods** We retrospectively analyzed 63 pregnancies who underwent MRI between April 2011 and August 2017. Single-shot turbo spin-echo sequence was used for analyzed. On the fetal coronary plane of T2-weighted images, each signal intensity of lung and liver was measured, and the ratio of lung to liver signal intensity (LLSIR) was calculated. Pulmonary hypoplasia was defined as follows: the neonates were required mandatory ventilation

or died due to respiratory trouble expect for prematurity. **Results** The median gestational age at MRI was 33 weeks (range: 27–35 weeks). There were 52 pulmonary hypoplasia cases, LLSIR of pulmonary hypoplasia group was significantly lower than that of without pulmonary hypoplasia group (1.83 (range: 1.35–2.23) vs 2.44 (range: 1.92–4.63),  $p < 0.001$ ). Using ROC curve analysis, a threshold of 1.93 for LLSIR had 91% sensitivity, 73% specificity, 100% positive predictive value, and 98% negative predictive value for the prediction of neonatal respiratory disorder. **Conclusion** LLSIR of fetuses complicated with neonatal respiratory disorder was significantly lower than that of normal pulmonary function, and LLSIR seems to be useful MRI parameter to predict fetal functional pulmonary hypoplasia. This result indicates that low LLSIR might reflect the characteristics of hypoplastic lung structures.

### ISP-12-5

**Measuring fetal lung volume through fetal MRI imaging prior to ex utero intrapartum treatment (EXIT) for fetal airway occlusion and stenosis could contribute to EXIT success: a retrospective multicenter joint study** Satoshi Dohi<sup>1</sup>, Kiyotake Ichizuka<sup>1</sup>, Ryu Matsuoka<sup>2</sup>, Kohei Seo<sup>1</sup>, Masaaki Nagatsuka<sup>1</sup>, Akihiko Sekizawa<sup>2</sup> *Showa University Northern Yokohama Hospital<sup>1</sup>, Showa University Hospital<sup>2</sup>*

**Objective** We used a multicenter joint study to verify whether fetal MRI imaging performed prior to ex utero intrapartum treatment (EXIT) helps to predict postpartum pulmonary hypoplasia. **Methods** In a questionnaire survey of 174 perinatal centers in the Kanto region of Japan, we received 114 responses (response rate 65.5%), of which 13 cases of EXIT performed for fetal airway occlusion/stenosis from 2005–2016 were used for this study. Fetal pulmonary volume in the EXIT cases was measured from the fetal MRI images using medical imaging analysis software; differences between cases reporting neonatal mortality and those reporting survival were studied. **Results** Airway management was achieved for all 13 cases where EXIT was performed. Rate of survival after birth was 84.6% (11/13 cases), with two cases of neonatal mortality. The causes of neonatal mortality were pulmonary hypoplasia (one case) and otocephaly (one case). Based on a test for outliers (Smirnov and Grubbs test) in the 11 cases where fetal MRI imaging (including the two cases of fetal mortality) was available and analyzed in this study, it was statistically found that fetal pulmonary hyperplasia was an obvious outlier ( $p = 0.031$ ). Definitive signs of pulmonary hypoplasia were not noted in the case with otocephaly. **Conclusion** Pulmonary hypoplasia can be quantitatively confirmed through fetal MRI, which may also provide information on the indication for EXIT. Due to the small sample population in this study, a statistical investigation based on a larger sample size, such as a nation-wide survey, is required to validate these findings.

### ISP-12-6

**Prediction of the severity of lung hypoplasia in congenital diaphragmatic hernia** Yuka Yamamoto<sup>1</sup>, Yojiro Maruyama<sup>2</sup>, Atsuo Itakura<sup>2</sup>, Michio Nojima<sup>1</sup>, Koyo Yoshida<sup>1</sup> *Juntendo University Urayasu Hospital<sup>1</sup>, Juntendo University Hospital, Juntendo University<sup>2</sup>*

**Objective** Congenital diaphragmatic hernia (CDH) is a challenging lesion complicated to lung hypoplasia (LH). The evaluation of LH is important for the perinatal counseling and postnatal plan for the treatment strategies, however the accurate evaluation of LH has been under investigation. The purpose of this study was to seek the better ultrasound parameters to evaluate the LH in fetal CDH. **Methods** We collected 31 prenatal diagnosed CDH fetuses in our institutes from 2012 to 2017 Septem-



ber. Pulmonary arterial (PA) size, observed/expected lung area/head circumference ratio (o/e LHR) and PA Doppler parameters such as acceleration/ejection time ratio (AT/ET), peak early diastolic reverse flow (PEDRF) and pulsatility index (PI) were measured. PA size was converted to z-score. Perinatal outcome including the survival and duration of intubation was evaluated.

**Results** PA z-score in contralateral PA was significant smaller in lethal group compared to survivor group ( $p < 0.05$ ). There was a decreased trend of AT/ET in lethal group compared to survivors ( $p = 0.05$ ). However, there were no significant differences in PEDRF or PI. o/e LHR was significantly lower in lethal group compared to the survivors ( $p < 0.01$ ). Interestingly, the duration of intubation related to AT/ET ratio rather than o/e LHR or PA z-score. **Conclusion** The risk of death in infants with CDH related to o/e LHR and contralateral PA z-score. The prognosis of morbidity about LH may more relate to AT/ET in PA.

### ISP-12-7

**A case of prenatal diagnosis of congenital hiatal hernia** Moe Yorozu, Naoki Okimoto, Kao Fukui, Naomi Oooka, Mizuho Yoshida, Saya Tsukahara, Satoko Masahiro, Yoko Tateishi, Kazumasa Kumazawa, Katsuhiko Tada *Okayama Medical Center*

Prenatal diagnosis of congenital hiatal hernia (HCC) is uncommon and is not considered in the differential diagnosis of prenatal abnormal sonographic findings of cystic chest anomalies. It is also difficult to differentiate HCC from bochdalek hernia. We report a case prenatally diagnosed as HCC. A 30 year old woman was referred at 35 weeks of gestation for fetal sonographic evaluation due to a cystic mass in the fetal thorax and suspected of bochdalek hernia. Sonographic examination revealed a cystic structure behind the heart and the stomach of the fetus was not visualized in the abdominal cavity. The cystic mass in the thorax was then suspected as the stomach. The heart appeared normally located but slightly shifted anteriorly, without mediastinal shift, and the lungs appeared to be of normal echogenicity and volume. Based on these findings, the stomach was suspected to be located specifically into the mediastinum and HCC was the possible diagnosis. At 36 weeks of gestation, the sonographic examination revealed the stomach was visible in the abdominal cavity. The sagittal section showed a small stomach located below the diaphragm that continues into the mediastinum. Magnetic Resonance Imaging of the fetus was performed at 36 weeks of gestation and reassured that the reduction of the lung volume was to be slight. At 39 weeks of gestation, A 2,944g male was born spontaneously and the pulmonary status of the new born was entirely normal. The postdelivery chest radiography confirmed the prenatal diagnosis. HCC should be considered in the differential diagnosis of fetal cystic chest anomalies.

### ISP-12-8

**A case of fetal megalocystis and oligohydramnios with bladder size reduction and amniotic fluid volume improvement during the second trimester** Eriko Iwane, Minoru Mitani, Hazuki Iwata, Kanae Kashiwazaki, Masakazu Katou, Aika Korai, Kana Maruta, Misato Akiyama, Hidefumi Tashiro, Masami Wada, Yoshiyuki Nakajima, Naoki Masaoka *Tokyo Women's Medical University Yachiyo Medical Center*

Currently, fetal urinary tract abnormalities can be diagnosed relatively easily using ultrasound in early pregnancy. We report the case of a fetus diagnosed with megalocystis, oligohydramnios, and bilateral hydronephrosis during the first trimester, whose bladder size was reduced. The amniotic fluid volume improved during the second trimester. The presence of urachal remnants was suspected after birth. A 33-year-old primiparous

woman. Abdominal ultrasonography at 12 gestational weeks, performed at another hospital, raised a suspicion of megalocystis and fetal bladder-outlet obstruction. After that oligohydramnios and bilateral hydronephrosis were diagnosed. At 23 gestational weeks, the fetal bladder was reduced in size and amniotic fluid volume was improved. At 31 gestational weeks, she consulted our hospital due to moving house. Abdominal ultrasonography was performed; the scrotum and penis were identified, but we could not confirm the status of the bladder and urine outflow tract. At 38 gestational weeks, she delivered by cesarean section due to breech presentation. The male neonate weighed 2,498 g, and Apgar scores were 3/5. He had a small penis and constriction of the urethra, and his testes could not be palpated in the scrotum. Due to urine leakage around the umbilicus, we suspected urachal remnants. Ultrasonography showed bilateral renal cysts and a hydroureter. We used a guidewire to insert a 3-Fr feeding tube, and urine excretion occurred. If megalocystis improves, bladder rupture and reopening of the urethral closure may be considered. Because spontaneous resolution of urachal remnants is relatively rare, we report our case with a literature review.

### ISP-12-9

**Familial campomelic dysplasia due to maternal germinal mosaicism** Daisuke Higeta<sup>1</sup>, Takeshi Takagi<sup>2</sup>, Takashi Minegishi<sup>1</sup> *Gunma University Hospital<sup>1</sup>, Gunma Children's Medical Center<sup>2</sup>* Campomelic dysplasia (CD) is an autosomal dominant skeletal dysplasia caused by heterozygous SOX9 mutations. Most patients are sporadic due to a de novo mutation. Familial occurrence of CD is very rare. We report on a family with CD caused by maternal germinal mosaicism. Two siblings (the first and third children) showed the classic CD phenotype with a novel SOX9 mutation (c.441delC, p.N147fsX182). Radiological examination of the mother showed mild skeletal changes, such as narrow ilia and elbow dislocation. Then, her somatic mosaicism of the mutation was ascertained. In the next pregnancy, she underwent a prenatal molecular analysis with amniocentesis, yielding a normal result, and gave birth to a healthy fourth child. This is the first report of molecularly confirmed maternal germinal mosaicism for a SOX9 mutation. We suggest that a meticulous clinical examination of the parents, even if they are superficially healthy, is needed to avoid overlooking germinal mosaicism of SOX9 mutations.

### ISP-12-10

**14 cases of fetal skeletal dysplasia : accuracy of prenatal diagnosis** Miyoko Waratani, Yukiko Tanaka, Aki Mabuchi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** Fetal skeletal dysplasia comprises disorders of prenatal onset that can be diagnosed in the antenatal period. These disorders are characterized by underdeveloped bone and cartilage. Although the diagnostic rate has increased with the widespread use of ultrasound, prenatal diagnosis is complicated, because the description of the phenotype is often inconclusive. Skeletal dysplasia mostly refers to monogenic disorders; thus, a definitive diagnosis is possible through the identification of a mutation in the defective gene. We report the results of our investigation of prenatal and definitive postnatal diagnoses in 14 cases of fetal skeletal dysplasia. **Methods** For cases in which skeletal dysplasia was suspected in the antenatal period, we refined the diagnosis by performing prenatal 3-dimensional computed tomography and magnetic resonance imaging. We compared the postnatal definitive diagnosis with the prenatal diagnosis. **Results** There were thanatophoric dysplasia, osteogenesis imperfecta, campomelic dysplasia, Desbuquois syndrome, achondroplasia (including 1 case with trisomy 21), hypochondro-

plasia, Elis-van Creveld syndrome, and 2 (siblings) with hypophosphatasia (HPP). In 1 case, definitive postnatal diagnosis differed from the prenatal diagnosis, and definitive diagnosis in another case was made through DNA testing following intrauterine death. In a patient with Desbuquois syndrome and HPP, a definitive diagnosis had been made in a sibling through DNA testing; thus, the diagnosis was easy following prenatal detection. **Conclusion** In order to identify the defective gene and make a definitive diagnosis, it is necessary to narrow down the target gene through precise clinical diagnosis. Establishing more accurate clinical diagnoses should be the goal of future studies.

### ISP-13-1

**Repairing fetal membranes using elastomeric sealant *in vivo* mouse model** Yosuke Kawamura, Eiji Kondoh, Shingo Io, Mai Sato, Hiroshi Takai, Yoshitsugu Chigusa, Haruta Mogami, Masaki Mandai *Kyoto University*

**Objective** Although preterm premature rupture of membranes (pPROM) is associated with adverse pregnancy outcomes, there is no effective treatment. The aim of this study was to evaluate the sealing and healing capacity of elastomeric sealant in mouse sterile pPROM model. **Methods** Murine uterus and fetal membranes were punctured with a 20-gauge needle at 15 days post-coitum (dpc) by laparotomy. After puncture, elastomeric sealant, a viscous diisocyanated prepolymer, or phosphate buffered saline (PBS) was injected between membrane and myometrium. At 18 dpc, rupture size was measured under microscope and fetal membranes were collected. We conducted histological and gene expression analysis of the membrane. **Results** Rupture size of chorio-decidua became significantly smaller by sealant injection than PBS ( $0.45 \pm 0.19$  vs  $1.43 \pm 0.16$  mm,  $P < 0.01$ ,  $n=14$  and  $20$ , respectively). Rupture size of amnion tended to be smaller by sealant, although it did not reach statistical significance ( $0.4 \pm 0.194$  vs  $0.74 \pm 0.186$  mm,  $P=0.23$ ). mRNA expression of wound healing growth factors, *Egf*, *Fgf2*, and *Tgfb3* was increased in sealant group compared to PBS ( $\times 3.1$ ,  $\times 2.6$ ,  $\times 1.8$ , respectively,  $P < 0.05$ ). In addition, *Mmp9*, and *Il10* mRNA were increased by sealant ( $\times 3.5$ ,  $\times 4.6$ , respectively,  $P < 0.05$ ). **Conclusion** Elastomeric sealant assists healing of ruptured fetal membranes by releasing growth factors and remodeling extracellular matrix.

### ISP-13-2

**An ex vivo model and case report using intracervical elastomeric sealant for previable spontaneous premature rupture of the membranes** Eiji Kondoh, Junzo Hamanishi, Shingo Io, Yoshitsugu Chigusa, Yoshihide Inayama, Haruta Mogami, Yosuke Kawamura, Noriomi Matsumura, Masaki Mandai *Kyoto University*

**Objective** To study an ex vivo model for sealing the uterine cervical canal and to report our experience with an intracervical elastomeric sealant for treatment of previable premature rupture of the membranes (PROM). **Methods** The sealant, which has been used as a hemostatic agent for arterial anastomosis, was applied to the cervix of uteruses removed for benign gynecological disease. Normal saline was administrated into the ex vivo uterine cavity through a catheter using a pressure infusion bag. We investigated whether the application of the sealant could prevent the leakage of normal saline from the cervical canal. This technique was then applied to a case of previable spontaneous PROM occurring at 19 weeks gestation. **Results** The sealant was effective in preventing fluid loss from the ex vivo uterine cavity even under conditions of infusion bag pressure beyond 150 mmHg. The intracervical sealant treatment, combined with cervical cerclage, prevented rapid decrease of the amniotic fluid volume after amnioinfusion in the case of previ-

able PROM, leading to prolongation of the pregnancy until 25 weeks gestation. The infant survived without severe sequelae. The study was approved by the ethics committee. **Conclusion** Intracervical elastomeric sealant can stop fluid leakage completely in an ex vivo model. Although the in vivo application requires improvement in practical use, the sealant would help increase amniotic fluid volume and improve outcomes of pregnancy complicated with previable PROM.

### ISP-13-3

**Development of a prognostic/diagnostic examination system of preterm birth, targeting serum galectin-3** Satoshi Urabe<sup>1</sup>, Haruhisa Konishi<sup>1</sup>, Yuko Teraoka<sup>1</sup>, Hiroshi Miyoshi<sup>2</sup>, Mutsumi Miyauchi<sup>3</sup>, Takashi Takata<sup>3</sup>, Yoshiki Kudo<sup>1</sup> *Hiroshima University<sup>1</sup>, Hiroshima Prefectural Hospital<sup>2</sup>, Department of Oral and Maxillofacial Pathobiology, Hiroshima University<sup>3</sup>*

**Objective** Preterm birth (PTB) is a leading cause of neonatal morbidity and mortality. We confirmed that a *Porphyromonas gingivalis* (*P.g.*) dental infection induced PTB mouse model showed 2 days of PTB. In the placenta, *P.g.* was detected; moreover, galectin-3 (Gal-3), an immune regulator, was significantly upregulated in the placenta, amniotic fluid, and serum. The purpose of this study was to establish a screening and/or monitoring system targeting serum Gal-3 levels in pregnant women at a high risk of PTB. **Methods** Following institutional review board approval and attainment of informed consent, we examined Gal-3 levels in maternal blood samples and their association with PTB. We carried out a case control study that included 106 puerperae who experienced a spontaneous delivery: 21 cases (premature) and 85 controls (full-term). **Results** We confirmed that serum Gal-3 level in cases of spontaneous PTB (71% of cases of PTB) is higher than that in cases of full-term birth in every gestation period. Moreover, pregnant women with serum Gal-3 levels greater than 15 ng/mL had a particularly high risk of PTB. **Conclusion** In this study, we demonstrated that Gal-3 could be a potential biomarker of PTB. We will next perform a large scale clinical evaluation study to clarify the usefulness of serum Gal-3 level for the prediction/diagnosis of PTB.

### ISP-13-4

**Analysis of bacterial floral profile of the amniotic fluid in the cases of intra-amniotic inflammation using next generation sequencer** Tsuyoshi Yamasaki<sup>1</sup>, Takashi Horinouchi<sup>2</sup>, Toshiyuki Yoshizato<sup>2</sup>, Kimio Ushijima<sup>2</sup>, Ryoko Kawatsu<sup>1</sup>, Hidetoshi Honda<sup>3</sup> *Kyushu Medical Center<sup>1</sup>, Kurume University<sup>2</sup>, Human Microbial Laboratory, Biogenomics, Co., Ltd.<sup>3</sup>*

**Objective** To analyze the amniotic fluid (AF) bacterial floral profile in the cases of intra-amniotic inflammation (IAI) using next generation sequencer. **Methods** Subjects consisted of 46 patients with threatened premature labor at <34 weeks gestation at our center with amniocentesis performed for bacterial culture. Maternal venous white blood cell (WBC) count, C-reactive protein (CRP) and AF interleukin (IL)-6 levels were simultaneously measured. Analyzed were 17 cases, with 9 cases in the control group having WBC of <12,000/ $\mu$ L, CRP of <0.5 mg/dL and AF IL-6 level of <2,600 pg/mL, and 7 cases in the IAI group, with AF IL-6 level of >2,600 pg/mL. After microbial genomic DNA was extracted, the V1-V2 regions of the 16S ribosomal RNA gene were amplified and 3,000 reads were randomly chosen. The strains were classified by operational taxonomic unit analysis and determined based on the reference database, while the composition ratio was calculated as the percentage of the number of reads in each strain. **Results** In the control group, the top five strains were all the same. In the top three strains, *Fusobacterium sp. 2\_1\_31*, *Staphylococcus haemolyticus*, and *Fuso-*

*bacterium periodonticum* were found in this order. In the IAI group, while 6 cases showed similar profile as the control 2 patients indicated a different composition among the top 5 strains, including *Faecalibacterium prausnitzii*, *Bacteroides massiliensis* and *Atopobium vaginae*, of which only trace amounts were contained in the control group. **Conclusion** Differences in the bacterial flora in the amniotic fluid may be related to intra-amniotic inflammation.

### ISP-13-5

**Risk factors for preterm birth in ureaplasma-infected pregnant women with preterm labor** Erina Hashimoto, Ai Kouno, Takuo Nakayama, Hiromitsu Azuma, Chuyu Hayashi, Go Ichikawa, Atsushi Komatsu, Yasuji Miyagawa, Shinichi Takada, Fumihisa Chishima, Kei Kawana *Nihon University Itabashi Hospital*

**Objective** High-level of ureaplasma infection to the vagina in pregnant women can be a risk factor for preterm birth and some previous studies show treatment of ureaplasma-positive women with preterm prelabor rupture of membrane (PROM) by antibiotics for ureaplasma may prolong the pregnancy. We here examined the risk factors for preterm birth in pregnant women with ureaplasma infection to the vagina. **Methods** Under approval by Ethical committee in our hospital, we investigated retrospectively medical records for 56 pregnant women who were hospitalized due to preterm labor in our hospital in 2017. Ureaplasma (parvum/urealiticum) test of the vaginal swab was done for all cases. All ureaplasma-positive cases were treated by azithromycin (1g×1) when diagnosed as positive (24–34 gestational weeks). All cases were treated by tocolytic agents regardless of positivity for ureaplasma. **Results** Positive rate of ureaplasma in the vagina among women with preterm labor was 27% (15/56). Preterm birth rate in ureaplasma-positive cases was clearly higher than that in ureaplasma-negative (47% vs 15%,  $p=0.0275$ ). The rate of other microbial infection in ureaplasma-positive cases was higher than that in ureaplasma-negative (40% vs. 10%,  $p=0.0163$ ). logistic regression multivariate analysis showed numbers of white blood cell (WBC) was independent risk factor for preterm birth with marginal significant ( $p=0.08$ ). **Conclusion** Ureaplasma infection was associated with preterm birth even though treatment by antibiotics for ureaplasma. Ureaplasma-positive women were likely to complicate other microbial infections. Taken together with logistic analysis, ureaplasma-based infection and inflammation in the vagina might be critical for preterm birth.

### ISP-13-6

**The association of progranulin level controlled by progesterone with cervical maturation** Taiki Samejima, Takeshi Nagamatsu, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Protease system is a key to tissue remodeling process of the uterine cervix. Progranulin, a secretory protein, exerts anti-protease activities, contributing to tissue-repairing processes. This study aimed to investigate the involvement of cervical progranulin in the process of cervical maturation. **Methods** This study was conducted under the approval of the ethics committee in our facility. From 166 women in uncomplicated pregnancy at 24–26 weeks of gestation, cervical mucus was collected and the cervical length (CL) was measured by transvaginal ultrasonography. Neutrophil elastase and progranulin protein levels in the mucus samples were measured by ELISA. The correlation of those substances with CL was analyzed. mRNA expression of cervical progranulin was measured in two mouse models: a preterm birth model by administration of a progesterone receptor antagonist, RU486 and a delayed birth model by exces-

sive progesterone administration. **Results** The progranulin level of the cervical mucus in women with  $CL \geq 35$  mm ( $n=142$ ) was significantly higher than that in women with  $CL < 35$  mm ( $n=24$ ): (58.9 vs 34.4 ng/mg,  $p > 0.05$ ). No remarkable difference between these two groups was observed in the cervical neutrophil elastase levels. While RU486 treatment reduced the expression of cervical progranulin, exogenous progesterone administration enhanced the expression of cervical progranulin. **Conclusion** Our findings suggest the possibility that anti-protease activity of progranulin is controlled by progesterone and is involved in the regulation of cervical maturation.

### ISP-14-1

**Time-series Analysis of Life-logs to Predict Hypertensive Disorders of Pregnancy in Maternity Log Study** Takafumi Yamauchi<sup>1</sup>, Daisuke Ochi<sup>1</sup>, Yoshiki Tsunemoto<sup>2</sup>, Maiko Wagata<sup>3</sup>, Yuki Harada<sup>4</sup>, Riu Yamashita<sup>5</sup>, Osamu Tanabe<sup>1</sup>, Nobuo Yaegashi<sup>6</sup>, Masao Nagasaki<sup>4</sup>, Junichi Sugawara<sup>3</sup> *NTT DOCOMO, INC./Tohoku University<sup>1</sup>, NTT DOCOMO, INC.<sup>2</sup>, Department of Community Medical Supports, Tohoku University Tohoku Medical Megabank Organization<sup>3</sup>, Department of Integrative Genomics, Tohoku University Tohoku Medical Megabank Organization<sup>4</sup>, Department of Biobank, Tohoku University Tohoku Medical Megabank Organization<sup>5</sup>, Tohoku University Hospital<sup>6</sup>*

**Objective** Pregnancy complications including hypertensive disorders of pregnancy (HDP) are multifactorial diseases caused by complex interactions of genetic and environmental factors. Therefore, analyses of both factors are important to develop methods of early detection and prevention of such diseases. However, most of the previous researches have used self-report questionnaires to collect information on environmental factors, and had limitations in the frequency of data acquisition and the objectivity of the information. **Methods** We are conducting a prospective cohort study Maternity Log Study of pregnant women. By using a smart phone and monitoring devices, participants ( $n=302$ ) upload daily life-logs including biometric information on more than 20 items such as household blood pressure, as well as lifestyle information on more than 10 items such as hours of sleep. Furthermore, we collected specimens such as blood, saliva, and urine of participants for multi-omics analyses. In this presentation, we report differences in life-logs between an HDP ( $n=17$ ) and control ( $n=124$ ) groups. **Results** We found significant differences in several items of life-logs between the two groups. For example, the HDP group experienced larger numbers of days with palpitation after the 28th-week of gestation. Next, we established prediction models using several life-logs. A leave-one-out cross-validation demonstrated the specificity of 0.82, and the sensitivity of 0.88 at the 24th week. **Conclusion** By the analyses of daily life-logs during pregnancy, we identified candidate life-log markers for HDP. On the presentation, it will be also reported whether the predictive performance is further improved by combining maternal omics data with life-logs.

### ISP-14-2

**Prediction of Hypertensive Disorders of Pregnancy by Using Genetic Information in Maternity Log Study** Yoshiki Tsunemoto<sup>1</sup>, Daisuke Ochi<sup>2</sup>, Takafumi Yamauchi<sup>3</sup>, Riu Yamashita<sup>3</sup>, Maiko Wagata<sup>4</sup>, Yuki Harada<sup>5</sup>, Osamu Tanabe<sup>5</sup>, Nobuo Yaegashi<sup>6</sup>, Masao Nagasaki<sup>3</sup>, Junichi Sugawara<sup>4</sup> *NTT DOCOMO, INC.<sup>1</sup>, NTT DOCOMO, INC./Tohoku University Tohoku Medical Megabank Organization<sup>2</sup>, Department of Biobank, Tohoku University Tohoku Medical Megabank Organization<sup>3</sup>, Department of Community Medical Supports, Tohoku University Tohoku Medical Megabank Organization<sup>4</sup>, Department of Integrative Genomics, Tohoku University Tohoku Medical*



*Megabank Organization*<sup>5</sup>, *Tohoku University Hospital*<sup>6</sup>

**Objective** Hypertensive Disorders of Pregnancy (HDP) is a major cause of maternal and fetal death. HDP is caused by complex interactions of genetic and environmental factors. Initially, we focused exclusively on genetic factors in HDP on the way to the future analysis of the complex interactions of both genetic and environmental factors. **Methods** In this study, we used whole-genome sequence data obtained from 24 HDP group and 278 control group. We first compiled 166 HDP-associated genes from public databases and several researches with HDP meta-analysis. We cataloged all the common SNPs in those HDP-associated genes with the minor allele frequency (MAF) >0.01 in our samples. From them, we selected SNPs potentially useful for prediction of HDP based on the CADD score that represents the deleteriousness of single nucleotide variants, and 10 SNPs highest in the CADD score in each gene were selected. We then performed prediction of HDP by using the adaptive elastic net, and the results were evaluated by the leave-one-out method. **Results** The sensitivity and specificity of this model was 0.22 and 0.75, respectively, when only the SNPs of MAF>0.05 in our samples were used. However, when only the SNPs of MAF>0.1 were used, the sensitivity fell to 0.00. **Conclusion** The results suggest that it is difficult to predict HDP only by the genetic information. However, the prediction accuracy may be improved by increasing the number of samples. In future, we also try to improve the accuracy by using both genetic and environmental factors.

#### ISP-14-3

**Characteristic changes of the circadian rhythm by ambulatory blood pressure monitoring seen in preeclamptic women** Yoshikatsu Suzuki, Tamao Yamamoto, Hiroshi Matsushita, Kazushi Watanabe, Akihiko Wakatsuki *Aichi Medical University*

**Objective** Blood pressure (BP) shows circadian rhythm similar to Cosine curve by ambulatory BP monitoring (ABPM). BP is higher in the afternoon and lower at midnight. Hypertension shows blunt nocturnal BP fall and reversed circadian BP rhythm due to disturbance in sympathetic system. We investigated the characteristic changes of circadian rhythm in women with hypertensive disorders of pregnancy (HDP), especially preeclampsia (PE) by ABPM. **Methods** In 106 pregnant women showed hypertension by clinic BP, 24 hour ABPM diagnosed with HDP (n=79), including PE (n=43) and gestational hypertension (GH, n=36), and white coat hypertension (WCH, n=27). Circadian rhythm was investigated for 1) fall of nighttime as dipper, non-dipper or riser, 2) and percent rhythm (PR : multiple regression) and acrophase (maximal BP time) by Cosinor method. This study was approved by ethics of local committee. **Results** Mean systolic BP (SBP) and diastolic BP (DBP) in PE and GH was higher than in WCH. The riser in SBP was seen in 21 in PE, 15 in GH and 0 in WCH. The PR of both BPs in three groups was similar, while, the PR of pulse was lower in PE ( $0.24 \pm 0.18$  for PE vs  $0.33 \pm 0.17$  for GH and  $0.33 \pm 0.21$ ). In PR more than 0.16, the acrophase of SBP in 57% of PE, 40% of GH and 0% of WCH were shifted to evening or night. **Conclusion** Characteristic changes in PE was reduction of PR in BP as well as pulse and shifted acrophase. The pathogenesis of PE might be involved in not only vascular dysfunction but also sympathetic disorders.

#### ISP-14-4

**Cardiac dysfunction in patients with preeclampsia** Eiji Yoshida, Risa Yoshimoto, Takuji Ueno, Takuma Yamada, Takehiko Takeda, Sho Tano, Kaname Uno, Mayu Ukai, Tepei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi

*Perinatal Medical Center, TOYOTA Memorial Hospital*

**Objective** Some preeclampsia patients develop left ventricular diastolic dysfunction (LVdD). However, few studies have illustrated prognostic factors for LVdD. We aimed to reveal the risk factors associated with LVdD in patients with preeclampsia. **Methods** This was a single center prospective cohort study. Single pregnant women with preeclampsia who delivered at our hospital between November 2011 and January 2015 were eligible. Echocardiography was conducted in 99 patients before delivery and in 163 patients a few days after delivery. Early transmitral velocity/early diastolic velocity of the mitral annulus (E/Ea) >15 was defined as LVdD. Logistic regression analysis was conducted to examine risk factors of LVdD. **Results** Age>35, plasma BNP>100 pg/mL, blood loss>1,000 mL, plasma creatinine>0.7 mg/dL and severe preeclampsia (systolic BP>160 mmHg or diastolic BP>110 mmHg) were included as independent variables for the analysis of LVdD. E/Ea>15 was detected in 12 (12.1%) patients before delivery and in 16 (9.8%) patients after delivery. While BNP>100 pg/mL was a risk factor of LVdD before delivery (OR=4.114, 95%CI=1.023-16.549, p=0.046), this was not an independent risk factor of LVdD after delivery (OR=2.396, 95%CI=0.681-8.431, p=0.173). Maternal age>35 was a risk factor after delivery (OR=6.002 ; 95%CI=1.536-23.464 ; p=0.01). Blood loss>1,000 mL, plasma creatinine>0.7 mg/dL and severe preeclampsia did not associate with LVdD. **Conclusion** LVdD was detected even after delivery. While BNP>100 pg/mL was the risk factor of LVdD before delivery, it was not an independent risk factor of LVdD after delivery.

#### ISP-14-5

**Maternal cardiac function in patients with preeclampsia compared with normal pregnant women** Takuma Yamada, Takehiko Takeda, Kaname Uno, Sho Tano, Michinori Mayama, Mayu Ukai, Tepei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi *TOYOTA Memorial Hospital*

**Objective** Preeclampsia is a risk factor of peripartum cardiomyopathy and increases the risks of cardiovascular diseases. The aim of this study was to examine maternal cardiac function in patients with preeclampsia during peripartum period. **Methods** Patients with preeclampsia were enrolled in this study from 2010 to 2016. Echocardiography was conducted three times : late stage of pregnancy, early and one-month postpartum. In the same period, pregnant women without high BP took echocardiography as a control group. **Results** Eighty seven patients with severe preeclampsia and 51 patients with mild preeclampsia were compared with 36 normal pregnant women. Left ventricular ejection fraction (LVEF) was not significantly different among three groups. Though LV diastolic parameter, which was measured by early transmitral velocity/early diastolic velocity of the mitral annulus E/Ea, became worse in mild group at late pregnancy, the cardiac parameters were not significantly different in normal pregnant after delivery. At late pregnancy, E/Ea, left ventricular (LV) diameter and LV wall thickness deteriorated in severe group compared with other groups. These deteriorations were shown after delivery, even at one-month postpartum. **Conclusion** Maternal cardiac function of mild preeclampsia became normal in early postpartum. On the other hand, severe preeclamptic patients experienced cardiac changes and these deteriorations did not recover completely at early and even one-month postpartum. These changes are assumed to correlate with future onset of cardiovascular diseases.

#### ISP-14-6

**Long-term outcomes of infants delivered between 24 and 34 weeks of gestation in women with early-onset hypertensive disorders of pregnancies (HDP)** Junsuke Muraoaka<sup>1</sup>, Masanao

Oohashi<sup>1</sup>, Kaori Michikata<sup>2</sup>, Yohei Maki<sup>2</sup>, Koutarou Doi<sup>2</sup>, Yasuyuki Kawagoe<sup>2</sup>, Yuki Kodama<sup>2</sup>, Masatoki Kaneko<sup>2</sup>, Hiroshi Sameshima<sup>2</sup> *Miyazaki Medical Association Hospital<sup>1</sup>, University of Miyazaki Hospital<sup>2</sup>*

**Objective** To assess the long-term outcomes of infants in early-onset HDPs and its antepartum fetal heart rate patterns correlated to the outcomes. **Methods** A retrospective, observational study was performed involving singleton, non-anomalous 282 infants born between 24 and 34 weeks of gestation at a tertiary center for a 13-year period (2003–2015), focusing on antenatal management including administration of antenatal corticosteroid and magnesium sulfate, fetal heart rate monitoring, mode of delivery, birth weight and its percentile, and infants outcome. Cases with intrapartum unavoidable events including placental abruption (n=17) and prolapse of umbilical cord (n=2) are excluded. Poor outcome included neonatal death (ND), cerebral palsy (CP), and developmental disorders (DD) at 2-year-old. **Results** Excluded 34 loss of follow-up infants, we enrolled 229 cases, in which 34 cases with HDPs and 195 cases without HDPs. In early-onset HDPs, nine infants (16%) resulted in poor outcome including one case of ND, three cases of CP, and five cases of DD. Minimal baseline variability associated with late decelerations of antepartum FHR monitoring patterns had tendency to result in poor neurological outcomes compared to any other abnormal FHR patterns. **Conclusion** Antepartum FHR patterns including minimal baseline variability associated with late decelerations may be risk factor for neurological sequela in early-onset HDPs

#### ISP-14-7

**The difference of the activated prorenin concentration between pregnant women with or without hypertensive disorder of pregnancy** Shoko Tamada, Kazumasa Tani, Jota Maki, Takeshi Eguchi, Takashi Mitsui, Eriko Eto, Kei Hayata, Hisashi Masuyama *Okayama University*

**Objective** The activated prorenin has an important role in the tissue RAS. The purpose of this study was to reveal the difference of activated prorenin concentration between pregnant women who developed hypertension disorder of pregnancy and normal pregnant women. **Methods** The subjects were 7 pregnant women who developed HDP and 30 normal pregnant women in Okayama University Hospital. The activated prorenin concentration was measured with the plasma sampled in the first, second and third trimesters of pregnancy and umbilical cord blood by ELISA and compared between pregnant women who developed HDP and normal pregnant women. This study was approved by the Institutional Ethical Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. **Results** The activated prorenin concentration in pregnant women who developed HDP on the second trimester was  $573.6 \pm 71.9$  pg/ml, and that on the third trimester was  $733.3 \pm 211.1$  pg/ml. The activated prorenin concentration in normal pregnant on the second trimester was  $1,170.2 \pm 251.1$  pg/ml, and that on the third trimester was  $1,089.7 \pm 386.0$  pg/ml. The activated prorenin concentration in pregnant women who developed HDP was significantly lower than that in normal pregnant women throughout the second and third trimesters of pregnancy. **Conclusion** Activated prorenin concentration in pregnant women who developed HDP was lower than that in normal pregnant women. Reduction of blood activated prorenin concentration in pregnant women who developed HDP may reduce vasodilatation by AT2 required during pregnancy and may be involved in placental blood flow failure.

#### ISP-15-1

**Relationship between 50-g glucose challenge test and large**

**for gestational age infants among pregnant women without gestational diabetes** Dittakarn Boriboonhirunsarn, Prasert Sunsaneevithayakul *Siriraj Hospital, Thailand*

**Objectives** To compare incidence of large for gestational age (LGA) between women with false positive and normal glucose challenge test (GCT), and to evaluate factors associated with LGA. **Methods** A retrospective cohort study included 480 pregnant women at risk for gestational diabetes (GDM); 160 with false positive GCT and 320 with normal GCT results. Incidence of LGA and other pregnancy outcomes were compared between normal and false positive GCT groups. Possible associated factors for LGA were evaluated by comparing various characteristics with those with appropriate for gestational age (AGA) infants. **Results** Women with false positive GCT were significantly older and more likely to be multiparous, and less likely to gain weight greater than recommendation. Incidence of LGA were comparable between false positive and normal GCT groups (15.6% vs. 13.1%,  $p=0.456$ ). Other pregnancy outcomes were also comparable. Logistic regression analysis showed that pre-pregnancy underweight significantly reduced the risk of LGA (adjusted OR 0.25, 95%CI 0.07–0.87,  $p=0.029$ ) while second trimester weight gain  $>7$  kg significantly increased the risk of LGA (adjusted OR 3.13, 95%CI 1.67–5.89,  $p<0.001$ ). **Conclusion** The risk of LGA was only slightly higher among women with false positive GCT. Pre-pregnancy underweight reduced the risk of LGA while second trimester weight gain  $>7$  kg increased the risk of LGA.

#### ISP-15-2

**Prevalence of false positive 50-g glucose challenge test and relationship with adverse pregnancy outcomes** Auakarn Thananyai, Dittakarn Boriboonhirunsarn, Tachjaree Panchalee *Siriraj Hospital, Thailand*

**Objective** To determine the prevalence of false positive results of 50-g GCT for early GDM screening and relationship with pregnancy outcomes. **Methods** A total of 500 singleton pregnancy who were at risk for GDM and received 50-g GCT for GDM screening before 20 weeks of gestation were included. Women with abnormal 50-g GCT received 100-g OGTT for GDM diagnosis. Data were extracted from medical records, including baseline characteristics, GDM risk factors, 50-g GCT and 100-g OGTT results, obstetric data, and pregnancy outcomes. Prevalence of false positive results of 50-g GCT and GDM were estimated. Various baseline characteristics and pregnancy outcomes were compared between women with normal GCT, false positive GCT, and GDM. **Results** Mean age was 33.4 years, mean BMI was  $22.9 \text{ kg/m}^2$ , and 45.6% were nulliparous. Common GDM risks were age  $\geq 30$  years (81.6%), family history of DM (30.4%), and overweight/obesity (24.6%). Mean GA at GDM screening was 9.8 weeks. Normal 50-g GCT was found in 243 women (48.6%). The other 257 women underwent 100-g OGTT and 187 (37.4%) had false positive GCT results (normal 100-g OGTT) and 70 (14%) had GDM. Women with GDM had significantly higher age, BMI, and more likely to be overweight or obese than those with normal and false positive GCT ( $p<0.05$ ). Gestational weight gain were comparable between normal and false positive GCT but it was significantly greater than GDM ( $p<0.001$ ). A significant trend of increasing in the rate of LGA was observed in normal GCT, false positive GCT, and GDM group (14.4%, 21.9%, and 25.7%, respectively,  $p=0.013$ ). **Conclusion** Prevalence of false positive GCT was 37.4%. Women with false positive GCT were at increased risk of LGA.

#### ISP-15-3

**Determination of an Optimal 50-g Oral Glucose Challenge Test Cutoff Value to Screen for Gestational Diabetes Mellitus**

Sakiko Matsuoka, Tatsuya Fukami, Miho Ando, Sumie Nakamura, Yoko To, Takahiro Koyanagi, Maki Goto, Haruhiko Kondo, Hiroshi Tsujioka, Fuyuki Eguchi *Aso Iizuka Hospital*

**Objective** The aim of this study was to evaluate the cutoff value of 50-g oral glucose challenge test for the screening of gestational diabetes mellitus. **Methods** 843 patients were analyzed using 50g GCT during 18 to 24 weeks of gestation. We set the cutoff value of blood glucose at 130 mg/dl and positive patients sequentially underwent 75g OGTT. Other patients also underwent 75g OGTT if consent for the test was available. Gestational diabetes mellitus (GDM) is/was diagnosed on the International Diabetes in Pregnancy Consensus Group (IADPCG) criteria. **Results** 381 patients were positive for the 130mg/dl cutoff value and 115 patients were diagnosed with GDM. 50g GCT negative patients numbered 462 and the 45 of them who agreed to our trial underwent 75g OGTT, of which 8 patients were diagnosed with GDM. ROC curve revealed the cutoff value of blood glucose for 50g GCT as 129mg/dl (sensitivity : 94%, specificity : 64%, area under the curve : 0.83,  $p > 0.05$ ). **Conclusion** We propose that the cutoff value of 50g GCT should be 130 mg/dl in the screening of GDM.

### ISP-15-4

**Present condition and problems of gestational diabetes mellitus care in our prefecture** Naoto Yonetani, Takashi Kaji, Atsuko Hichijo, Minoru Irahara *Tokushima University*

**Objective** The objective was to clarify the present condition and problems of gestational diabetes mellitus (GDM) care in our prefecture. **Methods** A self-administered questionnaire survey related to GDM was conducted for all birthing facilities in our prefecture. The number of singleton births in 2018, among which the number of GDM patients, the screening method of glycometabolism abnormality, the management during pregnancy and puerperium, the explanation about the future risk of developing diabetes were investigated. **Results** All 18 facilities (9 hospitals and 9 clinics) responded. The total number of singleton births was 5,969, among which 113 GDM patients delivered. The incidence of GDM was 1.9%, which was well below the assumed incidence at the new GDM diagnostic criteria (7 to 8%). One hospital and 3 clinics did not establish criteria for positive screening in the first trimester. In 6 hospitals all patients with GDM were referred to the internal medicine. In 3 hospitals and 2 clinics all patients had 75gOGTT during puerperium, and in five hospitals and 4 clinics all patients were explained about the future risk of diabetes. **Conclusion** The incidence of GDM in our prefecture was low. It was considered as one of the factors that screening criteria were not established at any facilities. The frequency with internal medicine physician involvement was high, we considered that the survey about the management method of physicians was also necessary. Furthermore, the improvement of postpartum educational methods was also desired.

### ISP-15-5

**Glycemic and metabolic features in gestational diabetes : singleton versus twin pregnancies** Yohei Akiba, Kei Miyakoshi, Yu Sato, Satoru Ikenoue, Yoshifumi Kasuga, Daigo Ochiai, Tadashi Matsumoto, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** The information on clinical features of gestational diabetes (GDM) in twin pregnancies is limited. The aim of this study was to compare the severity of dysglycemia between twin and singleton pregnancies with GDM (T-GDM and S-GDM). **Methods** We reviewed GDM women who underwent perinatal care from 2011 to 2016 in our hospital. During the study period, all GDM women underwent dietary management and self-monitoring of blood glucose measurements. Insulin administration

was initiated when dietary treatment did not achieve the glycemic goal. The glycemic and metabolic characteristics were compared between T-GDM and S-GDM, as follows : gestational week at the diagnosis of GDM, 75g oral glucose tolerance test (OGTT) results, HbA1c, insulin secretion (i.e. insulinogenic index [IGI] and Insulin Secretion-Sensitivity Index-2 [ISSI-2]), and insulin requirement before delivery. **Results** Of 3,322 deliveries (twin, n=123 ; singleton, n=3,199), there were 471 women with GDM (T-GDM, n=20 ; S-GDM, n=451). The rate of one abnormal OGTT value in T-GDM was similar to that in S-GDM (71% vs 60%). There were no significant differences in gestational week and levels of HbA1c at diagnosis, levels of IGI and ISSI-2 between T-GDM and S-GDM (median, 24 weeks vs 17 weeks, 5.3% vs 5.2%, 0.94 vs 0.79, 1.85 vs 1.97, respectively). The rate of insulin treatment and a median dosage of insulin needed before delivery was comparable between the two groups (T-GDM vs S-GDM : 32% vs 45% and 13 vs 14 unit/day). **Conclusion** Our data indicated that women with T-GDM was similar to those with in the severity of glucose intolerance.

### ISP-15-6

**Efficacy of the risk scoring system to triage patients with gestational diabetes** Hiroshi Yamashita, Megumi Koga, Ichiro Yasuhi, Satoshi Isokawa, Noriko Odani, So Sugimi, Yasushi Umezaki, Sachie Suga, Masashi Fukuda, Nobuko Kusuda *Nagasaki Medical Center*

**Objective** We have originally developed a risk scoring system to triage patients with gestational diabetes (GDM), depend on their perinatal risk. Our aim was to demonstrate whether the risk scoring system was effective for predicting of high-risk GDM patients to triage intensive care. **Methods** This is a prospective study including singleton pregnant women with GDM between 2015-2017. In the scoring system (10 points in total), we allocated 4 points to each risk factor : fasting PG=or  $> 84$  mg/dL at diagnosis, prepregnancy body mass index=or  $> 24$  kg/m<sup>2</sup>, and 1 point to : =or  $> 2$  abnormal values of OGTT, age=or  $> 40$  years. We defined the score 0, 1-2, and=or  $> 4$  as Category 1, 2, and 3, respectively. We also defined high-risk GDM as requiring insulin=or  $> 20$  U/day and/or having a large-for-gestational age infant. We evaluated the association between the categories and the high-risk GDM. **Results** Among 162 women, we found 48 (30%) high-risk GDM patients. By the scoring system, 53 (33%), 21 (13%) and 88 (54%) were categorized as Category 1, 2, and 3, respectively. The prevalence of high-risk GDM were 13.2%, 33.3%, and 38.6%, respectively. In comparison with Category 1 (reference), Category 3 was significantly associated with high-risk GDM with an odds ratio of 4.14 (95%CI 1.76-11.0,  $p < 0.01$ ). **Conclusion** The risk scoring system was confirmed as effective in this prospective study. Patients with GDM in Category 3 need more intensive care, while those in Category 1 may require less intensive management in the clinic type care system.

### ISP-15-7

**Epigenetic modifications of well-controlled gestational diabetes on cord blood using genome-wide methylation analysis** Yoshifumi Kasuga<sup>1,2</sup>, Kei Miyakoshi<sup>1</sup>, Yu Sato<sup>1</sup>, Toshimitsu Otani<sup>1</sup>, Yohei Akiba<sup>1</sup>, Marie Fukutake<sup>1</sup>, Satoru Ikenoue<sup>1</sup>, Daigo Ochiai<sup>1</sup>, Tadashi Matsumoto<sup>1</sup>, Kenichiro Hata<sup>3</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Kawasaki Municipal Hospital<sup>2</sup>, National Research Institute for Child Health and Development<sup>3</sup>*

**Objective** Epigenetic modifications associated with maternal hyperglycemia are assumed to mediate the susceptibility of metabolic disorders of the offspring. To date, however, the information on epigenetic influence on offspring in well-controlled

gestational diabetes mellitus (w-GDM) is limited. The aim of this study was to investigate genome-wide methylation variation in cord blood from offspring born to mothers with w-GDM. **Methods** Umbilical cord blood samples were collected from singleton term neonates born to Japanese mothers with w-GDM (n=165) or normal glucose tolerance (NGT, n=61) from 2011 to 2016. All GDM women underwent dietary management and self-monitoring of blood glucose measurements. Insulin administration was initiated when dietary treatment did not achieve the glycemic goal. Genome-wide DNA methylation over 850k CpG sites in cord blood was compared between the GDM and NGT groups using Illumina Infinium MethylationEPIC Beadchip (EPIC array). We scaled individual arrays to have the same median absolute deviation using limma package in R. **Results** There were no differences in maternal gestational weight gain (8.6kg vs 8.3kg), birthweight (3,014g vs 2,988g), sex (male : 54% vs 56%), heavy-for-date (birthweight>90%tile : 16% vs 15%) and small-for-date (birthweight<10%tile : 1% vs 3%) between the w-GDM and NGT groups. The EPIC array demonstrated no significant epigenetic differences between the two groups. Even if stratified by fetal sex, pregestational weight category, or heavy-for-date neonates, there were no differentially methylated loci associated with w-GDM. **Conclusion** Genome-wide methylation analysis demonstrated no significant methylation differences in cord blood from offspring born to mother with w-GDM, compared to those with NGT.

#### ISP-15-8

**Is the therapeutic intervention during early pregnancy effective in women with gestational diabetes diagnosed before 20 weeks' gestation?** Noriko Odani, Sachie Suga, Ichiro Yasuhi, Hiroshi Yamashita, Satoshi Isokawa, Megumi Koga, So Sugimi, Masashi Fukuda, Nobuko Kusuda *Nagasaki Medical Center*

**Objective** It is unclear whether the therapeutic intervention for women diagnosed as having gestational diabetes (GDM) during early gestation. In this preliminary study, we aimed to demonstrate whether therapeutic intervention before 20 weeks' gestation was effective in women with GDM diagnosed during early pregnancy. **Methods** This is a prospective study including women diagnosed as GDM by 75-g glucose tolerance test (OGTT) before 20 weeks. Those women did not have any therapeutic intervention except for regular prenatal care, and had the second OGTT between 24 to 26 weeks. We excluded women with fasting plasma glucose (PG)  $\leq 110$  mg/dl or obese women with fasting PG of 92-109 mg/dl. **Results** We included 12 subjects (36  $\pm$  5 years ; prepregnancy body mass index 24  $\pm$  5), including 4 obese women. They had the first OGTT at 15  $\pm$  2 weeks ; PGs during the OGTT were 86  $\pm$  8, 174  $\pm$  24, and 162  $\pm$  27 mg/dl at fasting, 1-hr, and 2-hr, respectively. The second OGTT were performed at 25  $\pm$  1 weeks ; the PGs during the test were 80  $\pm$  8, 144  $\pm$  27, and 134  $\pm$  29, respectively. By the second OGTT, only three women (25%) were diagnosed as GDM and the other had normal results. They delivered of infants with birthweight of 2,840  $\pm$  544 g, without any macrosomia, at 38  $\pm$  2 weeks. **Conclusion** In this preliminary study, three quarters of women diagnosed as GDM during early gestation showed normal results at the repeat OGTT during midpregnancy without any therapeutic intervention before 20 weeks' gestation. We suggest that the therapeutic intervention during early pregnancy may not be useful rather over treatment.

#### ISP-15-9

**Monochorionic diamniotic twin pregnancy complicated by type I diabetes treated with SAP therapy for blood sugar control** Miho Kondo, Aki Mabuchi, Miyoko Waratani, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Purpose** We are reporting on a monochorionic diamniotic (MD) twin pregnancy complicated by type I diabetes in which glucose level was controlled by Sensor Augmented Pump (SAP) therapy and led to vaginal delivery. **Case** The patient was a 38-year-old woman, gravida 3 para 1 who developed type I diabetes at 28 years and was on insulin therapy. She conceived MD twins naturally while she was being considered for switching to insulin pump due to poor glycemic control, and SAP therapy was initiated at 6 weeks of gestation. The MD twins were progressing normally without amniotic fluid imbalance or abnormal blood flow. Gestational hypertension and proteinuria was observed at 31 weeks, which required in-hospital management. However, she had uterine contractions on admission, which were inhibited with magnesium sulfate. Blood pressure was stable within the normal to mildly hypertensive range and proteinuria did not worsen. Glucose levels were well controlled with carbohydrate counting to adjust insulin dosage. Labor was induced at 37 weeks and 0 days and both babies were delivered vaginally. The first infant weighed 3,324 g, Apgar score 8/10 and the second infant weighed 2,644 g, Apgar score 8/10. The respective glucose levels of the two babies at birth were 71 mg/dl and 73 mg/dl. During induction of labor, the mother's glucose level was controlled between 100 to 120 mg/dl. **Conclusion** Glucose level was well controlled during pregnancy and delivery with SAP therapy in a MD twin pregnancy complicated with type I diabetes, and was managed without major perinatal complications.

#### ISP-15-10

**Correlation of early pregnancy body mass index, waist circumference and waist-to-hip ratio to gestational diabetes mellitus** Kathryn Bautista, Marie Cathleen Santiago *Manila Central University, Philippines*

**Introduction** Anthropometric measurements taken in early pregnancy can predict increased risk of gestational diabetes mellitus (GDM). Body mass index (BMI) may be a limited measure of total obesity because the association of diabetes with central obesity is stronger than the association with general fat. Thus, alternative measures that reflect abdominal adiposity, such as waist circumference, waist-hip ratio, have been suggested, because increased visceral adipose tissue is associated with metabolic abnormalities that predispose to GDM. **Objective** To determine the correlation of body mass index, waist circumference and waist-to-hip ratio to the development of GDM. **Methods** Measurements for height, weight, waist circumference and hip circumference were done at the first prenatal visit among 56 patients between 4-12 weeks age of gestation. Diagnosis of Gestational Diabetes Mellitus was made with fasting blood glucose and 75g oral glucose tolerance test. **Results** Results showed that BMI, and waist-to-hip ratio (WHR) were significantly associated with GDM. For this study, a cut-off value of > 23 kg/m<sup>2</sup> for GDM, and a waist-to-hip ratio of  $\geq 0.80$  were significantly associated with GDM. Results revealed that WHR is the most sensitive parameter to rule out GDM. **Conclusion** There is a progressive increase in GDM risk above a BMI of 23 kg/m<sup>2</sup> (OR 2.14 ; 95% CI 1.02, 4.76) with no apparent increase in risk for GDM among underweight women (BMI<18.5 kg/m<sup>2</sup>). There is a progressive increase in GDM risk above a WHR of  $\geq 0.8$ . There is no significant association between GDM and waist circumference.

#### ISP-16-1

**The Missing Link : A Case of Hydrops Fetalis in Alpha Thalassemia** Ivy Karen Romero, Angelita Reyes-Teotico *Manila Central University-Filemon D. Tanchoco Medical Foundation Hospital, Philippines*



Hemoglobin is the oxygen carrying component of RBCs. Its structure consists of a tetramer of globin polypeptide chains : a pair of alpha-like and a pair of beta-like chains. Normally, globin chain synthesis is balanced. Each newly synthesized alpha or non-alpha globin chain will have an available partner to pair with however, problems do arise when there is a missing link. This a case of a 21 year old, primigravid, pregnant for 28 5/7 weeks, referred to our institution for fetal cardiac anomaly. Ultrasound at 21 2/7 weeks age of gestation revealed fetal cardiomegaly, ASD, beginning ascites with hydrothorax. Anemia with decreased RBC indices was also noted. Iron supplementation was done, but anemia persisted. In our institution, biometry was compatible with age ; placentomegaly, fetal hydrops (ascites, pericardial effusion) were noted. Fetal echocardiography showed cardiomegaly, right atrial enlargement and normal outflow tracts. MCA Doppler revealed a peak systolic velocity of 52 cms/sec, equivalent to 1.4 MoM, indicative of mild to moderate anemia. Administration of corticosteroids was done. Patient and her partner underwent hemoglobin electrophoresis revealing Alpha Thalassemia trait. Cordocentesis and intrauterine fetal transfusion were done, however at 31 weeks, fetal monitoring showed non-reassuring fetal status. Cesarean section was done and delivered to a live, baby boy, BW 1,500g, Apgar score of 1, 1, 1, Ballard's score of 32 weeks. Unfortunately, despite fetal resuscitation, baby succumbed. We can therefore say that prompt diagnosis of maternal condition is important so that proper management may be instituted and possibly decrease neonatal morbidity and mortality.

## ISP-16-2

**Clinical characteristics of women developing perinatal venous thromboembolism under standardized prophylaxis management following JSOG guideline** Misako Kuramochi, Takeshi Nagamatsu, Eri Inoue, Hitomi Furuya, Takahiro Seyama, Toshio Nakayama, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Venous thromboembolism (VTE) is a life-threatening complication in perinatal period. This study aimed to reveal clinical characteristics of women developing VTE in perinatal periods to gain knowledge for better management for VTE prevention. **Methods** This study was conducted under approval of our facility ethics committee. The cases developing VTE in perinatal period were isolated among the women managed in our hospital from 2002 to 2016 (n=17 out of 11,896 deliveries, 0.14%). During the observational period, the prophylaxis using unfractionated heparin was conducted for the women with a past history of VTE and with thrombophilia confirmed before conception risk. Pneumatic device was used for all the cases having cesarean section. The clinical data associated with the incidence of VTE were analyzed by reviewing the medical records of the VTE cases. **Results** VTE occurred in the first trimester (n=9/17, 53%), in the second trimester (n=2/17, 12%), in the third trimester (n=1/17, 6%), and in postpartum (n=5/17, 29%). The cases developing VTE during the first trimester were characterized by advanced maternal age at 35 or over (n=7/9, 78%) and hyperemesis requiring hospitalization (n=3/9, 33%). There was no case developing VTE under heparin administration. **Conclusion** Advanced maternal age and hyperemesis would be risk factors for VTE in the first trimester. Considering relatively high frequency of VTE in the first trimester even under the so-far conducted VTE prevention management, it is necessary to establish a new prevention approach to evaluate VTE risk in early pregnancy.

## ISP-16-3

**Preeclampsia in Pregnancies with Systematic Lupus Erythe-**

**matusus** Hiroyo Meguro<sup>1</sup>, Hyo Kyozuka<sup>1</sup>, Makiho Ishibashi<sup>1</sup>, Satoshi Suzuki<sup>1</sup>, Daisuke Suzuki<sup>2</sup>, Akiko Yamaguchi<sup>1</sup>, Mikio Tanaka<sup>3</sup>, Keiyo Fujimori<sup>1</sup> *Fukushima Medical University<sup>1</sup>, Fukushima Medical Center for Children and Women<sup>2</sup>, Ohta-Nishinouti Hospital<sup>3</sup>*

**Objective** The aim of this study was to identify factors associated with preeclampsia (PE) in pregnancies with systematic lupus erythematosus (SLE). **Methods** We retrospectively conducted a case control study at two medical centers in Fukushima Prefecture between 2006 and 2017. Clinical information, including immunological data obtained during the first trimester and pregnancy outcomes, were reviewed. Pregnancies with SLE were divided into two groups (Case : pregnancy with PE ; Control : Pregnancy without PE). Then, clinical information obtained during the first trimester was compared. A p<0.05 was assumed to indicate significance. **Results** 35 pregnancies with SLE were identified during the period. Among the 35 pregnancies, preterm birth and low birth weight (i.e., <2,500 g) occurred in 31.4% and 42.9%, respectively. PE was observed in 9 cases (25.7%). Immunological data obtained during the first trimester revealed that the incidence of depressed levels of CH50, C3, C4, and anti-SSA antibody was significant higher in PE cases than in controls (77.8% vs 21.7%, 77.8% vs 9.1%, 77.8% vs 27.3%, and 100% vs 45.0%, respectively). The rates of anemia and thrombocytopenia were not significantly different between the two groups. **Conclusion** Pregnancy with SLE was related to obstetric complications. Immunological data obtained during the first trimester is useful for predicting the occurrence of PE in SLE pregnancy.

## ISP-16-4

**Postpartum thrombotic microangiopathy occurring secondary to systemic lupus erythematosus : a case report** Kenichiro Hirotani, Saki Kido, Takahiro Nakano, Masahiro Hachisuga, Nobuhiro Hidaka, Yasuyuki Fujita, Kiyoko Kato *Kyushu University*

A 32-year-old woman, gravida 1 para 0, was referred at 14 weeks' gestation with the diagnosis of pregnancy with systemic lupus erythematosus (SLE). SLE was controlled by administration of prednisolone, azathioprine, and cyclosporine during pregnancy. At 37 weeks' gestation, she was admitted to our hospital for premature rupture of membrane, and underwent induction of labor. Vacuum extraction was performed due to increased blood pressure in the second stage of labor, and manual removal of the placenta was needed. Six hours after delivery, she demonstrated severe anemia, thrombocytopenia, and hypofibrinogenemia. Estimated blood loss was 400g, indicating hemorrhagic disseminated intravascular coagulation (DIC) ; therefore, transfusion therapy was performed. Twelve hours after delivery, blood tests revealed elevated liver enzymes, lactate dehydrogenase (LDH), and serum creatinine levels, suggesting hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. However, after the peak-out of elevated liver enzymes and LDH, normalized coagulopathy, thrombocytopenia and renal injury worsened. Blood microscopy showed red cell fragments, suggesting thrombotic microangiopathy (TMA) ; we subsequently ceased transfusion therapy. Shiga toxin-producing *Escherichia coli* results were negative, and the activity of ADAMTS13 was more than 95% ; therefore, we diagnosed her with secondary TMA based on SLE. She was treated by plasma exchange, hemodialysis, steroid pulse therapy, and immunosuppressive agent administration, and discharged at 6 weeks after delivery. Postpartum thrombocytopenia and hemolytic anemia are common in DIC or HELLP syndrome. If thrombocytopenia and renal injury are prolonged after delivery despite normalization of coagulopathy or liver enzymes, other TMAs should be considered.

## ISP-16-5

**A case of treatment-resistant idiopathic thrombocytopenic purpura during pregnancy** Maki Okada, Ryo Maekawa, Haruka Takagi, Masahiro Shinagawa, Lifa Lee, Hiroshi Tamura, Norihiro Sugino *Yamaguchi University Hospital*

Idiopathic thrombocytopenic purpura (ITP) is an acquired thrombocytopenia without other clear cause of the thrombocytopenia. In general, patients with ITP experience a reduction of platelet counts during pregnancy. We report a severe case of ITP which was getting worse during pregnancy. A 30-year-old pregnant woman, gravida 0 para 0, had purpura and hematuria with a low platelet count of  $0.1 \times 10^9/\mu\text{L}$  at 16 weeks of gestation. She was admitted to our hospital for further evaluation of the thrombocytopenia. She had a lot of petechiae, ecchymosis and purpura in her skin and oral mucous membrane. After the exclusion of all other causes of thrombocytopenia by several tests including a bone marrow examination, she was diagnosis as ITP. She was treated with prednisolone and intravenous immunoglobulin (IVIg). These therapies were not effective to increase persistently the platelet count to the enough level. Even platelet transfusion didn't increase the platelet count. Because of the severity and treatment resistance, splenectomy was performed at 25 weeks of gestation. The platelet count was temporarily increased, but it decreased again shortly. Since it was difficult to keep the platelet count enough to continue the pregnancy, she received a caesarean section at 34 weeks of gestation together with intensive treatments with IVIg and platelet transfusion. After the caesarean section, the platelet count increased to the normal level. When any treatments are not effective to increase the platelet count in such a severe ITP case, a termination of pregnancy would be an only therapeutic option.

## ISP-16-6

**ARDS due to H3N2 Influenza A occurring in the second trimester of pregnancy: A case report** Yuri Sasaki, Akihiko Kikuchi, Gen Haba, Hideyuki Chida, Hiroki Onoue, Tomonobu Kanasugi, Chizuko Isurugi, Rie Oyama, Toru Sugiyama *Iwate Medical University*

Many pregnant women had serious complications from the H1N1 pandemic 2009 worldwide. However, there have been no reports of ARDS due to H3N2 influenza during pregnancy in English literature. We herein report such a case. A 41-year-old primigravida woman was admitted to our hospital at 24 weeks gestation for threatened premature labor. She became pregnant by in vitro fertilization with no other medical history. She was vaccinated against seasonal influenza one month before admission. Although there was no sign of infection on admission, she developed a fever on the second day and respiratory distress on the third day. Chest X-ray and CT showed clinical pictures of ARDS. Emergency caesarean section was performed because her respiratory condition deteriorated despite intubation. Influenza rapid tests at 12 hours and 24 hours after the onset of her fever were both negative. H3N2 influenza infection was finally confirmed several weeks later by a serological test done on the first day of her symptoms. General intensive care after caesarean delivery rapidly improved her general condition without extracorporeal circulation nor administration of anti-influenza medication. On the other hand, her infant died for complications due to immaturity on the 48th day after birth. Our case indicated that even a healthy pregnant woman can rapidly develop ARDS due to influenza infection. Based on our experience, immediate termination of pregnancy might be quite essential for rescuing such a patient from critical respiratory conditions.

## ISP-16-7

**Analysis of pregnant women with syphilis** Hidenori Sasa,

Masaya Nakatsuka, Takahiro Natsuyama, Takahiro Sakamoto, Haruka Kawachi, Hiroaki Soyama, Morikazu Miyamoto, Kiguna Sei, Masashi Takano, Kenichi Furuya *National Defense Medical College*

**Objective** The pregnant women with syphilis infection have been increased in recent years. We report the diagnosis and management of pregnant women with syphilis. **Methods** Six patients with syphilis were analyzed in our hospital for the past four years. Laboratory data, treatment, maternal and neonatal outcome were investigated for six pregnant women with syphilis. **Results** They were infected from their partner or unknown person and the time of the syphilis infection was unclear in all cases. The values of RPR and TPLA were high in two cases, and moderate in four cases. Ampicillin or amoxicillin were administered for 12 weeks in all cases. Three pregnant women without syphilis lesion were delivered uneventfully and their neonates were not infected with syphilis. Three pregnancies with head or genital lesions of syphilis terminated in artificial abortion for the economic reason and were diagnosed as the second stage of syphilis. **Conclusion** There was no maternal-fetal infection of syphilis in our case because of early treatment for maternal syphilis. It is necessary to diagnose and treat early for increasing number of maternal syphilis infection.

## ISP-16-8

**The meaning of Methicillin-resistant Staphylococcus aureus (MRSA) colonization in pregnant women: a prospective cohort study** Jumpei Ogura, Koji Yamano, Yoshihide Inayama, Tsutomu Ohara, Mie Sakai, Haruka Suzuki, Koh Suginami *Toyooka Hospital*

**Objective** Methicillin-resistant Staphylococcus aureus (MRSA) infection is a great concern. The objective of this prospective cohort study is to assess the effect of maternal MRSA colonization on the clinical events in the perinatal period. **Methods** For this prospective cohort study, pregnant women were enrolled at 32 to 36 weeks gestation. Nasal and vaginal swabs for culture were obtained at enrollment. We followed up their clinical events in the perinatal period, such as preterm birth, premature rupture of membrane, Apgar score, umbilical artery pH, vertical transmission of MRSA at delivery, fetal MRSA skin and soft tissue infection (SSI) and admission to NICU, etc. We also investigated maternal backgrounds, such as number of para, their careers and complications during pregnancy. **Results** From September 2016 to August 2017, 598 pregnant women and their 606 newborns were enrolled. Maternal MRSA colonization occurred in 33 pregnant women (M group; 5.5%), and did not occur in 565 pregnant women (non-M group). Among clinical events in the perinatal period, vertical MRSA transmission at delivery and fetal MRSA SSI occurred significantly higher in M group than in non-M group (12% vs 0.003%; RR 13.793 [95%CI: 7.07~26.9], 6% vs 0%; RR 19.5 [13.8~27.5]). Among maternal backgrounds, the frequency of usage of antibiotics during pregnancy, health provider and multi-paras were significantly higher in the M group compared to those in the non-M group ( $p < 0.05$ , respectively). **Conclusion** Maternal MRSA colonization is a significant risk of vertical transmission of MRSA and fetal MRSA SSI in the perinatal period. This is an ongoing study.

## ISP-16-9

**Acute Appendicitis during Pregnancy** Misako Hideshima, Masatoshi Yokoyama, Yoshifumi Nakao, Hiroaki Nakahashi, Tomoko Yamamoto, Makiko Kurihara, Satoko Tsuda, Satoshi Nishiyama *Saga University Hospital*

**Objective** Acute appendicitis during pregnancy is the most common complication requiring surgical treatment. The subjective and objective signs of appendicitis are different during

pregnancy in comparison to non-pregnant individuals. As a result, this condition is difficult to diagnose during pregnancy, which in turn exposes the fetus and mother to an increased risk of mortality. We report cases in which we diagnosed acute appendicitis during pregnancy and describe its clinical presentation, diagnostic methods, and management and outcomes. We also review relevant reports. **Methods** The clinical data of five pregnant women who were diagnosed as acute appendicitis at our hospital from April, 2007 to July, 2017 were collected retrospectively. **Results** The age of women ranged between 23 and 40 years (median : 32 years). Two cases occurred during the first trimester, one occurred during the second trimester, and the remaining two occurred during the third trimester. The mean gestational age was 16 weeks (range : 6-35 weeks). Three of the five cases underwent appendectomy, one underwent laparoscopic surgery, and two underwent open surgery, including one case of operated appendectomy after child delivery via a cesarean operation. All but one case, which involved an artificial abortion, were managed successfully without severe fetal complications or loss. **Conclusion** Among these cases, those that received prompt treatment exhibited good maternal and fetal prognoses. Acute appendicitis during pregnancy involves perforation or diffuse peritonitis, and is associated with severe fetal complications and loss. Therefore, early diagnosis and treatment is essential.

### ISP-17-1

**Obstetrical and perinatal outcomes of the chemotherapy in breast and cervical cancer during pregnancy** Mee Hyang Ko, Suk Young Kim, Kyung Joo Cho, Su Kyeong Kong, Sun Young Jung *Gachon University of Korea, Korea*

Recent trend for women to delay childbearing, we expect more cases of cancer to be diagnosed during pregnancy. We had experienced two cases of pregnant women with breast cancer and one case of cervical cancer who had administered to cancer chemotherapy during pregnancy. Two cases was diagnosed the pregnancy associated breast cancer at first trimester of gestation and took surgical excision and lymph node dissection confirmed intraductal carcinoma histologically. They had administered chemotherapy during second trimester. One case, at 37+2 weeks of gestation, had delivered repeat cesarean section male weighting 3,870g with normal Apgar score. After delivery she had taken additional 4 cycles of chemotherapy. The other case also had taken surgery and chemotherapy and now she is 34 weeks of gestation without any obstetrical and fetal adverse events. In one case of cervical cancer, she had visited for vaginal bleeding and had found about 5 cm in size exophytic mass on cervix and confirmed was with squamous cell carcinoma by tissue biopsy. She had undergone carboplatin monotherapy for two cycles until 30 weeks of gestation. She had occurred preeclampsia and had performed cesarean section at 33+1 weeks of gestation. After 1 week later, she underwent radical abdominal hysterectomy and lymph node dissection for treatment of cervical cancer. Chemotherapy use in pregnancy, an extensive discussion must be undertaken with the patient and her family and multidisciplinary team of physicians. Discussion should include the benefits and the risks involved based limited data of chemotherapy use during pregnancy.

### ISP-17-2

**Successful Heterotopic Pregnancy with Prior Radical Trachelectomy after TCIC with MTX Treatment** Eun-Jee Whang, Kyong-No Lee, Keun-Young Lee *Kangnam Sacred Heart Hospital of Hallym University of Korea, Korea*

**Background** Heterotopic pregnancy with cervical incompetence is very uncommon. And yet there is no definite treatment

for cervical incompetence occurring after radical trachelectomy. We are reporting a rare and novel case of a following in vitro fertilization (IVF) combined intrauterine pregnancy and interstitial pregnancy which was successfully treated with maintenance of the pregnancy to term. **Case** We report a case of a 32-year-old woman with heterotopic interstitial pregnancy combined with intrauterine pregnancy at 8 weeks of gestation, who had radical trachelectomy in the past. For her extremely short or almost absent cervix, transabdominal cervicoisthmic cerclage (TCIC) was performed with ultrasound-guided injection of methotrexate (MTX) to terminate the interstitial gestation while preserving the intrauterine gestation. The final outcome was the birth of healthy newborn at 38 weeks of gestation. **Conclusion** The heterotopic interstitial pregnancy was successfully aborted, and the intrauterine pregnancy was successfully maintained until 38 weeks of gestation. There is no standardized treatment for heterotopic pregnancy with cervical incompetence occurring after radical trachelectomy. TCIC with local injection of MTX can be performed successfully for treatment of interstitial heterotopic pregnancy in patients who have wants to preserve the intrauterine gestation. This case illustrates a multidisciplinary approach that may be useful as a template in similar situations.

### ISP-17-3

**Obstetrical prognosis of patients treated by vaginal radical trachelectomy during pregnancy** Takafumi Kuroda, Shinichi Ishioka, Mina Umemoto, Tadahi Okada, Kaoru Noro, Hazuki Kashiwagi, Miseon Kim, Kyoko Isoyama, Masahito Mizuuchi, Miyuki Morishita, Tsuyoshi Baba, Tsuyoshi Saito *Sapporo Medical University*

**Objective** Radical trachelectomy (RT) with pelvic lymphadenectomy has become an option for young patients with early invasive uterine cervical cancer who desire their fertility. However this operative method is at high risk for the following pregnancy due to its radicality. We investigated retrospectively the obstetrical prognosis of patients treated by vaginal RT during pregnancy. **Methods** We have performed vaginal RT for four pregnant patients with uterine cervical cancer whose FIGO stage were IBI according to the method by Dargent et al. **Results** Patients' age ranged from 30 to 34, and all patients were nulligravida. They were diagnosed as uterine cervical cancer at 11-25 weeks of pregnancy. And following 1-5 weeks later, vaginal RT was performed for them between 16 and 18 weeks of pregnancy without any troubles. Three of them continued their pregnancies till 34 weeks or longer gestation under our following-up schedule published before. One patient terminated at 26 weeks gestation due to a focal recurrence of the cervical cancer. **Conclusion** Application of RT for pregnant patients can be a challenge for both gynecologic oncologists and obstetricians. However, expansion of vaginal RT for pregnant patients with uterine cervical cancer could be a practical option for them.

### ISP-17-4

**Clinical features and the management of pregnancy-associated breast cancer : Retrospective analysis of 8 patients** Tadahi Okada, Shinichi Ishioka, Hazuki Kashiwagi, Kyoko Isoyama, Takafumi Kuroda, Masahito Mizuuchi, Miyuki Morishita, Mizue Teramoto, Tsuyoshi Baba, Tsuyoshi Saito *Sapporo Medical University Hospital*

The number of pregnant patients with breast cancer is increasing with the increase of the number of breast cancer patients among the younger generation. To better understand this situation, we conducted retrospective analysis of 8 pregnant patients with breast cancer treated in our department between January 2011 and March 2016, using medical charts. The aver-



age age of the patients was 36.5 years (range : 32 to 42 years). In all patients, the reason for tumor detection was awareness of a tumor nodule in self-examination. The clinical stages of the patients were stage 0-I for 3 patients, stage II or higher for 4 patients, and recurrent cancer for 1 patient. The median time of delivery for the patients was 33 weeks (range : 31w0d-40w0d). Seven of the patients underwent cesarean section, and 1 patient delivered vaginally. The timing of the operation for the breast cancer was before delivery (median 23 weeks) for 5 patients, at the same time as cesarean section for 1 patient, and 2 weeks after delivery for 1 patient. Six of the patients remain free of disease, one is under treatment due to recurrent cancer, and one died of the disease. Early detection of the cancer via self-examination, and early operative treatment are important for pregnant patients with breast cancer. It is also important to decide the most appropriate timing of delivery to start postoperative treatment of the cancer as soon as possible based on the pathological results for the cancer, with collaboration among obstetricians, neonatologists, and oncologists.

### ISP-17-5

**A case of colorectal cancer during pregnancy** Miho Saito, Hironobu Hyodo, Naoya Tsujimoto, Satoshi Nitta, Yuki Taketani, Saho Fujino, Etsuko Saito, Fusako Sue, Midori Funakura, Sorahiro Sunagawa, Takahiro Kasamatsu, Koji Kugu *Tokyo Metropolitan Bokutoh Hospital*

Colorectal cancer during pregnancy is relatively rare and is difficult to be diagnosed because the symptoms such as nausea, vomiting, constipation, abdominal pain are quite common and radiographic imaging examination may tend to be avoided during pregnancy. A 30-year-old woman primigravida was referred to our hospital from a primary clinic in the 28 weeks for suspect of torsion of an ovarian tumor. Her complaint was abdominal pain, constipation and diarrhea. Computed tomography showed a tumor of sigmoid colon, multiple liver tumor, enlarged ovaries and swollen lymphnodes and colonoscopy revealed an ulcerative mass in the sigmoid colon. The biopsy confirmed adenocarcinoma, which suggested the fourth stage of colon cancer. Considering a risk of intestinal obstruction, resection of the tumor following to c-section was conducted at 31 weeks and a 1,692 g healthy female infant was delivered. In the operation, metastasis to the both ovaries, dissemination to the uterine serosa, and rupture of the abscess was confirmed. The ovaries and the uterus were resected together with the tumor and the colon. Adjuvant chemotherapy with oxaliplatin, 5-FU, leucovorin was conducted nine days after the operation. Colorectal cancer during pregnancy is often diagnosed in advanced stage because the symptom may be non-specific during pregnancy and because the diagnostic method may be limited. It is very important to prepare for that the tumor may establish abscess and an emergent operation may sometimes be required for preventing intestinal obstruction or peritonitis, and that the lesion may be so extended that may require adnexectomy and hysterectomy.

### ISP-17-6

**Primary intramedullary spinal cord tumour in pregnancy : A case report** Kyoko Fujii, Makoto Orisaka, Makoto Yamamoto, Koji Nishijima, Yoshio Yoshida *University of Fukui Hospital*

**Introduction** Primary spinal cord tumours can lead to severe neurological complications and even death. Pregnant women often complain of discomfort of the lower limbs, which is usually caused by sciatica. Here we present the case of a pregnant woman, who was initially considered to have sciatica, but was finally diagnosed with a primary intramedullary spinal cord tumour. **Case Presentation** A 28-year-old pregnant woman presented to our hospital with inexplicable numbness in her lower

limbs. She was initially considered to have sciatica, but acute deterioration of neurological symptoms and plane MRI findings suggested malignancy. The patient was finally diagnosed with a primary intramedullary spinal cord tumour at the C3-Th5 region. An emergency caesarean section was performed, after which the spinal cord lesion was evaluated using contrast-enhanced MRI, 18F-FDG PET/CT, and spinal angiography, and further treatment was initiated. However, while the patient's spinal cord tumour surgery was performed in early postpartum, her neurological symptoms remained unchanged. **Discussion** Because of the low incidence of spinal cord tumours during pregnancy, no definite reports have been published on the treatment of pregnant patients with spinal cord tumours. Although safe imaging tests during pregnancy are limited, intervention in such patients should be performed as early as possible to avoid irreversible neurological deterioration.

### ISP-17-7

**A pregnancy with adenomyosis : A case report** Ayaka Tachibana, Rie Yanagihara, Takako Kawakita, Takeshi Iwasa, Kanako Yoshida, Minoru Irahara *Tokushima University Hospital*

We report a pregnancy with adenomyosis complicated. A 39-years-old woman was diagnosed with adenomyosis because the right and posterior wall of uterus were observed thickening of 7 cm, and it was introduced to our institution due to imminent abortion at gestational week 16. She was admitted and started continuous infusion of isoxsuprine hydrochloride. We changed to ritodrine hydrochloride at gestational week 16 but found lower abdominal pain enhancement, WBC 10,900/ $\mu$ l, CRP 2.99 mg/dl, ABPC 2g/day administration started. After that, FMOX 2g/day was administered and the inflammatory response improved. Since antibiotic was discontinued but lower abdominal pain was prolonged, we observed that after administration of acetaminophen and pentazocine, it became pregnancy hypertensive syndrome (PIH) from gestational week 34, and blood pressure rise (180/90mmHg) was confirmed. Because of severe PIH and pelvic position, cesarean section was performed on gestational week 37. Because of adhesion placenta, the total bleeding volume was 3,600ml and blood transfusion (RCC 6units, FFP 6 units) was performed. On the fifth postoperative day, blood pressure rise was observed and administration of nifedipine 20mg/day was started. Nifedipine administration was sustained after discharging on the 7th postoperative day, but it stopped after 3-months of delivery. Retained placenta was observed at 1 month checkup, blood flow wasn't observed by ultrasonography and MRI, so it was taken as follow-up observation. Even after 1-year after parturition, the mass remained, and 1 year 5 months after delivery, it was resected by hysteroscopic surgery. The mass was a placenta accompanied by calcification and hyalinization by pathological examination.

### ISP-17-8

**Current circumstance of the care for pregnancy complicated with adult congenital heart disease at a non-specialized tertiary perinatal center** Hironobu Hyodo, Satoshi Nitta, Naoya Tsujimoto, Saho Fujino, Miho Saito, Norihiko Nakazato, Etsuko Saito, Midori Funakura, Sorahiro Sunagawa, Takahiro Kasamatsu, Koji Kugu *Tokyo Metropolitan Bokutoh Hospital*

**Objective** Prognosis of congenital heart disease has been improved remarkably and many women with the disease have become able to reach to the reproductive age. The pregnant women of adult congenital heart disease (ACHD) has been therefore increasing and most of them have uneventful pregnancy. However, cardiac function and condition are diverse even in the same disease and the care for them are therefore different from

case by case. Experience of the care of many cases should be accumulated and shared in order to provide high-quality management. **Methods** The medical records of pregnancy in the ACHD women that managed at a tertiary perinatal center from 2010 to 2017 were reviewed. The situation of the management, the evaluation, the medication, and the strategy during and after pregnancy were investigated. **Results** Forty-one cases and fifty pregnancies were identified. VSD was the most major disease. All of them were in NYHA I at the first visit and none of them had cardiac events during and after pregnancy. A severe AS case was referred to the specialized institute for the care and the therapeutic approach based on more experience of ACHD. **Conclusion** It is possible that a pregnant woman with ACHD in NYHA I with no remarkable symptom may get worse in heart condition as the pregnancy progress. As ACHD has diverse condition even in the same disease, individual evaluation is very important and the most appropriate management should be provided.

### ISP-17-9

**Pregnant women with low TSH and normal FT4 in early pregnancy may have relatively low risk of preterm delivery** Masahiro Shiba, Koichiro Kido, Youhei Nagaya, Michiharu Seto, Rina Sakurai, Shigenari Namai, Rintaro Kishimoto, Haruko Hiraike, Yasuhiro Matsumoto, Yukifumi Sasamori, Eiji Ryo, Takuya Ayabe *Teikyo University*

**Objective** In early pregnancy, due to gestational transient thyrotoxicosis, TSH value of pregnant women with normal thyroid function often seem to be low. On the contrary, that of pregnant women with hypothyroidism, which might relate to preterm delivery, may seem to be normal in early gestation. Thus our aim is to investigate whether pregnant women with low TSH in early pregnancy show relatively low risk of preterm delivery or not. **Methods** Outcomes of 2,173 pregnant women who delivered singleton infant at 22 weeks of gestation or later were investigated retrospectively. TSH value less than 0.5  $\mu$ IU/ml was defined as low TSH. Preterm delivery rate was estimated by Chi-squared test. Informed consent was obtained from all participants. **Results** The whole rate of preterm delivery was 15.3% (333 of 2,173 cases). The rate of pregnant women with low TSH and normal FT4 in early pregnancy was 18.7% (407 of 2,173 cases). The rate of preterm delivery among the pregnant women with and without "low TSH and normal FT4 at early pregnancy" was 9.1% (37 of 407 cases) and 16.8% (296 of 1,766 cases), respectively ( $p < 0.05$ ). **Conclusion** Pregnant women with low TSH and normal FT4 in early pregnancy may have relatively low risk of preterm delivery. Many factors give effect on preterm delivery, and our data contain many high risk pregnancy cases. Further investigation is required to reveal the real effect of thyroid function on preterm delivery.

### ISP-18-1

**"In The Nick of Time" A perimortem cesarean delivery following pulmonary congestion and pre-eclampsia** Adeline Rose T. Escartin, Charisse P. Guerrero *Manila Central University-FDTMF Hospital, Philippines*

Cardio-pulmonary arrest occurs rarely in pregnancy and involves two patients: mother and fetus. Prompt cardio-pulmonary resuscitation and intervention can save both. Adequate chest compression and displacement of the gravid uterus off the venous return from the lower extremities are proven to improve maternal oxygenation. Peri-mortem cesarean delivery is a legitimate medical intervention in successfully salvaging the mother and the fetus. Emptying of the uterus improves maternal physiology and effectiveness of cardiopulmonary resuscitation. A 24 year-old, g1p0, was brought to the ER, unconscious

and suffering cardiorespiratory arrest at 38 weeks' gestation. Her current pregnancy was uneventful until 37 weeks' gestation when BP elevations and dyspnea were noted. Hours prior, she had BP of 160/110mmHg and difficulty of breathing. Few minutes prior, patient was unconscious with zero vital signs. CPR was started, intubation done, and epinephrine given. The fetus was evaluated and noted to have bradycardia. The decision was made to perform peri-mortem cesarean delivery at the ER. A midline abdominal incision was made to gain access to the uterine cavity and a female infant was delivered with Apgar of 0, 2, 6. The neonate was intubated, ventilated and chest compressions started, however died after 2 days. There was spontaneous return of cardiac output after delivery. After the operation, the patient was transferred to ICU for further ventilation and inotropic support and is still surviving 47 days after delivery and now at GCS 7. CPR was unresponsive until cesarean section was instituted, thus, PMCD is necessary for successful resuscitation for the mother.

### ISP-18-2

**Perimortem Cesarean Section (PMCS)-successful maternal resuscitation of out-hospital onset cardiopulmonary arrest, a case report** Chiyori Sakamoto, Susumu Miyashita, Shoko Ochiai, Emi Motegi, Tatsuya Kuno, Kazumi Tada, Ichio Fukasawa *Dokkyo Medical University Hospital*

**Case** A 36-year-old pregnant woman, 2-gravida 1-para, was transferred to our critical medical center on 38 weeks because of unconsciousness. She was complicated with WPW syndrome but needed no medication. She complained precordial oppression and fell down suddenly at her house. Her husband immediately brought her to our institute 19 minutes after the onset. Ventricular flutter (VF) was recorded at presentation and ACLS protocol was activated. Prolonged fetal bradycardia was also noted. PMCS was decided and carried out promptly. A male infant was born with APGAR Score of 0 (1min), 0 (5min) and 2 (10min) at 38 minutes after the onset. Chest compression was discontinued with support of ECMO after 50 minutes of the delivery. She needed intensive care for impaired cardiac function, coagulopathy and postpartum bleeding before the suspension of ECMO on day 3, and for post-cardiac arrest syndrome (PCAS) including renal failure before discharge on day 49 without major neurological sequela. There was no laboratory test result suggesting amniotic fluid embolism. The neonate had resuscitation, hypothermia therapy and needed continuous mechanical ventilation for 35 days but hypoxic encephalopathy was getting obvious. **Discussion** We encountered this case incidentally just before describing a PMCS protocol. PMCS itself was carried out smoothly and we could resuscitate the patient successfully. Several points were raised including the launch timing of ECMO, neonatal care, postpartum coagulopathy, multi-organ failure and rehabilitation for disuse extremities. A series of multidisciplinary meeting for debriefing of clinical action was essential to complete the PMCS protocol in our institute.

### ISP-18-3

**A retrospective cohort analysis of retained products of conception with vascularity after second-trimester abortion; incidence, outcomes in expectant management, and characteristic ultrasonographic features leading to future severe hemorrhage** Naoya Akiba<sup>1</sup>, Takayuki Iriyama<sup>2</sup>, Hitomi Furuya<sup>2</sup>, Takahiro Seyama<sup>2</sup>, Rieko Shitara<sup>2</sup>, Toshio Nakayama<sup>2</sup>, Takeshi Nagamatsu<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, The University of Tokyo Hospital<sup>2</sup>*

**Objective** The aim of this study was to investigate the incidence and spontaneous outcomes of retained products of conception (RPOC) with vascularity detected by ultrasonography after sec-

ond-trimester abortion, and to identify the sonographic features related to the development of severe hemorrhage. **Methods** This was a retrospective cohort study on 103 cases after second-trimester medical abortion managed at our institute between 2014 and 2016 under the approval of our ethics committee. RPOC with vascularity was defined by the presence of hyperechoic focus with blood flow by grey scale and color Doppler transvaginal ultrasonography. The vascularity of RPOC was assessed by categorizing cases as follows : type1 : vascularity confined to endometrium, type2 : vascularity reaching  $<1/2$  myometrium, type3 : vascularity reaching  $>1/2$  myometrium. **Results** Among a total of 103 cases, 19 cases (18.4%) were diagnosed as RPOC with vascularity. All cases were managed expectantly, and 5 cases (26.3%) eventually failed expectant management due to severe hemorrhage treated by uterine artery embolization and/or blood transfusion. Of them, 80% (4/5) of cases with type 3 developed severe hemorrhage as compared with 7.1% (1/14) of cases with type1/type2 ( $p<0.05$ , chi-square test). Cases in which expectant management failed showed the significantly larger maximum linear size of RPOC ( $43.0 \pm 12.0$  mm vs  $20.7 \pm 8.3$  mm,  $p<0.01$ , Mann-Whitney U test). **Conclusion** Our results suggested that the incidence of RPOC with vascularity is substantially high in cases after second-trimester abortion, and the degree of vascularity and the size of RPOC are associated with the development of spontaneous severe hemorrhage.

#### ISP-18-4

**The relationship of anesthetic amount with the prolonged second stage of labor and malrotation in labor analgesia** Hitomi Ando, Shintaro Makino, Jun Takeda, Yojiro Maruyama, Atsuo Itakura, Satoru Takeda *Juntendo University*

**Objective** Forceps delivery rate increased as the labor analgesia rate increased in our facility. To reveal the influence of local anesthetic on the prolonged second stage of labor and malrotation, the use amount of local anesthetic was examined. **Methods** A retrospective chart review from April 2017 to June 2017 was conducted. Term cephalic singleton pregnancies who had delivery with combined spinal-epidural analgesia were considered as inclusion criteria. The local anesthetic amount on the first stage of labor (1st), on the second stage of labor (2nd), during whole labor (WL), and during labor per minute (WL/M) were compared between prolonged second stage of labor and without prolonged labor, and malrotation and without malrotation. The prolonged second stage of labor was defined more than 3 hours. **Results** During the study period, 173 cases were met the inclusion criteria. Among them, 28.3% had prolonged second stage of labor, and 19.0% had malrotation. The amount of local anesthetic during WL and 2nd were significantly larger in prolonged second stage group (99.0ml vs. 66.0ml, 47.5ml vs. 20.9ml :  $p<0.05$ , respectively). No differences were found on 1st (52.0ml vs. 45.7 ml :  $p=0.43$ ), and WL/M (0.16ml vs. 0.17ml :  $p=0.6$ ). For the malrotation, WL, 1st, and 2nd had significantly larger amount of anesthetic (98.2ml vs. 70.0ml, 62.9ml vs. 43.8ml, 35.3ml vs. 26.7ml :  $p<0.05$ , respectively). However, no difference was found in WL/M (0.18ml vs. 0.16ml :  $p=0.3$ ). **Conclusion** There was no correlation factor of the prolonged second stage of labor and fetal head malrotation except for the total amount of local anesthetic.

#### ISP-18-5

**Perinatal maternal cases of disturbance of consciousness transferred to our facility** Yoshihiro Kuritani<sup>1</sup>, Takahide Maenaka<sup>1</sup>, Michihide Maeda<sup>1</sup>, Yukako Oi<sup>1</sup>, Naoya Shigeta<sup>1</sup>, Yangsil Chang<sup>1</sup>, Hiroaki Tsubouchi<sup>1</sup>, Kayoko Shikado<sup>1</sup>, Takeshi Yokoi<sup>2</sup>, Kazuhide Ogita<sup>1</sup> *Rinku General Medical Center<sup>1</sup>, Kaizuka City Hospital<sup>2</sup>*

**Introduction** Our facility is a tertiary medical center, accepting

on average 20 perinatal emergency cases per year. From 2011 to 2017 we have had 17 cases of disturbance of consciousness, 8 epilepsy (47.1%), 4 cerebral infarction (23.5%), 2 cerebral hemorrhage (11.8%) and 3 eclampsia (17.6%) cases. We show three representative cases below. **Case1** A 30s, primipara, 38 gestational weeks was transferred for sensory disturbance of left upper limb. Head MRI showed atherothrombotic infarction of right parietal lobe. Induced labor was planned but her infarction got worsen in the process. Then, cesarean section was performed. The antiplatelet agent was administered after the operation. No subsequent complication was seen. **Case2** A 20s, multipara, 35 gestational weeks was transferred for transient loss of consciousness and headache. Motor disturbance of bilateral lower limbs was observed. Head CT showed the rupture of aortic aneurysm of right anterior cerebral artery. Termination by cesarean section was performed to ease cerebral vascular treatment. On postoperative day 2, stent placement and coil embolization were performed. Anticoagulant and antiplatelet agents were administered. No subsequent complication was seen. **Case3** A 30s, multipara, 37 gestational weeks was transferred for seizure soon after her delivery. Head MRI showed PRES. We diagnosed eclampsia with HELLP syndrome. No medical treatment was added after arriving at our facility. **Conclusion** All cases had good prognosis because of early diagnosis and treatment. It might be important to transfer patients with cerebral events as soon as possible to a facility where CT, MRI and neurosurgery are available in an emergency.

#### ISP-18-6

**The challenge to quantify the uterine contraction ; usability of handheld muscle hardness meter (HMH meter) and its clinical application to obstetric bleeding management** Kenji Imai, Tomomi Kotani, Teruyuki Mizutani, Yuri Niwa, Asuka Tachi, Masataka Nomoto, Yukako Iitani, Mayo Miura, Yoshinori Moriyama, Takafumi Ushida, Tomoko Nakano, Fumitaka Kikkawa *Nagoya University*

**Objective** To report a new method to easily and objectively quantify the uterine contraction during cesarean section (CS) with handheld muscle hardness meter (HMH meter). **Methods** Under Institutional Review Board approval and informed consent, a total of 34 term pregnant women who underwent elective CS were recruited. HMH meter could measure tissue hardness with a few seconds contact time. With the HMH meter, we measured the uterine hardness twice in each CS : Time A=immediately after placental separation and Time B=just before abdominal closure. Each measurement was conducted at 2 standardized points : Point A=fundus uteri and Point B=corpus uteri. Also, the operator subjectively judged the uterine contraction into 3 grades : weak, normal, strong. **Results** HMH meter could clearly quantify the subjective judgments of uterine contraction, especially at Point A (weak :  $47.9 \pm 1.96$ , normal :  $59.3 \pm 0.85$ , strong :  $64.0 \pm 0.92$ ,  $p<0.001$ ). Simple linear regression revealed that the measurements at Time A were significantly correlated with the amount of intraoperative hemorrhage (Point A :  $r=-0.64$ ,  $p<0.001$ , Point B :  $r=-0.44$ ,  $p=0.017$ , respectively). Massive intraoperative hemorrhage ( $>1,000$  mL) occurred in 58.8% (10/17) of cases with HMH meter  $<60$  at Time A and Point A, whereas in 5.9% (1/17) of cases with HMH meter  $\geq 60$  at the same time and point ( $p=0.002$ ). **Conclusion** These results showed the feasibility of HMH meter for the quantification of uterine contraction, and HMH meter  $>60$  might be proposed as a novel criteria for management of uterine atony.

#### ISP-18-7

**For 10 years prospective study : trial of labor after cesarean (TOLAC) versus repetitive cesarean based on informed**

**choice** Kaname Uno, Eiji Yoshida, Hatsuo Isogai, Takuji Ueno, Takuma Yamada, Takehiko Takeda, Sho Tano, Mayu Ukai, Teppei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi *Perinatal Medical Center, TOYOTA Memorial Hospital*

**Objective** Though the successful rate of trial of labor after cesarean (TOLAC) is reported 60–80%. In Japan, most patients eligible for TOLAC undergo elective repetitive cesarean delivery (ERCD). To reveal the benefits and risks of TOLAC, we conducted 10-year prospective study. **Methods** From 2005 to 2016, patients who had undertaken CS were enrolled in this study. Patients who met our criteria chose their delivery way after being explained the risks and benefits of both TOLAC and ERCD. Our criteria were only one previous lower segment transverse CS, singleton vertex presentation and no history of myomectomy. We collected the maternal and neonatal data at delivery and maternal backgrounds to identify more eligible patients. **Results** A total of 982 patients with prior CS were enrolled, and 311 patients were excluded because of still birth before labor, severe preeclampsia and not meeting our criteria. 671 patients could choose their desirable delivery way. In these patients, 433 patients (64.5%) chose TOLAC. Of 433 patients, 395 patients (91.2%) succeeded in vaginal delivery and 2 (0.45%) had uterine rupture. There was no significant difference in Apgar score at 5 minutes ( $p=0.56$ ). The amount of bleeding at delivery in TOLAC group were significantly less than ERCD group ( $p=0.01$ ). No maternal and neonatal deaths and sequels were occurred. **Conclusion** If the risks and benefits of both TOLAC and ERCD are explained, over half of patients choose TOLAC as their desirable way. TOLAC was thought to be a reasonable way of delivery and the choice of TOLAC should be offered for suitable candidates.

#### ISP-18-8

**Induction of labor with metreurynter at or after 39 weeks of gestation in women with one previous cesarean delivery increases the likelihood of failed trial of labor after cesarean delivery** Kento Misawa<sup>1</sup>, Madoka Furuhashi<sup>2</sup>, Yoshiaki Maseki<sup>1</sup>, Atsuko Tezuka<sup>1</sup> *Japanese Red Cross Nagoya Daiichi Hospital<sup>1</sup>, Nagara Medical Center<sup>2</sup>*

**Objective** To elucidate the safety and efficacy of metreurynter as an induction tool for women with one previous cesarean delivery. **Methods** A database was reviewed to identify women with singleton and vertex pregnancies who underwent trial of labor after one cesarean delivery (TOLAC) at or after 39 weeks of gestation between the years 2010 and 2016. **Results** Fifty-one women underwent induction of labor, and 230 women had spontaneous onset of labor pain. Successful TOLAC was observed in 95.2% (219/230) and 74.5% (38/51) of women with spontaneous onset of labor pain and induction, respectively ( $p<0.001$ ). A case of uterine rupture was seen in a woman with induction, where the baby was born dead by cesarean section. Women with induction of labor were less likely to have successful TOLAC (adjusted odds ratio 0.21 and 95% confidence interval 0.07–0.65) compared with women with spontaneous onset of labor. Vacuum extraction (23.7% vs 6.8%,  $p<0.001$ ) and amniotomy (55.3% vs 33.3%,  $p=0.010$ ) were more frequent in women who had successful TOLAC withinduction than those with spontaneous onset of labor. **Conclusion** Induction with metreurynter decreases the success of TOLAC but is satisfactory in clinical practice based on its success rate and safety.

#### ISP-19-1

**Which risk factor is the most useful to predict placenta accreta pre-operatively? : a retrospective study on placenta previa** Hiromitsu Azuma, Ai Kouno, Takuo Nakayama, Chuyu Hayashi, Go Ichikawa, Atsushi Komatsu, Yasuji Miyagawa,

Shinichi Takada, Fumihisa Chishima, Kei Kawana *Nihon University Itabashi Hospital*

**Objective** Since placenta accreta is a life-threatening complication of placenta previa at caesarean section (C/S), pre-operative assessment of placenta is important. Risk factors for placenta accreta are well-reported. We here examined which risk factors are the most useful to predict placenta accreta. **Methods** A retrospective study on pregnant women with placenta previa was designed under approval by ethical committee in our hospital. 29 women with total placenta previa underwent C/S for delivery in our hospital. Typical images of placenta accreta (lacunae, loss of clear zone, and paracervical varix) were evaluated by MRI and ultrasonography (US) and scored (0–2 for MRI and 0–3 for US) pre-operatively. Placenta accreta was diagnosed pathologically. Comparison in clinical factors between placenta accreta (n=10) and non-accreta (n=19) groups was made by several statistical methods. **Results** Previous uterine surgery correlated strongly with placenta accreta ( $p=0.005$ ) whereas age, gestational weeks, alert bleeding, position of placenta did not correlate. Univariate analysis showed US score, but not MRI, correlated strongly with placenta accreta ( $p=0.001$ ). Multi-variate logistic regression analysis revealed that previous uterine surgery was an independent risk factor for placenta accreta ( $p=0.03$ ) and high US score was also important risk factor with marginal significance ( $p=0.08$ ). ROC curve showed combination of previous uterine surgery and US score predicted placenta accreta with high accuracy ( $p<0.001$ ). **Conclusion** For women with placenta previa, US was more useful for prediction of placenta accreta rather than MRI. Placenta accreta can be predicted preoperatively by combination of previous uterine surgery and US findings.

#### ISP-19-2

**The usefulness of preoperative autologous blood donation before caesarean section of placenta previa based on SBOE (the surgical blood order equation)** Junki Imaizumi, Sumika Matsui, Atsuko Hichijo, Naoto Yonetani, Takeshi Iwasa, Takashi Kaji, Minoru Irahara *Tokushima University*

**Objective** Autologous blood donation has been performed for case with high risk of excessive bleeding. However, because it is difficult to preoperatively predict the amount of bleeding, excess amount of blood has tended to be stored for obstetric surgery, and high discard ratio is one of the problems to be solved. In this study, we retrospectively evaluated whether the discard rate and allogeneic blood transfusion rate can be reduced using SBOE. **Methods** From January 1st, 2013 to June 30th, 2017, 40 pregnant women with placenta previa underwent preoperative autologous blood donation. The volume of autologous blood donation, intraoperative bleeding, volume of autologous blood transfusion, discard ratio and volume of allogeneic blood transfusion were analyzed. In addition, necessary blood volume was retrospectively calculated by SBOE in each case and it was compared with actual date. **Results** 75% women underwent autologous blood transfusion. The autologous blood discard ratio was 42%, whereas 7.5% women underwent allogeneic blood transfusion. If autologous blood was collected based on SBOE, the assumed discard ratios would be 38%, and 35% women would undergo allogeneic blood transfusion. **Conclusion** Autologous blood donation seems to be effective for avoiding allogeneic blood transfusion. However, the discard ratio is high and some patients would be needed to undergo allogeneic blood transfusion besides autologous blood due to excessive bleeding. If SBOE is used to determine the necessary volume of autologous blood collection, it is concerned that the case needed for allogeneic blood transfusion may be increased. Thus, SBOE seemed to be less useful in case with placenta previa.



## ISP-19-3

**The optimal amount of preoperative autologous blood donation for placenta previa and low lying placenta** Ayumi Sakai<sup>1</sup>, Shigetaka Matsunaga<sup>2</sup>, Eishin Nakamura<sup>2</sup>, Kouki Samejima<sup>2</sup>, Hiroko Masuko<sup>1</sup>, Yukiko Mikami<sup>1</sup>, Sumiko Era<sup>1</sup>, Yoshihisa Ono<sup>1</sup>, Yasushi Takai<sup>2</sup>, Masahiro Saitoh<sup>1</sup>, Kazunori Baba<sup>1</sup>, Hiroyuki Seki<sup>1</sup> *Center for Maternal, Fetal and Neonatal Medicine, Saitama Medical University Saitama Medical Center<sup>1</sup>, Saitama Medical Center Saitama Medical University<sup>2</sup>*

**Objective** Preoperative autologous blood donation (PAD) is considered to be an effective method for avoiding allogeneic blood transfusion. Recently, high rejection rate of PAD is regarded as a serious problem. Therefore, we investigated optimal PAD volume for avoiding allogeneic blood transfusion in patients with placenta previa and low lying placenta retrospectively. **Methods** Of the 383 patients who underwent PAD from 2008 to 2013, we examined 269 patients with placenta previa and low lying placenta by reviewing medical chart. One bag of PAD volume was determined as 300 ml for a pregnant woman, the cases enrolled were stratified by PAD volume every 300 ml, and compared the frequency of allogeneic blood transfusion. **Results** PAD was used for 124 patients (46.1%) and allogeneic blood was transfused to 12 cases (4.5%). The rejection volume of PAD was 23,940 ml (70.5%) per year in average. The allogeneic blood transfusion rate was significantly higher in the 300 ml PAD group than in the other groups (17.2%, 1.69%, 3.82%, 0% in 300, 600, 900, 1,200 ml PAD groups, respectively,  $p < 0.05$ ). The cut-off value of PAD for avoiding allogeneic blood transfusion was determined as 300 ml by receiver operating characteristic analysis, and the odds ratio of  $\leq 300$  ml PAD in multivariate analysis was 14.278 ( $p = 0.0303$ ). **Conclusion** 600 ml or more amount of PAD showed no difference in the rate of allogeneic blood transfusion. To minimize the rejection rate, the optimal amount of PAD for the patients with placenta previa and low lying placenta is considered to be 600 ml (300 ml twice).

## ISP-19-4

**Placenta accreta following hysteroscopic lysis of adhesions caused by Asherman's syndrome** Yuko Sonan<sup>1</sup>, Shigeru Aoki<sup>1</sup>, Tamaki Cho<sup>1</sup>, Yuriko Yamamoto<sup>1</sup>, Soichiro Obata<sup>1</sup>, Azusa Tochio<sup>1</sup>, Mio Takami<sup>1</sup>, Kimiko Enomoto<sup>1</sup>, Michi Kasai<sup>1</sup>, Junko Kasai<sup>1</sup>, Etsuko Miyagi<sup>2</sup> *Yokohama City University Medical Center<sup>1</sup>, Yokohama City University Hospital<sup>2</sup>*

Asherman's syndrome is defined as partial or complete obstruction of the uterine cavity primarily caused by intrauterine procedures and infections. Hysteroscopic adhesiolysis is commonly used to treat Asherman's syndrome. Although the frequency of placenta accreta is known to increase with pregnancy after hysteroscopic adhesiolysis, precise data remain unknown. Here, we report a case of placenta accreta following hysteroscopic lysis of adhesions caused by Asherman's syndrome, and review the literature on placenta accreta following hysteroscopic adhesiolysis. The patient is a 40-year-old primipara who underwent underwent hysteroscopic myomectomy for 1–3-cm submucosal fibroids located in the uterine fundus. Asherman's syndrome was suspected after the patient exhibited secondary hypomenorrhea 10 months after surgery. Eight months after diagnosis, the patient underwent hysteroscopic adhesiolysis. Seven years after hysteroscopic adhesiolysis, the patient became pregnant through IVF. The course of pregnancy was uneventful thereafter, and an elective cesarean section was performed at 38 weeks and 2 days of gestation because of a breech presentation. The placenta remained firmly adherent to the uterine wall, and although there was almost no bleeding from the uterine cavity, cesarean hysterectomy was performed. The operative time was 101 minutes, while the total blood loss was 1,584 ml. Blood trans-

fusion was not required. Placenta increta was confirmed based on postpartum histological findings. The postoperative course was uneventful, and the patient was discharged in good health on the 7th postpartum day. It is necessary to consider placenta accreta as a complication of pregnancies after hysteroscopic adhesiolysis for Asherman's syndrome, particularly in those conceived using IVF.

## ISP-19-5

**Risk factors for the placenta with velamentous umbilical cord insertion among term singleton ART pregnancies** Satoshi Furuya<sup>1</sup>, Takashi Yamaguchi<sup>2</sup>, Tamaki Kagawa<sup>2</sup>, Kiyoshi Kubonoya<sup>1</sup>, Ken Kubonoya<sup>1</sup> *Kubonoya Ob/Gyn Clinic<sup>1</sup>, Kubonoya IVF Clinic<sup>2</sup>*

**Objective** The placenta with velamentous umbilical cord insertion (VCI) is a rare pathologic condition that is supposed to increase the risk of perinatal complications. In this research we examined the ART-conceived cases for the purpose of identifying the ART-associated risk factors that might affect the incidence of the placenta with VCI. **Methods** We reviewed the records of 551 consecutive singleton term labor and delivery ART-conceived cases, from January 2010 to August 2017. Our study population was divided into two categories as follows: cases with VCI (Group A:  $n = 31$ ), and cases without VCI (Group B:  $n = 520$ ). Odds ratios (OR) for VCI, 95% confidence intervals (CI), and significance of the odds ratio were calculated according to ART-related variables, using multivariate logistic regression. **Results** The incidence of VCI in our study population was 5.6% (31/551). The rate of delivery necessitating emergency C-section or operative vaginal delivery in Group A (58%, 18/31) was higher than in Group B (36%, 189/520). Blastocyst transfer (OR: 6.63, 95%CI: 1.55–28.28,  $P = 0.01$ ) and female fetus (OR: 2.69, 95%CI: 1.18–6.15,  $P = 0.02$ ) significantly increased the likelihood of developing the placenta with VCI. Maternal age, parity, fertilization method (conventional IVF or ICSI), and type of embryo (fresh embryo or frozen thaw embryo) did not affect the incidence of the placenta with VCI. **Conclusion** As velamentous umbilical cord insertion often brings about serious obstetric complications, ART pregnancies achieved by blastocyst transfer and female fetus are optimal candidates for checking up and identifying the umbilical cord insertion site more proactively during routine obstetric ultrasound examinations.

## ISP-19-6

**The importance of fetal/placental weight ratio for the evaluation of small for date** Toshiya Itoh<sup>1</sup>, Yoshio Matsuda<sup>2</sup>, Hiroaki Itoh<sup>1</sup>, Toshiyuki Uchida<sup>1</sup>, Kazunao Suzuki<sup>1</sup>, Kazuhiro Sugihara<sup>1</sup>, Masaki Ogawa<sup>3</sup>, Naohiro Kanayama<sup>3</sup> *Hamamatsu University School of Medicine Hospital<sup>1</sup>, Mishima General Hospital<sup>2</sup>, Tokyo Women's Medical University Hospital<sup>3</sup>*

**Objective** To clarify the importance of fetal/placental weight ratio (F/P) as well as placental weight (PW) for the evaluation of small for date (SFD). **Methods** From 93,034 placentas/infants of mothers vaginally delivered a singleton infant (Japan Perinatal Registry Network database 2013), SFD ( $n = 3,379$ ) was chosen according to infant's weight referring to the Japanese neonatal growth chart (Itabashi, 2010). PW and F/P Z scores based on the standard curves of a sex-, parity- and gestational-age-specific PW and F/P (Ogawa & Matsuda, 2016) were calculated. The population was classified into 9 blocks according to the combination of 'low vs. middle vs. high' i) PW Z score and ii) F/P Z score. In both i) and ii),  $\pm 1.28$  standard deviations in the Z scores was used for classifying low vs. middle vs. high, with 3  $\times$  3 making 9 blocks. Block I (high PW Z score and low F/P Z score) is considered as inappropriately heavy placenta. **Results** (1) All cases distributed into 6 blocks: 11.7% in Block A, 40% in

Block D, 37.6% in Block E (both PW and F/P Z scores are middle), 0.5% in Block G, 9.9% in Block H, and 0.3% in Block I. (2) Minimum perinatal death rate was 10.2/1,000 in Block E. **Conclusion** Inappropriately heavy placenta is very rare in SFD. Perinatal mortality rate is the lowest in Block E as balanced growth of placenta and infant. Measuring not only PW but F/P are important and helpful for the evaluation of SFD.

### ISP-19-7

**Placental mesenchymal dysplasia with severe fetal growth restriction in one side of placenta of dichorionic diamniotic twin pregnancy** Shoko Jitsumori, Michihisa Shiro, Nami Ota, Sawako Minami, Kazuhiko Ino *Wakayama Medical University*  
Placental mesenchymal dysplasia (PMD) is a rare condition of swelling stem villi and placentomegaly without trophoblast proliferation. We report an extremely rare case of PMD with FGR fetus in one side of placenta of DD twin pregnancy. A 24-year-old para 1 female was referred to our hospital at 24+1 weeks' gestation of DD twin with one fetal FGR and placental anomaly. Ultrasound examination revealed only one fetus was FGR ( $-2.6$  SD) and multiple cysts in the ipsilateral placenta. Maternal serum hCG level was within the reference range (44,084 mIU/mL) and we clinically diagnosed PMD. There were no ultrasound findings of characteristics of BWS in the FGR. MRI at 32 weeks' gestation showed cystic lesion in the placenta of FGR. Because development of biparietal diameter of FGR fetus was restricted ( $-4.5$ SD), we performed cesarean section at 32+5 weeks' gestation. The both neonates were females, weighed 1,799g ( $-0.1$  SD) and 1,215g ( $-2.5$ SD). The weight of twin placenta was 1066 g (above 90th percentile). There were prominent enlarged chorionic vessels on the placental surface of the small for gestational age (SGA) birth. The lesion of PMD was showed in about 37% of the SGA side of placenta. Microscopic examination revealed large swelling stem villi and increase of stromal cells without trophoblast proliferation. Immunohistochemically, expression of p57<sup>Kip2</sup> was lost in the stromal cells and trophoblasts of swelling stem villi. It was suggested that PMD occurred in one placenta of DD twin, leading to early-onset FGR.

### ISP-19-8

**A case report of chorioamniotic membrane separation with chorionic hematoma and inflammation** Kumiko Nakata, Michihisa Shiro, Nami Ota, Yasushi Mabuchi, Shigetaka Yagi, Sawako Minami, Kazuhiko Ino *Wakayama Medical University Hospital*

The amnion and chorion usually fuse between 14 and 16 weeks of pregnancy. Chorioamniotic membrane separation (CMS) can lead to preterm delivery, premature rupture of the membrane and fetal death. As CMS is rare, there have been few reports, and management for CMS has yet to be determined. We report a patient with CMS with chorionic hematoma. A 29-year-old woman was hospitalized for lower abdominal pain, cervical length shortening and genital bleeding at 15 weeks of pregnancy. Laboratory data indicated inflammation, and she received antibiotics and tocolysis. Chorionic hematoma, followed by CMS at 16 weeks were observed on ultrasound. She was transported to our hospital at 19 weeks 6 days of pregnancy. Soon after, the amniotic cavity became narrower, and the fetus became wrapped by the amniotic membrane. We considered continuation of pregnancy to be difficult because of severe pulmonary hypoplasia and the complications resulting from contracture of the fetus. The fetus was stillborn at 21 weeks 3 days gestation. Macroscopically, the fetus was wrapped in a thin film and had limb contracture, but other obvious anomalies were not observed. Pathological examination demonstrated CMS with hematoma and diffuse inflammation. This case was like chronic

abruption oligohydramnios sequence (CAOS).

### ISP-20-1

**Practical applications of uterine compression sutures** Jun Takeda, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Junendo University*

**Objective** Postpartum hemorrhage is one of the leading causes of maternal morbidity and mortality. Several hemostatic surgical techniques during cesarean section have been reported previously. Among them, compression sutures are a relatively easy and effective way of achieving hemostasis during cesarean section. However, in particular cases, it is difficult to achieve hemostasis only with the compression sutures. **Methods** For the original method of the compression sutures, threads were placed through the anterior wall and posterior wall of the uterus and compress the uterine cavity by apposing the anterior and posterior walls. Three cases needed contrivances to achieve hemostasis and to act against complication as practical applications of compression sutures. **Results** As the practical applications of this technique, one case needed medical and wider compression suture due to effaced cervix, who had cesarean section during the trial of labor for low lying placenta. One case needed removal of the compression sutures thread for uterine isthmus ischemia due to excessive reduction of uterine blood supply. One case applied only uterine isthmus vertical compression sutures for severe uterine atony; however, decrease of uterine corpus blood flow with ligating anastomosis of arcuate or/and radial arteries between ascending and descending uterine arteries helped to achieve hemostasis. **Conclusion** Some contrivances aided compression sutures for the reliable hemostasis and minimal invasive procedure.

### ISP-20-2

**Transabdominal Cervical Cerclage via Laparotomy : 5 cases** Yuri Hasegawa, Atsushi Yoshida, Ai Higashijima, Shuhei Abe, Kiyonori Miura, Hideaki Masuzaki *Nagasaki University*

**Objective** We estimated the obstetrical outcomes in 5 cases of transabdominal cervical cerclage (TAC) via laparotomy. **Methods** From 2014 to 2017, we performed TAC via laparotomy in 5 pregnant women with cervical incompetence. They were diagnosed cervical incompetence at 8 to 13 weeks gestation. Four pregnant women have been performed conization for Cervical Intraepithelial Neoplasia (CIN) or micro invasive cervical carcinoma. One pregnant woman had transvaginal cervical cerclage at previous pregnancy, but cervical laceration had been happened. TAC was performed at 10 to 14 weeks gestation. As the obstetrical outcomes, operation time, blood loss, length of hospital stay, gestation at delivery, birth weight of neonates and Apgar Score were estimated. **Results** The average of operation time was 112.4 (74-153) minutes, blood loss was 80.6 (5-270) grams and length of hospital stay was 16.6 (7-29) days, respectively. In all cases, there were not severe complications during operations. Two women delivered healthy babies by cesarean section at term. Their birth weight was 3,168 grams and 3,298 grams. Apgar Score of 5 minutes was 8 and 9, respectively. **Conclusion** TAC could be recommended as safe procedure for the cases of transvaginal cervical cerclage impossible.

### ISP-20-3

**Analgesic effect of regular intravenous administration of acetaminophen for pain due to post-cesarean delivery : a retrospective study** Keiko Yabuzaki, Hiroaki Aoki, Miki Muto, Akihiro Hasegawa, Tomona Matsuoka, Michihiro Yamamura, Haruhiko Udagawa, Yuki Ito, Kazuhiro Kajiwara, Osamu Samura, Aikou Okamoto *The Jikei University Hospital*

**Objective** Multimodal analgesia is recommended for postopera-



tive pain management. To control further pain due to post-cesarean delivery, we started prescribing the regular administration of intravenous acetaminophen since July 2016. The objective of this study was to evaluate whether the regular administration of intravenous acetaminophen reduces the need for additional analgesic drugs. **Methods** We performed a retrospective chart review of women who underwent cesarean delivery with spinal anesthesia containing intrathecal morphine from July 2015 to June 2017. Patients in the first group received an intravenous analgesic drug as needed from July 2015 to June 2016. Patients in the second group received intravenous acetaminophen (1,000 mg every 6 hours) postoperatively with other intravenous analgesic drugs as needed from July 2016 to June 2017. The primary outcome was the number of additional analgesic medications administered until oral medication was taken. The secondary outcome was the Numerical Rating Scale (NRS) score for pain. Outcome measures between the groups were compared using the t test for continuous variables and  $\chi^2$  test for ordinal variables. **Results** Four hundred eleven patients were analyzed (first group, 183; second group, 228). The proportion of patients requiring additional analgesic medications was significantly lower in the second group than in the first group (22.8% [52] vs. 60.7% [111],  $p < 0.0001$ ). One hundred twenty-four (54.4%) and 84 (45.9%) patients in the second and first groups, respectively, had mild pain (NRS score 0-3) ( $p = 0.0924$ ). **Conclusion** The regular intravenous administration of acetaminophen following cesarean delivery increases the drug analgesic effect and reduces the number of additional analgesic drugs administered.

#### ISP-20-4

**The efficacy of uterine compression suture as a procedure in the management of primary atonic bleeding : a historical cohort study** Masaaki Sawada, Shinya Matsuzaki, Tatsuya Miyake, Aiko Kakigano, Tsuyoshi Takiuchi, Kazuya Mimura, Keiichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

**Objective** Uterine compression suture (UCS) is recognized as a useful procedure in the management of atonic bleeding. However, appropriate hemorrhage volume to perform UCS is not well understood. Our institution policy was to use UCS only in cesarean deliveries (CD) and when atonic bleeding persisted with an estimated blood loss of  $>1,500$  mL. Although the strategy used to control atonic bleeding depends on the clinicians preference, UCS was performed more commonly during CD after August 2013. We performed a historical cohort study to assess the efficacy of UCS for atonic bleeding ( $>1,500$  mL) during CD before (period A) and after August 2013 (period B). **Methods** In a retrospective analysis, data from CD patients with at least 1,500 mL of atonic bleeding between January 2010 and December 2016 were reviewed (except placenta previa cases). Data on surgical outcomes were compared between period A and B. **Results** Data from 128 patients were included in this study (64 patients in both period A and B). There was no significant difference in baseline characteristics between period A and B. UCS was performed more commonly in period B than in period A [6/64 (9.3%) vs 25/64 (39.0%) ;  $P=0.0001$ ]. However, the surgical outcome of CD, such as mean intraoperative bleeding (2,307mL vs 2,306 mL ;  $P=0.32$ ), the rate of transfusion [27/64 (42.2%) vs 30/64 (46.9%) ;  $P=0.72$ ], and the rate of uterine preservation [62/64 (96.9%) vs 58/64 (90.6%) ;  $P=0.27$ ], was not significantly improved. **Conclusion** Our indication of UCS for atonic bleeding during CD did not improve the surgical outcome.

#### ISP-20-5

**Two cases of Vertical Rupture at Side Wall of the Uterine**

**Cervix : Unusual Clinical Courses and How the Ruptures were Repaired** Yasunori Fukuoka, Hiroki Kato, Takashi Shibata, Satoshi Nakago, Tetsuya Oishi, Fumikazu Kotsuji, Hisato Tokuda, Sayoko Hosono, Tomoki Kotera, Shota Asano, Shigeki Nishikawa, Noriaki Iiduka *Takatsuki General Hospital*

**Objective** We encountered two cases of vertical laceration at sidewall of uterine cervix. Both patients were 35 y.o. primipara and undertook induction labor with epidural anesthesia. We report unusual clinical courses of them and how the uterine wound was repaired. **Case** case 1 : The patient was performed vacuum extraction with Kristeller method. 5days later, she visited us for lower abdominal pain. CT showed free air leaking from the uterine cavity to extraperitoneal space, suggesting uterine rupture. When the broad ligament was opened, vertical laceration appeared at the sidewall of uterine cervix. After trimming necrotic tissue, fresh muscle layer was sutured. MRI after a year showed perfect repair of the wound. case2 : After 30 hours of labor induction, she undertook caesarian section. Five days later, she explained lower abdominal pain. MRI suggested laceration of left-side-wall of the uterine cervix and hemoretroperitoneum. Since false aneurysm of the uterine artery was suspected, we performed UAE and then uterine rupture was repaired as case1. 12days later, recurrence of retroperitoneal abscess was diagnosed. A small hole leading to the abscess was found at left-side-wall of the uterine cervix by the probing using a specillum. By washing the abscess with serine for 38 days, it was vanished. MRI taken a year later showed perfect repair of the wound. **Conclusion** Violent physical birr under epidural anesthesia might produce this type of rupture. It is possible that UAE inhibited wound healing, so UAE should be avoided when repair the rupture is considered.

#### ISP-20-6

**The efficacy of a new combined uterine compression suture technique for severe postpartum hemorrhage** Hasumi Tomita, Masatoshi Saito, Tomoko Uehara, Yasuhiro Kurosawa, Sayaka Ooshio, Michiyo Kurakata, Tetsuro Hoshiai, Hidekazu Nishigori, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** Many studies had reported that uterine compression suture (UCS) was effective for postpartum hemorrhage (PPH). In these studies, UCS was performed mainly during caesarean section. The aim of the current study was to reveal the effectiveness of our new UCS technique (combination of Hayman's sutures and parallel vertical compression sutures) for severe PPH occurred in other situations. **Methods** Patients who had severe PPH not responding to conservative treatment, and underwent UCS in our hospital between January 2015 and August 2017 were included. Patients who underwent uterine compression sutures during caesarean section were excluded. We retrospectively examined the medical record of these patients to evaluate the efficacy of our UCS technique. **Results** 15 women were included in this study, 7 women were after vaginal delivery (included 3 vacuum deliveries) and 8 women were after caesarean section. Mean blood loss before UCS was 2,920g (range 1,400-5,000g), and all cases required blood transfusion. In all cases, our UCS was successful, and the uterus preserved. Mean blood loss during operation was 1,727g (range 157-4,529g), and mean operation time was 96minutes (range 58-177minutes). One case needed uterine artery ligation because of artery injury during caesarean section, but other cases did not need other surgical treatment. None of the women developed complications related to the procedure. **Conclusion** Our uterine compression suture technique might be very effective and safety treatment for severe PPH.

## ISP-20-7

**Usefulness of vertical compression suture for placenta previa in caesarean section** Tomoko Uehara, Masatoshi Saito, Hasumi Tomita, Yasuhiro Kurosawa, Sayaka Ooshio, Tetsuro Hoshiai, Hidekazu Nishigori, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** Sometime, it is difficult to control bleeding from the cervical side after placenta delivery in caesarean section of placenta previa. To reduce massive hemorrhage, various methods such as gauze packing have been suggested, but there is no certain method. Since 2013, we has used vertical compression suture (VCS) for that situation and obtained favorable outcomes. So, the aim of current study was to investigate the availability of VCS for C-section of placenta previa. **Methods** 85 patients who diagnosed as placenta previa from June 2013 to June 2017 were eligible to current study and divided into two groups, VCS group (n=31) and non-VCS group (n=54). The volume of total blood loss, operation time, the time from delivery to the end of operation (D-E period), postoperative labo data and postoperative hospital day were analyzed retrospectively. **Results** There was no significant difference between two groups in the total blood loss (1,548 ± 573 g vs. 1,395 ± 611 g, p=0.26). Operation time was 60.7 ± 16.9 min in VCS group and 47.7 ± 14.5 min in non-VCS group (p<0.05). D-E period of VCS was significantly longer compared with non-VCS (54.0 ± 16.3 min vs. 41.5 ± 12.4 min, p<0.05). No significant differences were observed in postoperative value of WBC, CRP and Hb and postoperative hospital day in two groups. **Conclusion** This data showed that VCS is one of the convenient and valid methods to control bleeding in caesarean section of placenta previa with minimal invasion.

## ISP-20-8

**The experience of CIABO (common iliac artery balloon occlusion)** Shotaro Kai, Takahiro Nakano, Saki Kido, Masahiro Hachisuga, Nobuhiro Hidaka, Yasuyuki Fujita, Kiyoko Kato *Kyushu University Hospital*

In our hospital, before cesarean section we insert common iliac artery balloon to occlude and reduce the bleeding for patients at risk for massive bleeding such as placenta accreta, cesarean scar pregnancy, cervico isthmic pregnancy. If the bleeding is uncontrolled, we perform total hysterectomy after cesarean section. We experienced 11 cases inserted common iliac artery balloon from January 2013 through August 2017 and review retrospectively. The cases with balloon occlusion was 7 cases and resulted in hysterectomy. Occlusion time was 11 to 20 minutes. Blood loss was 2,200 to 6,758g. They were received homologous or autologous transfusion, Operation time was 140 to 262 minutes. One case had thrombosis at extra iliac artery, she needed anticoagulant therapy by heparin. CIABO may be effective for reducing blood loss and transfusion, but also has risks of severe complications. Therefore we should consider the indication of this procedure.

## ISP-21-1

**Novel function of a transcription factor WT1 in regulating decidualization in human endometrial stromal cells and its molecular mechanism** Isao Tamura, Haruka Takagi, Yuichiro Shirafuta, Yumiko Mihara, Masahiro Shinagawa, Ryo Maekawa, Toshiaki Taketani, Hiromi Asada, Hiroshi Tamura, Norihiro Sugino *Yamaguchi University*

**Objective** The Wilms' tumor suppressor gene (WT1) encodes an essential transcription factor regulating urogenital development. However, the function of WT1 in human endometrium is unclear. The present study examined the involvement of WT1 in the regulation of IGF-binding protein-1 (IGFBP-1) and prolactin (PRL), which are specific markers of decidualization,

in human endometrial stromal cells (ESCs) undergoing decidualization. **Methods** ESCs isolated from proliferative phase endometrium were incubated with cAMP to induce decidualization. mRNA expressions were examined by qPCR. The recruitment of transcription factors was examined by ChIP assay. Knockdown was performed by siRNA. Genome editing was performed using CRISPR/Cas9 system. **Results** cAMP increased WT1 expression with the inductions of IGFBP1 and PRL. Knockdown of WT1 inhibited the expressions of IGFBP1 and PRL. cAMP also induced the recruitment of WT1 to the IGFBP-1 and PRL promoters. To investigate the regulation mechanism of WT1, we focused on C/EBP $\beta$ , a gene that regulates many gene expressions during decidualization. Knockdown of C/EBP $\beta$  decreased cAMP-increased WT1 expression. cAMP increased the recruitment of C/EBP $\beta$  to the WT1 enhancer that is located 14,000 bp downstream from the transcription start site. To test the endogenous function of the WT1 enhancer region on WT1 expression, the endogenous WT1 enhancer region was deleted by genome editing technique. The increase of WT1 expression by cAMP was not observed in the enhancer-deleted clones. **Conclusion** The present study shows the novel role of WT1 in regulating decidualization in human ESCs. C/EBP $\beta$  regulates WT1 expression by binding to the novel enhancer region, which is identified by genome editing technique.

## ISP-21-2

**Bone morphogenetic protein 4 (BMP4) is required for establishment of an adequate uterine decidualization and vascularization to support normal pregnancy** Takashi Nagashima, Manami Ishida, Kei Tanaka, Miho Matsushima, Yukiko Matsuzawa, Tomoko Izawa, Seishi Furukawa, Yoichi Kobayashi, Mitsutoshi Iwashita *Kyorin University*

**Objective** Bone morphogenetic proteins (BMPs), known to regulate a variety of cellular functions, are members of transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily and thought to play a critical role in female reproduction. To define the physiological role of BMP4 in female reproduction, we used conditional knockout (cKO) strategies to generate female mice lacking functional BMP4 in different type of the female reproductive tract. **Methods** Of note, mutant embryos homozygous for a *Bmp4* null allele (*Bmp4*<sup>-/-</sup>) die during gastrulation. To overcome the early embryonic lethality, we generated *Bmp4* cKO models using *Cre*-mediated recombination under the control of Anti-Müllerian hormone receptor type 2 (AMHR2) and progesterone receptor (PGR) to conditionally disrupt *Bmp4* gene in the ovary (*Bmp4* cKO (*Amhr2*)) and uterus (*Bmp4* cKO (*Pgr*)). **Results** Though *Bmp4* cKO (*Amhr2*) mice showed normal fertility, *Bmp4* cKO (*Pgr*) mice showed severe subfertility. However, implantation and early placental/fetal development were normal, mid-gestational abnormalities were detected in decidualization of *Bmp4* cKO (*Pgr*) uteri, resulted from defective proliferation and differentiation of uterine stromal cells. Additionally, vascularization defect was detected in decidual *Bmp4* cKO (*Pgr*) uteri, caused by reduction of blood vessel formation, leading to fetal-growth retardation and loss of the fetus before birth. **Conclusion** In our previous reports, we showed similar abnormalities in pregnant *Bmpr2* cKO (*Pgr*) mice, which demonstrated decidualization and vascularization defects resulted in fetal-growth retardation, placental abruption, and female infertility. Therefore, our findings indicate that BMP4 is one of the key ligands for uterine BMPR2 during placentation and is indispensable for the establishment of an adequate uterine environment to support normal pregnancy.

## ISP-21-3

**Possible Role of Neurotensin and CRH in the Feedback Regu-**

### lation by Estradiol : A Study Using Hypothalamic ARC and AVPV Cell Models

Tuvshintugs Tumurbaatar, Haruhiko Kanasaki, Aki Oride, Tomomi Hara, Hiroe Okada, Satoru Kyo Shimane University

**Objective** Hypothalamic kisspeptin (encoded by Kiss-1 gene) control the release and synthesis of GnRH through kisspeptin receptor (Kiss1R) within the GnRH neurons. In rodent, kisspeptin neurons within the arcuate nucleus (ARC) are the center for negative feedback by  $17\beta$ -estradiol (E2), whereas those in the anteroventral periventricular (AVPV) are defined as the center of positive feedback. These conclusions are based on the observations that Kiss-1 expression in the ARC is inhibited by E2, whereas AVPV Kiss-1 expression is stimulated by E2. In this study, we examined the involvement of neurotensin (NT) and corticotropin-releasing hormone (CRH) in the kisspeptin-mediated feedback control by E2. **Methods** mHypoA-50 and mHypoA-55 cells were used as cell models for AVPV and ARC kisspeptin neurons, respectively. Expression levels of kisspeptin mRNA were measured by real-time RT-PCR. **Results** Kiss-1 gene expression in mHypoA-50 cells was upregulated by E2, whereas it was downregulated by E2 under certain conditions in mHypoA-55 cells. NT was expressed and its expression was upregulated in the presence of E2 in both cell models. Stimulation of mHypoA-50 cells with NT increased Kiss-1 mRNA expression, whereas NT significantly reduced Kiss-1 expression in mHypoA-55 cells. CRH was also expressed in these cells and was also upregulated by E2. CRH stimulated Kiss-1 gene expression in mHypoA-50 cells, but it reduced Kiss-1 expression in mHypoA-55 cells. **Conclusion** Our observations using hypothalamic AVPV and ARC cell models suggest that NT and CRH have divergent effects on Kiss-1 gene expression under the influence of E2 in both hypothalamic regions. These neuropeptides might be involved in E2-induced feedback mechanisms.

### ISP-21-4

#### 14-3-3 sigma is a novel Basonuclin1-binding protein in oocyte

Motomasa Ihara, Masahito Tachibana, Takashi Kuno, Ayako Fujimine, Keiko Tanaka, Saori Igeta, Emi Yokoyama, Masumi Ishibashi, Zen Watanabe, Naomi Shiga, Nobuo Yaegashi Tohoku University Hospital

**Objective** There are multiple factors related to infertility. The loss of zinc-finger transcription factor Basonuclin1 (Bnc1) causes meiosis arrest at metaphase II during oocyte maturation. In order to find out a part of mechanism for meiosis abnormality in oocyte, novel Bnc1-binding proteins have been explored. **Methods** Lysates of 10,000 GV-stage oocytes of adult mice, and 293 cells were immuno-precipitated with coupling beads using anti-Bnc1 or rabbit serum, and analyzed with mass spectrometry, independently. The data were analyzed by sequence alignment using Mascot and Sequest algorithms. Protein database utilized Swiss-Plot. One of the proteins identified as a novel Bnc1-binding protein from both oocyte and 293 cell data, was cloned using mouse ovary cDNA. The GFP-tagged Bnc1-binding protein and Bnc1-His-Myc were immune-precipitated with anti-GFP antibody and analyzed with western blotting. The endogenous target protein in oocyte was immunostained and observed with confocal laser scanning microscopy. **Results** 56 candidates from oocytes, and 80 candidates from 293 cells were identified as more than  $\geq 2$  of  $\Sigma\#$  PSMs (peptide spectrum matches) by MS analysis. Of these, 14-3-3sigma ( $\Sigma\#$  PSMs=3) was identified from oocyte and 14-3-3epsilon ( $\Sigma\#$  PSMs=1,666) was identified from 293 cells. Bnc1 was specifically immune-precipitated with GFP-14-3-3sigma. Selective GPER (G protein-coupled estrogen receptor) agonist enhanced endogenous nuclear localization of 14-3-3sigma in oocyte. **Conclusion** 14-3-3 family proteins induce cross-talk with various signal transductions through protein complex formation. 14-3-3sigma

was identified as a novel Bnc1-binding protein. It is implicated that Bnc1 may possibly regulate various signal transduction through 14-3-3sigma.

### ISP-21-5

#### Genome-wide gene expression analysis in mouse granulosa cells undergoing luteinization during ovulation

Yuichiro Shirafuta, Isao Tamura, Haruka Takagi, Yumiko Mihara, Masahiro Shinagawa, Maki Okada, Lifa Lee, Ryo Maekawa, Hiromi Asada, Toshiaki Taketani, Hiroshi Tamura, Norihiro Sugino Yamaguchi University

**Objective** Dramatic changes of gene expressions occur in granulosa cells (GCs) undergoing luteinization during ovulation after the LH surge. Here, we genome-widely investigated the changes in mRNA expressions in mice GCs undergoing luteinization during ovulation. **Methods** 3-week-old immature mice were injected with equine chorionic gonadotropin (CG) (4IU) followed by human CG (5IU). The ovaries were removed, luteinized GCs were obtained before (0h) and 4, 12h after hCG injection, and mRNA was isolated. To investigate the genome-wide mRNA expression, RNA sequencing was performed. Gene expression values were calculated as fragment per kilobase of exon unit per million mapped reads (FPKM). The genes whose FPKM values increased or decreased more than 2-fold by hCG injection were defined as differentially expressed genes. The roles of those genes were analyzed by Gene ontology analysis and KEGG pathway analysis. **Results** (1) 2,592 genes were up-regulated 4h after hCG injection. They were associated with angiogenesis, cholesterol metabolism, progesterone production, histone modifications, and epithelial-mesenchymal transition (EMT). EMT may be involved in the changes of cell morphology form granulosa cells to luteal cells. These rapid changes of gene expression may be regulated by epigenetic mechanisms : histone modifications. (2) 1,831 genes were up-regulated 12h after hCG injection, and some of them were associated with protection of cells from DNA damage. **Conclusion** Genome-wide gene expression analysis using RNA sequencing revealed that rapid changes of gene expression occur in GCs immediately after hCG injection, which contribute to corpus luteum formation through various physiological functions.

### ISP-21-6

#### Mitochondria-eating protein is essential for sperm function, but not oocyte quality, in *in vitro* fertilization

Makoto Orisaka, Makoto Yamamoto, Yoshio Yoshida University of Fukui

**Objective** Mitochondria-eating protein (Mieap) is a key regulator of mitochondrial quality control system in cells. Although Mieap plays a critical role in maintaining healthy mitochondria in various pathophysiological states, its role in reproduction is unknown. **Methods** In vitro fertilization (IVF) was conducted by using sperm from male wild type (WT-sperm) and Mieap-knockout (Mieap-KO-sperm) mice, and oocytes from female WT (WT-oocytes) and Mieap-KO (Mieap-KO-oocytes) mice. The developed blastocysts were transferred into the uterus of pseudopregnant female mice. Data expressed as percentages were analyzed using Fisher's exact test. **Results** Mieap-KO-sperm exhibited reduced motility and increased morphological abnormalities. The number of Mieap-KO-oocytes after ovarian stimulation was identical to that of WT-oocytes. The fertilization rate and percentage of 4-cell embryos/2-cell embryos were significantly lower between Mieap-KO-sperm and WT-oocytes (41.5% [174/419] and 55.2% [96/174], respectively) and Mieap-KO-sperm and Mieap-KO-oocytes (29.9% [53/177] and 66.0% [33/53], respectively), than between WT-sperm and WT-oocytes (76.8% [413/538] and 94.9% [392/413], respectively) and

WT-sperm and Micap-KO-oocytes (83.7% [144/172] and 96.5% [139/144], respectively). Live birth rate after blastocyst transfer was comparable among embryos from WT-sperm and WT-oocytes (17.8% [21/118]), WT-sperm and Micap-KO-oocytes (18.8% [15/80]), Micap-KO-sperm and WT-oocytes (23.5% [4/17]), and Micap-KO-sperm and Micap-KO-oocytes (20.0% [5/25]). **Conclusion** Micap, a key regulator of mitochondrial quality control, is required for sperm motility and structural integrity. Micap-KO-sperm increased 2-cell stage block of embryos suggesting that the down-regulation of Micap in sperm induces oxidative stress in embryos during IVF. Micap is not essential for oocyte quality nor implantation of blastocysts.

## ISP-21-7

**Identification of the genes associated with endometrial cell aging** Teruhiko Kawamura, Ichiro Onoyama, Keiko Kawamura, Natsuko Yokota, Kana Hiasa, Katsuko Egashira, Kiyoko Kato *Kyushu University*

**Objective** As the age of reproduction among women is extended, the infertility rate has increased and the birth rate has declined. We assume that not only aging of oocyte but also endometrium, cause infertility, but the mechanism of endometrial cell aging is unknown. In the present study, we try to identify the genes associated with endometrial cell aging. **Methods** We purified total RNA from murine uteri resected from C57BL/6 at 5, 8 and over 60 weeks of age and the klothe mouse at 5 weeks of age, which is known as a model of progeria, and analyzed them with RNA-sequencing and bioinformatics analysis including cluster dendrogram, Gene ontology analysis and Pathway analysis. We validated the expression of candidate genes by real time PCR. All mouse experiments were approved by the animal ethics committee. **Results** In cluster dendrogram, gene expression profile of klothe mice is similar to young mice, but not aged mice. We detected continuously changing 6 up-regulated genes and 5 down-regulated genes with aging. In global comparison of young mice with aged mice, ALDH1a and KLF4, which are stemness markers, were downregulated with aging. Pathway analysis demonstrated that the genes involved in the pathway associated with the cell cycle or mitosis are downregulated with aging. Among the differentially expressed genes, the expression of IL17 receptor was validated and confirmed its upregulation. **Conclusion** We identified several genes as markers of endometrial cell aging.

## ISP-21-8

**Forced lipophagy reveals that lipid droplets are required for the development of preimplantation embryos in mice** Takayuki Tatsumi<sup>1</sup>, Atsushi Yamamoto<sup>3</sup>, Toshiro Kubota<sup>4</sup>, Naoyuki Miyasaka<sup>1</sup>, Satoshi Tsukamoto<sup>2</sup> *Tokyo Medical and Dental University<sup>1</sup>, National Institute for Quantum and Radiological Science and Technology<sup>2</sup>, Dokkyo Medical University Saitama Medical Center<sup>3</sup>, Tokyo Kyosai Hospital<sup>4</sup>*

**Objective** Although large amount of lipid droplets (LDs) are accumulated during oogenesis, the physiological function of LDs after fertilization remains largely unknown. Previously, we demonstrated that autophagy is highly activated after fertilization, and that autophagy-deficient embryos are lethal before implantation. Although autophagy is basically a non-selective degradation pathway, recent studies have revealed the existence of selective autophagy. We established a novel technique that could reduce LDs artificially, which we called forced lipophagy, and adopted this technique for the mouse fertilized embryo to examine the relationships between the reduction of LDs and the development of preimplantation embryos. **Methods** p62 (also known as Sqstm1), that is essential for selective autophagy, was used as autophagy-adaptor for LD degradation. To express p62

specifically on the surface of LDs, we generated mRNA which encoded fusion protein of p62 and LD-binding domain, and microinjected it into the cytoplasm of 1-cell embryos to induce forced lipophagy after fertilization. These lipophagy-induced embryos were further cultured and analyzed. **Results** In the lipophagy-induced embryos, LDs were clustered and translocated to the cell periphery, where autophagosomes and lysosomes were abundant. Induction of forced lipophagy caused a reduction in LD size and number, and decreased the triglyceride level throughout embryonic development. We confirmed that the lipophagy induction was dependent on autophagic activity. Finally, we found that the lipophagy induction decreases the developmental ability reaching to the blastocyst stage. **Conclusion** We demonstrate that the lipophagy-induction decreases the developmental potential, indicating that proper amount of LDs is essential for preimplantation embryo development in mice.

## ISP-21-9

**HAND2 regulates IL-15 in human endometrium during progesterone-induced decidualization** Hiromi Murata, Naoko Kida, Takeharu Kido, Maiko Kobayashi, Yoji Hisamatsu, Toshiko Ono, Sonoko Okada, Tomoko Tsuzuki, Hidetaka Okada *Kansai Medical University*

**Objective** Heart and neural crest derivatives-expressed transcript2 (HAND2) is a key transcription factor during progesterone-induced endometrial decidualization. The present study was undertaken in order to understand the mechanism underlying HAND2 regulates decidualization of human endometrium, putting its focus on Interleukin-15 (IL-15) which contributes to maturation of uterine natural killer (uNK) cells. **Methods** This study was approved by the institutional review board. Informed consent was obtained from each patient. Human endometrial tissues were collected from 24 patients who underwent hysterectomies with regular menstrual cycles. Cultured hESCs were treated with estradiol (E<sub>2</sub>) and medroxyprogesterone (MPA) for 2 h-12 d, and HAND2 siRNA-transfected hESCs were cultured in the presence of E<sub>2</sub>+MPA for 3 d. HAND2 and IL-15 mRNA expression change were analyzed by real-time PCR. Moreover, total RNA was extracted from endometrial tissues which were frozen in liquid nitrogen as soon as were collected, and the HAND2 and IL-15 mRNA levels were measured. **Results** The expression of IL-15 mRNA increased later than the induction of HAND2 mRNA in cultured hESCs primed with E<sub>2</sub>+MPA. IL-15 mRNA expression in hESCs treated with E<sub>2</sub>+MPA for 3 d decreased with siRNA knockdown of HAND2 compared with control. Furthermore, there existed a statistically significant positive correlation between the mRNA levels of HAND2 and IL-15 in human endometrium. Both of HAND2 and IL-15 mRNA expression of the endometrium during secretory phase were significantly higher than those during proliferative phase. **Conclusion** This study suggests that HAND2 regulates IL-15 in human endometrium during progesterone-induced decidualization.

## ISP-22-1

**New Strategies of preimplantation genetic haplotyping for patients with de novo mutation and couples with no available DNA samples from family members** Junko Maki, Suguru Sato, Kou Sueoka, Kenji Sato, Hiroshi Semba, Yuki Mizuguchi, Nobuhiko Higuchi, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** The scarcity of template DNA is a leading cause of misdiagnosis in preimplantation genetic diagnosis (PGD) using direct analysis of mutations. To overcome this limitation, indirect linkage analysis using polymorphic markers should be performed. We aimed to establish a novel PGD strategy that is ef-



fective for patients with de novo mutations or when affected-DNA samples from deceased family members are not available.

**Methods** Family 1) Both parents were carriers of the short rib-polydactyly syndrome, a lethal recessive skeletal disease. As blood samples of the affected proband had been depleted in the analyses by foreign institutions, we extracted DNA from dried umbilical cord preserved according to the Japanese traditions. Family 2) The patient had a de novo mutation for myotonic dystrophy, where the causative mutation was not identified in family members. We performed PGD on the basis of the results of a direct analysis coupled with a linkage analysis using DNA derived from poorly developed embryos subject to discard. **Results** Family 1) The average quantity of DNA from a dried umbilical cord was 20.1 µg/100 mg, sufficient for identifying linkage markers for haplotyping. Family 2) All the cells from two poorly developed embryos consisting of 7 and 4 blastomeres, respectively, were subjected to whole genome amplification on day 5, followed by a multi-locus analysis of short-tandem repeat markers. Family haplotypes were constructed successfully. **Conclusion** We established a robust PGD system for cases where mutated-DNA samples from affected family members are no longer available or not present originally.

## ISP-22-2

**Incidence and predictive factors for complete fertilization failure in *in vitro* fertilization treatment cycles : a retrospective cohort study using the assisted reproductive technology registry of Japan** Toshifumi Takahashi<sup>1</sup>, Ryota Suganuma<sup>2</sup>, Keiya Fujimori<sup>2</sup>, Hideki Mizunuma<sup>1</sup> *Fukushima Medical Center for Children and Women Fukushima Medical University<sup>1</sup>, Fukushima Medical University<sup>2</sup>*

**Objective** The purpose of this study was to evaluate the incidence and predictive factors for complete fertilization failure (CFF) in patients undergoing in vitro fertilization (IVF) treatment cycles. **Methods** The present study was a retrospective cohort study approved by the ethical committee on human subjects. The data analyzed in this study were part of the Japanese assisted reproductive technology (ART) registry database. We analyzed the data of 220,065 fresh cycles of IVF with one or more oocytes retrieved. An instance of CFF was defined as zero fertilized oocytes obtained. The IVF cycles with CFF and with one or more oocytes fertilized were compared with each other to determine predictive factors for CFF using multivariate logistic regression analyses. **Results** The number of IVF cycles with CFF was 29,076 (13.2%). On the multivariate analysis, oocyte number (odds ratio [OR] : 0.78, 95% confidence interval [CI] : 0.77–0.79) and sperm motility (OR : 0.99, 95% CI : 0.98–0.99) were the independent predictive factors for CFF. The percentages of CFF cycles in terms of one, two, three, four, and five oocytes retrieved were 34.2%, 15.3%, 8.6%, 6.0%, and 4.6%, respectively. The efficacy of oocyte number and sperm motility for predicting CFF was evaluated using receiver operating characteristic curves. The areas under the curves for oocyte number and sperm motility were 0.79 and 0.59, respectively. **Conclusion** Predictive factors for IVF cycles with CFF might be related with a specific oocyte number and sperm motility. These results provide information that may be useful for counseling patients prior to their undergoing ART treatments.

## ISP-22-3

**Polyunsaturated fatty acid concentration in the human follicular fluid may affect fertilization** Keiko Mekaru, Maho Miyagi, Kozue Akamine, Chiaki Heshiki, Yoichi Aoki *University of the Ryukyus*

**Objective** The metabolite composition of the follicular fluid, which represents the intrafollicular environment, may be an im-

portant factor affecting fertilization and subsequent early embryo development. PUFAs are essential fatty acids that are not synthesised in the body, but are utilised as an energy source for processes from oocyte nuclear maturation to embryonic development. Objective is to clarify the concentration of polyunsaturated fatty acids (PUFAs) in the follicular fluid affect fertilization and the quality of embryos. **Methods** A prospective study was conducted on 28 women eligible for in-vitro fertilization and embryo transfer between August 2015 and December 2016. Twenty-eight serum and 140 follicle fluid samples were collected and analysed. This study was approved by the clinical research ethics investigation committee in our institution. PUFAs fractions from the serum and follicular fluid were analysed using gas chromatography. Two millilitres of follicular fluid was collected from six consecutive follicles of each patient. Each individual follicle was aspirated independently and matched to an oocyte growing in this particular follicular milieu. **Results** The concentration of  $\gamma$ -Linolenic acid, an n-6 type PUFA, in the follicular fluid of fertilised oocytes was significantly higher than that in the follicular fluid of non-fertilised oocytes (1.1 vs 0.9,  $p=0.007$ ). Similarly, the concentrations of EPA and docosapentaenoic acid, which are n-3 type PUFAs, in the follicular fluid of fertilised oocytes were significantly lower than those in the follicular fluid of non-fertilised oocytes. **Conclusion** The concentration of PUFAs in the follicular fluid plays an important role in fertilisation.

## ISP-22-4

**Does variable luteal support according to the serum progesterone level at the embryo transfer improve the clinical pregnancy rate of natural frozen-thawed embryo transfer?** Takuhiko Ichiyama, Motoharu Ohno, Takashi Yamaguchi, Motoi Nagayoshi, Atsushi Tanaka *Saint Mother Hospital*

**Objective** To verify the clinical usefulness of the variable luteal support according to the serum progesterone levels in the cycle of natural frozen-thawed embryo transfer. **Methods** 1. 993 patients under 39 years old participated in 1,280 frozen-thawed transfer natural cycles from January 2015 to August 2017. They were divided into two groups, with variable luteal support (VLS) in 351 cycles and no luteal support in 929 cycles (NLS). The two groups were further divided into five groups according to the progesterone levels (ng/ml) : GroupA (Progesterone  $\leq 5$ ), GroupB ( $5 < \text{Progesterone} \leq 10$ ), GroupC ( $10 < \text{Progesterone} \leq 15$ ), GroupD ( $15 < \text{Progesterone} \leq 20$ ), GroupE ( $20 < \text{Progesterone}$ ). 2. In the VLS group, progesterone suppositories were given according to the serum progesterone levels at the embryo transfer of the 5th day from the spontaneous ovulation. 3. In the NLS group, no luteal support was given regardless of the progesterone levels. **Results** Pregnancy rate (VLS vs NLS) : GroupA (50% (8/16) vs 33% (2/6)), GroupB (45% (45/101) vs 40% (21/53)), GroupC (45% (94/208) vs 47% (99/211)), GroupD (55% (12/22) vs 40% (149/368)), GroupE (50% (2/4) vs 47% (136/291)). Miscarriage rate : GroupA (25% (2/8) vs 50% (1/2)), GroupB (18% (8/45) vs 19% (4/21)), GroupC (17% (16/94) vs 15% (15/99)), GroupD (25% (3/12) vs 19% (28/149)), GroupE (0% (0/2) vs 20% (27/136)). **Conclusion** There were no statistically significant differences between the VLS and NLS groups. Variable luteal support according to serum progesterone level in natural frozen-thawed embryo transfer showed no beneficial effect for improving the clinical outcome.

## ISP-22-5

**Egg activation of sperm factor, phospholipase C zeta 1 (PLCZ1) as future clinical applications** Takashi Yamaguchi<sup>1</sup>, Takuhiko Ichiyama<sup>1</sup>, Motoharu Ohno<sup>1</sup>, Motoi Nagayoshi<sup>1</sup>, Atsushi Tanaka<sup>1</sup>, Keiji Kuroda<sup>2</sup> *Saint Mother Hospital<sup>1</sup>, Juntendo*

University<sup>2</sup>

**Objective** In this study, to establish the best egg activation method and improve development rates after ICSI or ROSI, we compared the pattern of  $[Ca^{2+}]_i$  elevation after stimulation by cytosolic aspiration, electrical stimulation, ionomycin treatment and human PLCZ1 RNA injection. We found that the pattern of  $Ca^{2+}$  oscillations after hPLCZ1 RNA injection exhibited similar characteristics to that after ICSI treatment. **Methods** M-II oocytes were incubated in 4 $\mu$ M Fluo-8H AM in SPS medium and optimal RNA concentrations for oocyte activation were examined by injecting various concentrations of in vitro transcribed hPLCZ1 RNA by conventional Piezo-ICSI methods into the human M-II oocytes. After injection, the rate of pronucleus (PN) and polar body (PB) formation was checked and the intracellular  $Ca^{2+}$  concentrations were monitored by fluorescent  $Ca^{2+}$  indicator among four groups: (A) electrical stimulation, (B) Mechanical stimulation, (C) Ionomycin, (D) hPLCZ1 RNA. **Results** From the pattern of  $Ca^{2+}$  concentrations and PN formation rate, optimal concentration of hPLCZ1 RNA to activate human oocytes was 100 ng/ $\mu$ l. The duration and interspike intervals of  $Ca^{2+}$  oscillations were similar to that of ICSI. And we also compared the effect among 3 groups (A, C, D) in ROSI cycles. Group D showed higher embryonic development without significant differences. **Conclusion** hPLCZ1 has the ability to generate ideal and physiological egg activation, leading to subsequent embryo development. In the future, for clinical application, the safety of hPLCZ1 injection to human health should be examined in more detail.

### ISP-22-6

**An analysis of follicular oxidative stress and oocyte development in ART treatment cycle** Hiromi Terao, Osamu Hiraike, Nana Akino, Harunori Honjoh, Mana Hirano, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Kaori Koga, Tomoyuki Fujii, Yutaka Osuga *The University of Tokyo*

**Objective** Oxidative stress is defined as an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants. This study was conducted to clarify influence of the oxidative stress on the development of oocytes. **Methods** Under the approval of IRB and patient's consent, follicular fluid of patients who underwent ICSI treatment in the Hospital were collected. The ovum was fertilized and individually cultured, and the development status was recorded. The follicular fluid corresponding to the ovum was analyzed by measuring the oxidative stress marker such as the reactive oxygen metabolites (d-ROMs test) and the antioxidant marker (BAP test). **Results** We collected 107 follicular fluid from 57 patients. The age of participants was  $37.89 \pm 4.54$ , and the number of the ovum collected was  $5.648 \pm 4.23$ . The fertilization rate of the ovum judged by the presence of 2 pronucleus in Day 1 was 71.0%. Although the age, AMH, the number of ovum collected and the embryonic development did not show significant correlation with oxidative stress markers, the value of d-ROMs test was significantly elevated in abnormal fertilization group ( $508.77 \pm 129.15$ ) than that of normal fertilization group ( $398.06 \pm 108.70$   $p < 0.001$ ). **Conclusion** We found that the oxidative stress in follicular fluid mainly influenced on fertilization rate of the ovum, and the correlation of BAP test with several biomarkers should be further investigated.

### ISP-22-7

**Progesterone/estradiol ratio as a predictor of obtaining usable blastocyst in clomiphene IVF cycle** Kenichiro Watanabe, Yoshimitsu Kuwabara, Mirei Yonezawa, Shuichi Ono, Tomoko Ichikawa, Shigeo Akira, Toshiyuki Takeshita *Nippon Medical School*

**Objective** To examine the relationship between the outcome of obtaining usable blastocyst (3 BB or more) in clomiphene IVF cycle and the serum progesterone (P4)/estradiol ( $E_2$ ) ratio which is an indicator of early luteinization. **Methods** In 367 patients who underwent clomiphene IVF cycle from January 2013 to June 2015, the serum P4/ $E_2$  ratio at two days before the egg collection was calculated. The data was separated into 300 cycles in the usable embryo acquisition group (Group A), 38 cycles in which the oocyte could be picked up but did not result in obtaining usable embryos (Group B), and 29 cycles for which the follicle was pierced but the eggs could not be obtained (Group C). **Results** The P4/ $E_2$  ratio was significantly lower in group A ( $3.9 \pm 0.1 \times 10^{-4}$ ) than in group B ( $5.5 \pm 0.7 \times 10^{-4}$ ) and C ( $7.9 \pm 1.5 \times 10^{-4}$ ) (Mean  $\pm$  S. E. M., A vs B;  $p < 0.01$ , A vs C;  $p < 0.0001$ ). The ROC curve was drawn for the effective embryo-obtained group (A), and for the effective embryo un-acquired group (B+C), the AUC was 0.69, the cut-off point of effective embryo acquisition was  $3.5 \times 10^{-4}$  (if  $E_2 = 1,000$  pg,  $P = 0.35$  ng/ml), the sensitivity was 80.6%, and the specificity was 52.33%. **Conclusion** The P4/ $E_2$  ratio is considered to be a predictor of usable embryo acquisition in the clomiphene IVF cycle.

### ISP-23-1

**Polycystic ovarian morphology in reproductive-aged Thai women with polycystic ovary syndrome** Vichuta Unalome, Thanayarat Wongwananurak *Siriraj Hospital, Mahidol University, Thailand*

**Objectives** To determine the prevalence and factors associated of polycystic ovarian morphology (PCOM) in reproductive Thai woman with polycystic ovary syndrome (PCOS). **Study design** Cross sectional study. **Subject** Thai PCOS 143 woman diagnosed by Revised Rotterdam criteria who attended at Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Siriraj Hospital during February 2016 to May 2017. **Methods** The participants were interviewed and examined for weight, height, waist circumference and blood pressure. Blood sample were drawn for fasting plasma glucose, lipid profile, testosterone, and 2 hour post loading 75 glucose tolerance test (OGTT). Transvaginal or transrectal ultrasonography was performed to evaluate PCOM. **Results** Mean age and BMI of population were  $25.2 \pm 5.3$  years old and  $24.3 \pm 6.0$  kg/m<sup>2</sup>. Clinical presentation showed 77.6% had acne and 64.3% had hirsutism. The blood test revealed 16.1% had abnormal OGTT in these 5.6% had diabetes mellitus. Mean total testosterone was  $0.47 \pm 0.1$  ng/mL. The overall prevalence of PCOM was 55.2%. Prevalence of PCOM by ovarian follicle, ovarian volume was 36.4% and 42% respectively. Mean follicle number per ovary, follicle number per cross section and ovarian volume were  $20.0 \pm 9.5$  follicles,  $8.3 \pm 3.1$  follicles,  $7.9 \pm 3.0$  cm<sup>3</sup> respectively. Univariate analysis of clinical predictor founded that no associated factor with PCOM. **Conclusion** The overall prevalence of PCOM in Thai woman with PCOS was 55.2%. There was no significance predictor associated with PCOM.

### ISP-23-2

**The effect of androgen on secondary follicle development might be species-specific** Yuya Fujibe, Tsuyoshi Baba, Sachiko Nagao, Tsuyoshi Saito *Sapporo Medical University Hospital*

**Objective** Excess androgen is thought to play a key role in the pathogenesis of polycystic ovary syndrome (PCOS). Several animal models exposed to androgens are used to examine the effects of androgens on follicle development. However, experimental animals exposed to androgens do not completely mimic PCOS. In addition, extremely high level of androgen exposure in female-to-male transsexualism does not cause PCOS-like phenotype. We therefore investigated the effects of various dose of



androgen on mice follicle development and compared with our previous study of nonhuman primate models. **Methods** Secondary follicles from 6-week-old female ICR mice (n=3) were isolated and assigned to 4 culture conditions: 1) control (33 ng/ml FSH); 2) dihydrotestosterone (DHT) 50 ng/ml; 3) DHT 500 ng/ml; and DHT 1,250 ng/ml. Follicles were cultured at 37°C in a 5% CO<sub>2</sub> environment for two weeks. Follicle survival and follicle diameters were determined. **Results** Follicle survival rates in control, DHT 50, DHT 500, and DHT 1,250 groups were 83 ± 8%, 49 ± 7%, 45 ± 5%, and 54 ± 13%, respectively (p=0.057). Follicle diameter at day13 in each group are 218.3 ± 33.4 μm, 236.7 ± 10.7 μm, 181.2 ± 47.5 μm, and 253.7 ± 19.7 μm, respectively (p=0.52). **Conclusion** In our previous study using maquette, at the preantral stage, DHT can replace FSH action to promote follicle survival rate, but in rodents, androgen does not seem to support secondary follicle survival. In addition, the dose escalation of DHT does not alter folliculogenesis in rodents. The effects of androgens on secondary follicle development might be species-dependent.

### ISP-23-3

#### Large uterine myoma with erythropoietin messenger RNA and erythrocytosis Takafumi Kohama *Keiju Medical Center*

**Background** Erythrocytosis reported in association with a uterine myoma is well known as the myomas erythrocytosis syndrome. Although several etiologies for this syndrome have been forth, altered erythropoietin-production is the most likely to which there are few cases reported. **Case** A 28 year old, gravida 0, para 0, with a chief complaint of infertility, presented with a 34-36 weeks gestation-sized, solitary, degenerated uterine myoma and erythrocytosis. After Gn-RH agonist treatment, a myomectomy was performed and the tumor analyzed by reverse transcription-polymerase chain reaction (PCR) with specific erythropoietin primer with erythropoietin-mRNA was observed. Randomly selected 8 cases of uterine myoma from the patients with no finding of erythrocytosis were analyzed in the same way for the control at the same time. **Conclusion** Our finding suggests that erythropoietin production by myomas might cause erythrocytosis in the myomatous erythrocytosis syndrome. After the surgery, she had 2 pregnancies, showing no abnormalities all the courses of pregnancy and delivery (cesarean section).

### ISP-23-4

#### Application of Computer-Aided Sperm Analysis (CASA) for Sperm Immobilization Test Yu Wakimoto<sup>1</sup>, Atsushi Fukui<sup>1</sup>, Akiko Hasegawa<sup>1</sup>, Yukiko Sugiyama<sup>1</sup>, Yuji Ukita<sup>1</sup>, Minoru Shigeta<sup>2</sup>, Hiroaki Shibahara<sup>1</sup> *The Hospital of Hyogo College of Medicine<sup>1</sup>, Fuchu Nozomi Clinic<sup>2</sup>*

**Objective** Complement-dependent sperm-immobilizing test (SIT) and quantitative SIT have been used as a useful tool for diagnosis to female infertility in clinical sites. These tests are subjective judgement of the operator due to counting motile sperm by eye. It is possible to evaluate objectively data on sperm motility using computer-aided sperm analysis (CASA) instruments. In this study, we developed a novel method of SIT and quantitative SIT using CASA. **Methods** 78 serum samples and motile sperm by a swim-up method were prepared. Mixtures of 10 μL of serum, 1 μL of the sperm suspension, and 2 μL of complement were incubated. We compared the classical method counting sperm by eye of a highly skilled embryologist with a novel method counting sperm using CASA through the chamber slides. The mixtures were incubated respectively on Terasakis microplates in the classical method and after being applied to chamber slides in the novel method. Sperm motility was measured after one-hour incubation in both methods. **Re-**

**sults** The results of SIT were completely same in both methods. 25 of 78 samples tested were positive and 53 samples were negative. In case sperm immobilizing value was 2 or higher, the values of SI50 were determined and closely correlated with high co-efficiency in both methods (r=0.84). **Conclusion** We showed that it is possible to perform SIT and quantitative SIT in the novel method using CASA presented here.

### ISP-23-5

#### A successful pregnancy in a patient with 46,XY pure gonadal dysgenesis after transfer of a frozen-thawed embryo derived from donor oocytes Misato Ukita, Yuji Ukita, Yukiko Sugiyama, Toru Kato, Kayoko Harada, Hideaki Sawai, Hiroaki Shibahara *The Hospital of Hyogo College of Medicine*

**Background** The 46, XY pure gonadal dysgenesis (PGD) is one of atypical sex disorders and named after Swyer, who first described this syndrome. Swyer patients (approximately 1 : 30,000) have a male genotype (46, XY) but reveal no male gonadal differentiation. They show sex reversal with normal female external genitalia and a vagina. However, the uterus is mostly hypoplastic and the Fallopian tubes are rudimentary and dysfunctional. Here we report a successful pregnancy in a patient with PGD after transfer of frozen-thawed embryo derived from donor oocytes. **Case** A 27-years-old female presented with primary amenorrhea. Physical examination revealed a phenotypic female with a normal vagina and cervix, no clitoral enlargement and other evidence of virilization. The uterus accepted it by an ultrasonography, but the both ovaries were indistinct. Her serum FSH level was 75.71mIU/mL, LH level was 11.68mIU/mL, and testosterone level was 0.09ng/dL. A karyotype performed on peripheral leukocytes analyzed 100 cells, all of which contained a 46, XY chromosome. Laparoscopic surgery revealed an infantile uterus, hypoplastic Fallopian tubes, and bilateral streak gonads, which were excised. Pathologic examination documented only fibrous tissue. Six years later she conceived after transfer of a frozen-thawed embryo derived from donor oocytes at USA. She delivered a normal male infant weighing 2,780g with Apgar scores of 8 and 9 at 1 and 5 minutes by Cesarean section after her 37 weeks of pregnancy due to partial placenta previa.

### ISP-23-6

#### Determining the safe cut-off point for preimplantation genetic diagnosis (PGD) of mitochondrial DNA (mtDNA) disorders Yuki Mizuguchi, Kou Sueoka, Suguru Sato, Junko Maki, Kenji Sato, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** mtDNA disorders are usually heteroplasmic, with cells harbouring both wild-type and mutated mtDNA. Prerequisites for PGD of mtDNA disorders are that the mutant load has: 1) correlation between tissues and cells, 2) no time-dependent change, 3) correlation with phenotype. The most difficult problem of PGD for mtDNA disorders is the inability to determine the cut-off point for embryo transfer. Too stringent criterion would lead to a loss of a presumably healthy embryo. We aimed to determine the safe cut-off point for PGD of mtDNA disorders. **Methods** Four cases of Leigh encephalopathy have been approved by the hospital and Japan Society of Obstetrics and Gynecology (JSOG) ethical committees. Amongst those, PGD was carried out with 2 cases with m.8993T>G mutation. **Results** The number of transferrable/biopsied embryos were: case 1 (0/1), case 2 (1/8). None of these cases have resulted in successful pregnancy. For the m.8993T>G mutation, the chance of having an affected offspring is highly unlikely when the mutant load is below 20% and in most cases the threshold for a severe clinical outcome is 90%. When setting a cut-off point: 1) mutant load below the carrier, 2) preventing the loss of healthy

embryos, 3) prevention of the disease, are taken into consideration. The JSOG ethical committee proposed that mutant load below 80% would be feasible so we set our cut-off point at 45% taking patients desire in consideration. **Conclusion** Although there is no definite cut-off level for PGD of mtDNA disorders, lower mutant load below 20% is likely to be a safe and efficient cut-off point.

### ISP-23-7

**Establishment of female athlete outpatient in our hospital and current problems for female athlete triad** Sayaka Nose-Ogura, Osamu Hiraike, Akari Nakazawa, Kaoru Morishima, Mana Hirano, Mayuko Kanatani, Miyuki Harada, Tomoyuki Fujii, Yutaka Osuga *The University of Tokyo Hospital*

**Objective** Recently, it has been well recognized a set of health problems occurs for female athletes. After recognition of female athlete triad (FAT) in 1992 and its update in 2007, low energy availability, functional hypothalamic amenorrhea, and osteoporosis have been keenly attracting attention and our hospital established an outpatient for female athletes in April 2017. Herein we report the current status of the outpatient. **Methods** Under approval of IRB and patients consent, we retrospectively reviewed the medical records from April to September in 2017 to reveal the clinical characteristics of female athletes. **Results** Total number of cases was 145 (26 in international-level and 49 in national-level) and average age of participants was 21.5. Athletes who visited for menstrual cycle control with the aim of conditioning were 9 (12%). Forty patients (66.7%) were diagnosed as menstrual dysfunction (39 secondary amenorrhea, 1 primary amenorrhea, and 10 oligoamenorrhea) accompanying with low energy availability, and they were consulted to sports dietary specialist and four patients with apparent eating disorder were consulted to sports psychiatrist. **Conclusion** As expected, the most frequent disease in female athletes who visited our hospital was amenorrhea due to low energy availability. We should note that amenorrheic athletes may be complicated by eating disorder, and cooperation with sports dietitian and sports psychiatrist is mandatory.

### ISP-23-8

**What is OHVIRA syndrome? The Müllerian duct anomaly and unilateral renal agenesis in our 17 cases** Takashi Kuno, Zen Watanabe, Saori Igeta, Keiko Tanaka, Ayako Fujimine, Emi Yokoyama, Masumi Ishibashi, Naomi Shiga, Motomasa Ihara, Junichi Sugawara, Masahito Tachibana, Nobuo Yaegashi *Tohoku University Hospital*

**Introduction** OHVIRA syndrome was first described in 2007 and is emerging a generic term for diseases that merge uterine anomalies with unilateral obstructed vagina and ipsilateral renal abnormality. OHVIRA syndrome and related diseases vary in phenotype and symptoms due to variety of congenital anomaly of Müllerian duct associated mesonephric duct anomaly. We investigated 17 cases of the Müllerian duct anomaly and unilateral renal agenesis in our hospital. **Methods** Patient age at first visit, symptoms, classification of female genital tract malformations, laterality of renal hemiagenesis, surgical interventions, endometriosis, pregnancy and delivery style were investigated for those of 17 cases from 2002 to 2017. **Results** The median age of patients at first visit was 16 years. Chief complaints were as follows: 5 with dysmenorrhea, 2 with associated abdominal pain, 4 with desire for baby, and others. The laterality of renal hemiagenesis was 7 right and 10 left cases. In almost all 13 surgical cases, the vaginal septectomy was performed. The operation was performed for 8 cases in early adolescence and for 5 cases in adulthood. The combined laparoscopy was performed for 8 out of 13 cases and the pelvic endometriosis was revealed in 5.

Of 5 patients desired for baby, 4 became pregnant and all gave birth at term (3 caesarean section and one vaginal). **Conclusion** OHVIRA syndrome and related diseases involved variety of anomalies. Physician should be aware of those varieties of phenotypes and symptoms for accurate diagnosis and individualized management.

### ISP-23-9

**Serum AMH levels in adolescent and young women under 25 years with irregular menstrual cycles** Akari Watanabe, Michio Kitajima, Yuriko Kitajima, Ozora Tsukamoto, Naoko Murakami, Ken Taniguchi, Kiyonori Miura, Hideaki Masuzaki *Nagasaki University Hospital*

**Objective** Serum AMH levels have been introduced to infertility care to predict responsiveness for controlled ovarian stimulations. They also may be useful in the diagnosis of premature ovarian insufficiency (POI) and polycystic ovarian syndrome (PCOS), though, its value is uncertain in young women under 25 years of age. In this study, we evaluated clinical significance of serum AMH levels in women under 25 years who showed irregular menstrual cycles from various reasons. **Methods** From July 2011 to March 2017, women who visited our department due to menstrual disturbances were recruited. Women with ovarian tumor, endometriosis, and under hormonal therapy were excluded. Menstrual disturbances were classified as POI, PCOS, and hypothalamic from endocrinological examinations. Serum AMH levels were measured by ELISA. The relationship between serum AMH levels and clinical features are evaluated. **Results** Fifty-three women were enrolled. In five idiopathic POI patients, serum AMH were all undetectable. Mean serum AMH levels were  $0.23 \pm 0.26$  ng/mL in eight iatrogenic POI patients. In obese PCOS (n=7) and non-obese PCOS (n=8) patients, serum AMH levels were  $11.4 \pm 4.07$  ng/mL and  $14.3 \pm 7.14$  ng/mL, respectively. In hypothalamic amenorrhea (n=25), two out of five athletes, two out of three women in wasting state, such as cancer, and one out of seven weight loss women showed serum AMH levels below 1.5 ng/mL and significantly lower than amenorrheic women with unknown causes (n=10,  $6.58 \pm 3.37$  ng/mL). **Conclusion** Young women with hypothalamic amenorrhea due to systemic exhaustions may show low serum AMH values, which may need careful interpretations of the results.

### ISP-24-1

**Association of eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio with second trimester miscarriage** Nobuko Mimura, Takeshi Nagamatsu, Rieko Shitara, Hitomi Furuya, Aki Hara, Takahiro Seyama, Toshio Nakayama, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio is a representative marker to evaluate dietary intake balance of omega-3 and omega-6 fatty acids. This study aimed to investigate the relevance of serum EPA/AA ratio to the pathoetiology of recurrent miscarriage (RM). **Methods** This study was conducted under approval of our facility ethics committee. Medical records of 772 women visiting our special clinic for RM from Nov. 2010 to Jul. 2017 were retrospectively reviewed. In addition to routine screening tests for RM, serum EPA/AA ratio was examined. The women without specific causal factors identified were divided into two age groups: the women at age  $\geq 35$  (group A, n=470) and the women at age  $< 35$  (group B, n=248). The relevance of EPA/AA ratio to their past history of miscarriage was analyzed. **Results** There was no correlation between the past miscarriage number and EPA/AA ratio in both groups. In group B, EPA/AA ratio was significantly lower in the women with a history of second trimester

miscarriage ( $0.18 \pm 0.10$ ,  $n=33$ ) compared with the women without it ( $0.24 \pm 0.14$ ,  $n=215$ ) ( $p=0.02$ ). This phenomenon was more obvious in the women who experienced the second trimester miscarriage resulting from cervical incompetence and chorioamnionitis (EPA/AA ratio= $0.11 \pm 0.03$ ,  $n=6$ ). No remarkable association of EPA/AA ratio with the history of second trimester miscarriage was observed in group A. **Conclusion** Low omega-3/omega-6 intake would be a hidden factor associated the pathoetiology of the second trimester miscarriage among unexplained RM women at age <35.

## ISP-24-2

**Domain V of  $\beta$ 2GPI has very high affinity with MHC class II** Yuuki Sasagawa<sup>1</sup>, Kenji Tanimura<sup>1</sup>, Satoko Morikami<sup>2</sup>, Masashi Deguchi<sup>1</sup>, Yasuhiko Ebina<sup>1</sup>, Hideto Yamada<sup>1</sup>, Hisashi Arase<sup>3</sup> *Kobe University<sup>1</sup>, Kobe City Nishi-Kobe Medical Center<sup>2</sup>, Osaka University Immunology Frontier Research Center<sup>3</sup>*

**Objective** Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thrombosis and/or pregnancy complications.  $\beta$ 2-glycoprotein I ( $\beta$ 2GPI) complexed with phospholipid is known to be the major target for autoantibodies in APS.  $\beta$ 2 GPI associated with HLA class II molecules is the major autoantibody target in antiphospholipid syndrome.  $\beta$ 2GPI is composed with 5 domains. It is suggested that autoantibodies bind to domain I of  $\beta$ 2GPI, whereas phospholipids bind to domain V. In this study, we analyzed how autoantibodies recognize  $\beta$ 2GPI/HLA class II complex. **Methods** We made domain deletion mutants of  $\beta$ 2GPI. Using these mutants of  $\beta$ 2GPI, we analyzed the domains of  $\beta$ 2GPI to associate with HLA class II molecules using cell lines, latex beads and SDS-PAGE. **Results** We found that the domain V of  $\beta$ 2GPI is responsible to the association with HLA class II molecules. On the other hand, autoantibodies preferentially bound to the domain I of  $\beta$ 2GPI. These results suggest that the binding region of  $\beta$ 2GPI to phospholipids and HLA class II molecules is similar. **Conclusion** These studies provide important information to understand how HLA class II molecules are involved in the pathogenesis of antiphospholipid syndrome.

## ISP-24-3

**Reevaluation of the RPL management based on the villus chromosomal analysis after miscarriage despite previous treatment** Ai Sakamoto<sup>1</sup>, Hirofumi Matsuoka<sup>1</sup>, Shiho Fujita<sup>1</sup>, Kotaro Kubo<sup>1</sup>, Toru Hasegawa<sup>1</sup>, Sayoko Kotani<sup>1</sup>, Yasuhiko Kamada<sup>1</sup>, Mikiya Nakatsuka<sup>2</sup>, Hisashi Masuyama<sup>1</sup> *Okayama University<sup>1</sup>, Okayama University Graduate School of Health Sciences<sup>2</sup>*

**Objective** In our hospital, outpatients with RPL (recurrent pregnancy loss) are examined for risk factors of miscarriage which include autoimmunological, endocrine, and coagulation factors. Based on the results, a treatment plan was developed for subsequent pregnancies. When miscarriages occurred despite the management, chorionic villus chromosomal analysis was conducted after obtaining a consent to ascertain the cause of pregnancy loss. **Methods** Women with singleton pregnancies, who were treated for RPL and underwent a chorionic villus chromosomal analysis after miscarriage at our hospital from January 2006 to April 2017 (158 cases) were analysed retrospectively. Fourteen cases associated with parental chromosomal translocation were excluded. **Results** Out of 44 cases (27.8%) showing normal karyotype, subsequent pregnancies were recorded in 18 cases. Fetal morphological abnormalities were not detected during the previous pregnancies in 14 cases, they were managed with a method strengthened from previous treatments. As a result, 15 cases (83.3%) were able to deliver babies. However, repeated miscarriages with normal karyotype were recorded in 2 cases. In addition, 98 cases (62.0%) showed abnormal karyotype,

and 56 cases out of the above group achieved following pregnancies and managed with the same treatments. As a result, 49 cases (87.5%) were able to deliver babies. **Conclusion** By ascertaining the cause of miscarriage and reevaluating the management, high rate of delivering a baby was achieved on subsequent pregnancies. This data is expected to help the patients with RPL understand the importance of villus chromosomal analysis after miscarriage.

## ISP-24-4

**Induction and clearance of decidual senescent cells in cycling human endometrium** Yojiro Maruyama, Keiji Kuroda, Keisuke Murakami, Atsuo Itakura, Satoru Takeda *Juntendo University*

**Objective** Immune clearance of accumulating senescent cells followed by stem cell activation and repair maintains homeostasis of many ageing tissues. To examine it is happened in endometrial stromal cells (EnSCs), we checked cellular senescence and immune clearance in vivo and in vitro. **Methods** EnSCs and immune cells are isolated from endometrial biopsies. Decidualization is induced by progesterone and cAMP. **Results** Here we show that cyclic decidualization of the human endometrium triggers cellular senescence in a subpopulation of EnSCs, characterized by accumulation of senescence-associated  $\beta$ -galactosidase, heterochromatin formation, epigenetic changes and induction of a complex pro-inflammatory response. Treatment of primary cultures with rapamycin, a selective mTOR inhibitor, abrogated senescence but also blocked induction of decidual markers genes (PRL and IGFBP1). However, selective ablation of senescent cells with dasatinib, a senolytic drug, had no effect on subsequent induction of PRL or IGFBP1 in primary EnSCs but attenuated the decidual pro-inflammatory secretory response and resulted in loss of clonal endometrial mesenchymal stem cells (eMSCs). Further, we demonstrate that IL15-activated uterine NK (uNK) cells target and clear senescent EnSCs both in vitro and in vivo. Taken together, these observations demonstrate that the intense endometrial remodelling underpinning the mid-luteal window of implantation involves induction of a senescence-associated pro-inflammatory response. Activated uNK cells then clear senescent EnSCs, which in turn triggers differentiation of eMSCs as the decidual process unfolds. **Conclusion** Our results suggest that imbalance of eMSCs, decidual senescent cells and uNK cells may be a major cause of reproductive failure.

## ISP-24-5

**The distribution of etiology and therapy outcomes of recurrent pregnancy loss at our recurrent pregnancy loss clinic** Maho Miyaji, Masashi Deguchi, Kenji Tanimura, Mayumi Morizane, Yasuhiko Ebina, Hideto Yamada *Kobe University Hospital*

**Objective** The aim of this cohort study was to reveal etiology/risk factor and pregnancy outcome in women with recurrent pregnancy loss (RPL). **Methods** The institutional ethic boards approved this study. Three hundred forty-five women with RPL who consecutively visited our hospital between June 2009 and July 2015 were enrolled, and their etiologies/risk factors of RPL were assessed. Pregnancy outcomes were evaluated, and compared among 283 women with each etiology/risk factor of RPL. High natural killer (NK) cell activity, luteal insufficiency or positive anti-phosphatidylethanolamine antibody was considered unexplained etiology/risk factor. All patients received standard therapies before and during pregnancy. **Results** Of 283 patients, 257 patients became pregnant, and pregnancy rate was 91%. A total of 163 women had explained etiology/risk of RPL, while 182 women had unexplained etiology/risk. Pregnancy rate (67%) in women with uterine abnormality was lower than

that (89%) in women without it ( $p < 0.01$ ). Pregnancy rate (98%) and live birth rate (94%) in women with PS deficiency was higher than those (86%, 76%) in women without it ( $p < 0.01$ ). Live birth rate (58%) in women with high NK cell activity was lower than that (86%) in women without it ( $p < 0.01$ ). **Conclusion** Pregnancy rate in women with uterine abnormality was low, while pregnancy rate and live birth rate in women with PS deficiency was high. Live birth rate in women with high NK cell activity was found to be low. These results provide useful information for clinical practitioners. Alternative therapy such as immunoglobulin might improve the pregnancy outcome of patient with NK.

## ISP-24-6

**Subclinical hypothyroidism in women with recurrent pregnancy loss** Kotaro Kubo<sup>1</sup>, Yasuhiko Kamada<sup>1</sup>, Yuri Miyahara<sup>1</sup>, Hirofumi Matsuoka<sup>1</sup>, Shiho Fujita<sup>1</sup>, Toru Hasegawa<sup>1</sup>, Ai Sakamoto<sup>1</sup>, Sayoko Kotani<sup>1</sup>, Mikiya Nakatsuka<sup>2</sup>, Hisashi Masuyama<sup>1</sup> *Okayama University<sup>1</sup>, Okayama University Graduate School of Health Sciences<sup>2</sup>*

**Objective** Thyroid dysfunction is associated with various obstetrical complications. The guidelines of the American Thyroid Association 2011 remarked that thyroid autoantibody-positive women were high-risk for miscarriage and subclinical hypothyroidism during pregnancy. But management of subclinical hypothyroidism women with recurrent pregnancy loss (RPL) remains to be established. We evaluated the thyroid function in RPL women with anti-thyroid autoantibodies including anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb). **Methods** Four hundred and twenty-one women with RPL (Age,  $36.0 \pm 4.4$ , mean  $\pm$  S.D.), who visited RPL clinic in our hospital from April 2013 to December 2016 were enrolled into the study after informed consent. Women who have already received medical treatment for thyroid dysfunction were excluded in this study. Thyroid function (free T4, TSH) and anti-thyroid autoantibodies (TgAb, TPOAb) were examined before pregnancy and during early pregnancy with other routine examinations. **Results** Prevalence of hyperthyroidism, subclinical hypothyroidism ( $TSH > 2.5 \mu\text{U/mL}$ ), and hypothyroidism ( $TSH > 10 \mu\text{U/mL}$ ) were 0.7%, 17.1%, and 0.7%, respectively. Prevalence of TgAb or TPOAb in RPL women was 16.3% or 8.3%, respectively. Two hundred and sixty women became pregnant in study duration, fifty-six (21.5%) were newly discovered as subclinical hypothyroidism at early pregnancy. In RPL women, serum TSH levels were significantly elevated at early pregnancy compared with TSH levels before they became pregnant. **Conclusion** In certain ratio of RPL women were newly diagnosed as subclinical hypothyroidism at early pregnancy. And it may be necessary for them to be treated for newly developed thyroid dysfunction. It is important to evaluate the thyroid function in RPL women at early pregnancy.

## ISP-24-7

**Studies on the outcome of pregnancies which had continued after the immunosuppressive and anticoagulation therapy for patients with reproductive failure who are positive for anti-phospholipid antibodies (APLs)** Taro Nonaka, Makiko Takahashi, Kunihiro Yoshida, Koichi Takakuwa, Takayuki Enomoto *Niigata University Medical and Dental Hospital*

**Objective** To investigate the outcome of pregnancies which had continued after the immunosuppressive and anticoagulation therapy for patients with reproductive failure who are positive for APLs. **Methods** We treated patients with recurrent fetal miscarriages positive for APLs using Saireito, which has similar pharmacologic effect as corticosteroid hormone, as immunosuppressive therapy, and low dose aspirin as anticoagulation ther-

apy. In cases with a high titer of APLs, prednisolone was administered from the early stage of pregnancy. The pregnancy had continued in 110 cases after these therapy. The gestational weeks of delivery (GW), the body weight (BW) of infants, as well as major complications, were analyzed in these patients. As control, the pregnancy outcome was analyzed in 243 cases with no complication. **Results** Of 110 cases, the pregnancy had terminated before 37 WG (32-36WG) in 9 cases. And the pregnancy had terminated at term in 101 (91.8%), which was not significantly different compared with that in control (209/243, 86.0%, by Chi-square test). The average WG of delivery in study population and control was  $38W5D \pm 2W4D$  and  $38W4D \pm 2W3D$ , respectively (n.s. by non-paired t-test). The average BW of infants born to the patients in the study population and control was  $2,959 \pm 465\text{g}$  and  $2,904 \pm 583\text{g}$ , respectively (n.s. by non-paired t-test). There was also no significant difference concerning the major complications between two groups. **Conclusion** The outcome of pregnancies, especially the condition of infants who were born to patients after the immunosuppressive and anticoagulation therapy, was not significantly different compared with normal population.

## ISP-24-8

**A case of germline mosaicism detected in infertile man with a 47, XYY karyotype** Kentaro Kai<sup>1</sup>, Atsushi Tanaka<sup>2</sup>, Yuichi Furukawa<sup>1</sup>, Satoshi Eto<sup>1</sup>, Tomoko Oishi<sup>1</sup>, Yoko Aoyagi<sup>1</sup> *Nakatsu Municipal Hospital<sup>1</sup>, St. Mother Hospital<sup>2</sup>*

**Introduction** 47, XYY syndrome occurs in 1 out of 1,000 live male births and is caused by the presence of an extra copy of the Y chromosome in each of a males cells. Most individuals with this syndrome were diagnosed as teenagers, and their appearance, intelligence, sexual development, and fertility are usually normal, but learning disabilities may be present. We report here a 39-year-old man with 47, XYY syndrome who is presenting with infertility. **Case** A 39-year-old Japanese man was seen in our hospital because of infertility. He was 178-cm tall ( $+1.35$  SD), a high-school graduate, and a service-station operator. Multiple semen tests showed oligospermia. His 39-year-old wife had a history of unexplained recurrent pregnancy loss: two spontaneous miscarriages in the first trimester. A fourth round of artificial insemination and a couples karyotype analysis were simultaneously performed in parallel. Subsequently, his wife became pregnant, and his chromosomal karyotype of 47, XYY was discovered. After genetic counseling, he underwent fluorescence in situ hybridization analysis of sperm, which showed no disomy XY and YY based on 500 sperm counts. He was diagnosed as a germline mosaic 47, XYY karyotype, and the couple did not undergo additional prenatal genetic testing. His wife continued to take aspirin alone and gave birth to a girl of 3,032 g at 37 weeks. **Conclusion** The diverse clinical presentations of 47, XYY syndrome and controversial academic findings on infertility in people with this syndrome made the counseling difficult. Accurate diagnosis of this constitutional karyotype is a valuable aid in counseling.

## ISP-25-1

**The Effects of Five-year Hormone Therapy, Alendronate, Tibolone, and Raloxifene on Bone Mineral Densities in Postmenopausal Women (Second Study)** Hoe-Saeng Yang, Mi-Woon Kim *Dongguk University of Korea, Korea*

**Objective** To evaluate the effects of ten-year hormone therapy, tibolone, alendronate and raloxifene on bone mineral density (BMD) in postmenopausal women. **Methods** We studied 348 postmenopausal women who had visited the menopausal clinic of Dongguk university hospital between January 2001 and December 2010. These patients were divided into estrogen therapy



(ET) (n=51), estrogen-progesterone therapy (EPT) (n=84), tibolone (n=70), alendronate (n=82) and raloxifene (n=61) groups. The mean patients age, height, weight and body mass index were 55.28±3.34 (range of 45-67) years, 157±5cm, 60.12±7.22kg and 24.18±6.37, respectively. We evaluated BMD by measuring lumbar spines (L1-4) and femoral neck at baseline, 1, 2, 3, 4 and 5 years after treatment. **Results** The BMD of the femoral neck increased significantly in the alendronate group by 6.6, 7.4, 7.9, 8.3 and 8.5% at 1, 2, 3, 4, and 5 years after treatment initiation, respectively. It increased in the EPT group by 3.4 and 2.5% at 1 and 2 years after, respectively. It increased in the tibolone group by 2.2 and 2.7% at 1 and 2 years after, respectively. It increased by 2.1% in the raloxifene group at 2 years after. The BMD of the lumbar spine increased significantly in the alendronate group by 3.4, 5.7, 5.3, 5.3 and 4.7% at 1, 2, 3, 4, and 5 years after treatment initiation, respectively. It increased by 1.2% in the EPT group at 1 year after. It increased by 1.4% in the raloxifene group at 1 year after. **Conclusion** Thus, these findings suggest that alendronate is most effective in improving the BMD levels. In postmenopausal women, any treatment with hormone therapy, alendronate, tibolone or raloxifene increases bone mineral density in the femoral neck and lumbar spines.

### ISP-25-2

**Polysaccharide isolated from Hyuganatsu orange that suppressed rat osteoclast formation should be an arabinogalactan** Masatoshi Yamaguchi, Hiroko Hata, Hiroshi Sameshima *University of Miyazaki Hospital*

**Objective** Recently, we reported polysaccharide derived from Hyuganatsu orange containing drink suppressed TRACP5b level of postmenopausal women. In this study, we sought to find an information of characteristics of polysaccharide. **Methods** 1) In HPTLC analysis, a few possible peak were identified in high molecular weight area. We collected each peak. Collected suppression activity for rat osteoclast formation was measured in each fraction. 2) Optical density of IR and UV area were measured with spectrophotometer. 3) Nuclear resonance spectrum was analyzed 4) Sugar structure was analyzed with methylation analysis method. **Results** 1) Suppression activity of osteoclast formation was identified in single peak. Therefore, this peak was analyzed. 2) There was no peak in UV spectrophotometry, suggesting this peak did not contains polyphenol. IR spectrophotometry indicated this peak contains polysaccharide. 3) NMR spectrum suggested polysaccharide. 4) With methylation analysis, 6 type of methylated sugar (1,3,5-tri-O-acetyl-2,4,6-tri-O-methylhexitol, 1,3,4-tri-O-acetyl-2,5-di-O-methylpentitol, 1,4,5-tri-O-acetyl-2,3-di-O-methylpentitol, 2,3,6-tri-O-methyl-D-galactopyranose, 2,3,6-tri-O-methyl-D-galactopyranose and 1,3,4,6-tetra-O-acetyl-2,4-di-O-methylhexitol) were identified. methylation analysis suggested that >-3-Gal-(1->chain is main structure. And ->3)-Ara(-1-> or ->5)-Ara-1-> side chain is divided from 6 position. Therefore, we concluded that this polysaccharide is arabinogalactan. **Conclusion** Polysaccharide isolated from Hyuganatsu orange that suppressed rat osteoclast formation should be an arabinogalactan.

### ISP-25-3

**The relation of remaining ovaries and risk of osteopenia : a retrospective study in patients with ovarian endometrioma** Nana Akino, Osamu Hiraike, Hiromi Terao, Harunori Honjoh, Mana Hirano, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Kaori Koga, Tomoyuki Fujii, Yutaka Osuga *The University of Tokyo*

**Objective** Endometriosis is a common disease in reproductive aged female. Treatment of ovarian endometrioma can be a matter of concern since concomitant with ovarian suppression ther-

apy, salpingo-oophorectomy or ovarian cystectomy is commonly performed, but ovarian surgery results in a decreased ovarian reserve. Beneficial effects of the ovary to prevent osteopenia are known but the relation with remaining ovaries and risk of osteopenia remains unclear. **Methods** Under the approval of IRB and patient's consent, patients in their 40s attending our department with present or history of endometrioma were retrospectively reviewed. Demographic data and blood-sampling tests were recorded, and the relation with bone mineral density (BMD) was analyzed. **Results** In this study, 173 patients aged 40-53 were enrolled and 137 had a history of ovarian surgery. Among them, 6 patients (3.5%) had Young Adult Mean (YAM) levels lower than 80%, and 78 patients with 2 remaining ovaries and 54 patients with 1 remaining ovary were selected in this study. Although BMD between 2 groups showed no significant difference, the former exhibited higher levels of AMH, E<sub>2</sub> and FSH, and decreased level of TRACP-5b and BAP. **Conclusion** Our results indicate that preserving both ovaries leads to higher ovarian reserve, thus it could result in lowering the risks of osteoporosis in the future, and changes over the years should be required.

### ISP-25-4

**A study to evaluate the impact of surgical menopause on bone metabolism in women below 50 years of age** Kanae Matsuno, Kazu Ueda, Chihiro Goto, Yoko Nagayoshi, Ayako Kawabata, Asuka Morikawa, Kazuaki Takahashi, Satoshi Yanagida, Nozomu Yanaihara, Kyosuke Yamada, Naoki Kamiya, Aikou Okamoto *The Jikei University Hospital*

**Objective** Oophorectomy is often required for premenopausal women to treat gynecological cancer. Increased bone resorption is an adverse sequela that increases the patient's risk for fracture. In this study, we assessed the risk of acquiring osteopenia or osteoporosis after surgical menopause in 27 women who had oophorectomies performed at our hospital. **Methods** We measured bone mineral density (BMD) and bone metabolic markers (BAP, TRACP-5b) in 27 women treated for gynecologic cancer by oophorectomy in the last decade. For 8 patients who we identified to have osteopenia, we received informed consent, began treatment, and followed their response. **Results** The median investigation period was 17 months (range : 2-115 month) and the median age at the time of operation was 39 years (range : 28-47 years). We identified 8 patients (30%) to have osteopenia and 1 (3%) to have osteoporosis by BMD. There was a significant increase in the median time since oophorectomy between patients with a disorder of bone metabolism and those without, 54 months and 12 months respectively (p =0.045). There was a trend for TRACP-5b levels to increase with time. BMD levels increased and TRACP-5b levels decreased in all 8 cases of osteopenia after treatment with a bone resorption inhibitor. **Conclusion** Our data suggests the risk of developing a disorder of bone metabolism increases over time in patients with surgical menopause. Additionally, early administration of a bone resorption inhibitor may partially restore normal BMD and bone markers in high risk osteopenic patients.

### ISP-25-5

**Investigation of long-term use of bisphosphonate** Emi Motegi, Yoshiko Mochizuki, Wakana Soeda, Ichio Fukasawa *Dokkyo Medical University*

**Objective** Bisphosphonates are drugs for osteoporosis with high fracture prevention effect and widely used. But bisphosphonates have adverse effects of osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). Therefore, recently it has been proposed to consider the setting of the optimum use period and the drug holiday period. However, in the treatment of osteo-

porosis, there is no clear criteria to stop the drug. We investigated retrospectively for osteoporotic patients using long-term bisphosphonates. **Methods** We investigated retrospectively the changes in bone mineral density (BMD), fluctuation of bone turnover markers, and side effects about the patients using bisphosphonates for over 5 years. **Results** There were 20 cases of bisphosphonates taken over 5 years, 11.3% of patients treated with osteoporosis. Their average age was 68.4 years old, the average use period was 9.6 years. One case showed a history of fracture at the beginning of therapy. There were no cases of new fractures, ONJ and AFF during the management period. The mean lumbar spine BMD increase rate for 5 years after taking the bisphosphonates was 5.8%. In the latest BMD there were 15 patients with T score < -2.5. Bone resorption markers remained within the normal range in long-term users. **Conclusion** The majority of patients using bisphosphonates for a long time had significantly reduced BMD. It is necessary to determine the drug holiday, or the continuation by reference to the value of bone turnover markers and FRAX in patients with osteopenia.

### ISP-25-6

**Undernourishment in utero programs CIDEA & CIDEc genes expression and deteriorates hepatic steatosis : Role of endoplasmic reticulum (ER) stress** Jeenat Urmi, Keiko Muramatsu, Yukiko Kohmura, Hiroaki Itoh, Naohiro Kanayama *Hamamatsu University School of Medicine*

**Objective** Undernourishment in utero deteriorates hepatosteatosis (HS) in later life. Cell Death-Inducing DFFA Like-Effector-A and C (CIDEA and CIDEc) are present in the membrane of endoplasmic reticulum (ER) and enhance lipid droplet (LD) growth deteriorating HS. We investigated the effect of undernourishment in utero on hepatic LD size, and the gene expression of CIDEA/C genes by using mice animal model. **Methods** Sampling of blood and liver of CN57Bl mice (n=16) aged 22 weeks, pups (NN ; n=8) obtained from dams with *ad libitum* and pups (UN ; n=8) from dams with 40% caloric-restriction. Pups were fed high fat diet throughout 17 to 22 weeks with vehicle (Veh) or Tauroursodeoxycholic acid (TUDCA, ER-stress alleviator). Oil Red O staining was used to assess diameter ( $\mu\text{m}$ ) and area ( $\mu\text{m}^2$ ) of the hepatic LD and mRNA was used for micro-array and quantitative PCR. **Results** UN in utero enlarged LD area by 2.5-fold ( $p < 0.01$ ) compared to NN concomitant with the upregulation of 38 genes (NN vs UN ; Fold change  $> 2$  or  $< -2$ ,  $p < 0.05$ ). CIDEA/C genes were highly expressed (Fold change 11.5 & 5.6,  $p < 0.001$ , respectively) confirmed by quantitative PCR. ER-stress alleviation, by TUDCA administration not only reduced expression of these genes but also reduced the size of LD significantly. **Conclusion** We propose that UN in utero programs hepatic ER stress integration in later life and deteriorates hepatosteatosis (HS) by activation of CIDEA and CIDEc genes expression.

### ISP-25-7

**Metabolomic profiling of prediabetes and diabetes among Japanese postmenopausal women** Miho Iida<sup>1</sup>, Toru Takebayashi<sup>2</sup>, Haruko Kunitomi<sup>1</sup>, Yusuke Matoba<sup>1</sup>, Keiko Watanabe<sup>1</sup>, Hayato Iseki<sup>1</sup>, Asako Sera<sup>1</sup>, Yusuke Kobayashi<sup>1</sup>, Eiichiro Tominaga<sup>1</sup>, Kouji Banno<sup>1</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Department of Preventive Medicine and Public Health, Keio University<sup>2</sup>*

**Objective** Prediabetes (PD) is the precursor condition of type 2 diabetes (T2D), and early identification contributes to the prevention of further diseases. In this study, we performed metabolomics profiling in Japanese postmenopausal women to identify key plasma compounds associated with PD. **Methods** Subjects were 3,273 naturally postmenopausal women who par-

ticipated in a cohort study (n=1,336, normal glucose tolerance (NGT) : n=1,685, PD ; n=252, T2D). Among them, 1,033 subjects visited the three-year follow-up. Each of the 75 metabolites profiled on fasting plasma samples using capillary electrophoresis mass spectrometry was assessed for associations with diabetic status cross-sectionally, and the impact of metabolite concentrations on PD development was assessed using logistic regression analyses. This study was approved by the ethics committee of our institute and written informed consent was obtained from each subject. **Results** A total of 23 plasma metabolites were significantly increased in PD compared with NGT after adjustment for confounders. They included branched-chain amino acids (BCAAs) : valine (200.4 $\mu\text{M}$ , 205.2 $\mu\text{M}$ ,  $p < 0.01$ ), isoleucine (50.8 $\mu\text{M}$ , 52.7 $\mu\text{M}$ ,  $p < 0.01$ ), leucine (102.7 $\mu\text{M}$ , 105.6 $\mu\text{M}$ ,  $p < 0.01$ ) ; and aromatic amino acids (AAAs) : tyrosine (59.4 $\mu\text{M}$ , 60.8 $\mu\text{M}$ ,  $p < 0.01$ ), phenylalanine (51.6 $\mu\text{M}$ , 52.7 $\mu\text{M}$ ,  $p < 0.01$ ). Concentrations of these metabolites were further increased in T2D subjects. Logistic analyses revealed insignificant associations with the prediction of PD. **Conclusion** Metabolites such as BCAAs and AAAs are altered in individuals with PD/T2D among postmenopausal women in Japan.

### ISP-25-8

**The risk of dyslipidemia after a cystectomy or oophorectomy in endometriosis** Mana Hirano, Osamu Hiraike, Nana Akino, Hiromi Terao, Harunori Honjoh, Michihiro Tanikawa, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Kaori Koga, Tomoyuki Fujii, Yutaka Osuga *The University of Tokyo Hospital*

**Objective** Endometriosis causes heavy burden for women, and 10-30% of reproductive aged women suffer from endometriosis. The treatment of ovarian endometrioma consists of surgery and/or hormonal therapy and it often results in a decreased ovarian reserve. Herein we evaluate the risk of dyslipidemia of patients with history of ovarian cystectomy and/or oophorectomy in endometriosis. **Methods** After IRB's approval and informed consents of patients, we reviewed outpatients at over 40 years old with a history of endometriosis without familial history of dyslipidemia. We examined BMI, blood tests (TC, TG, LDL), and CAVI (cardio-ankle vascular index). **Results** In this study, 173 patients aged 40-53 were enrolled. These patients had a history of ovarian surgery, and these participants with data of CAVI were finally selected. Thus we reviewed 91 patients, and 52 patients possess 2 ovaries and 39 patients possess 1 ovary. Although average BMI of 2 groups were comparable, patients with two ovaries showed the lower level of CAVI, TC, LDL, TG than with 1 ovary. In particular, the value of TC (195  $\pm$  33 vs 220  $\pm$  35 mg/dL,  $p = 0.001$ ) and LDL (115  $\pm$  25 vs 132  $\pm$  36 mg/dL,  $p = 0.016$ ) were significantly lower. **Conclusion** Remaining 2 ovaries at surgery is effective in improving lipid metabolism, and it may have beneficial effects to prevent future arteriosclerosis.

### ISP-26-1

**Abdominal palpation with Ou MC manipulation for women with acute abdomen** Ming Cheh Ou<sup>1,2</sup>, Dennis Ou<sup>3</sup>, Chung Chu Pang<sup>1</sup> *Taipei City Hospital, Taiwan<sup>1</sup>, Taipei Medical University, Taiwan<sup>2</sup>, Oxford University, Taiwan<sup>3</sup>, Su Women Hospital, Taiwan<sup>4</sup>*

**Objective** Abdominal palpation with Ou MC manipulation (APOM ; AJEM, 2012) has showed to be more sensitive than bimanual pelvic examination for the diagnosis of pelvic inflammatory disease in women with acute abdomen. This study demonstrated APOM with Ou MC descending phenomenon (OuDP ; Cancer Res, 2016) for diagnostic reliability for women with acute abdomen causing muscle guarding or diffuse pain. **Methods** 113 women with acute abdomen attending an emergency



department received AP and APOM. Of the 113 women, 91 had pelvic organ disease, whereas 21 had nonpelvic organ disease and 1 had pelvic and nonpelvic organ disease concurrently. **Results** Excluding the case with concurrent pelvic and nonpelvic organ disease, the sensitivity of APOM for the diagnosis of pelvic organ disease was significantly greater than that of AP ( $P = .003$ ). APOM also showed greater specificity of excluding pelvic organ disease than did AP ( $P = .003$ ). APOM with OuDP performed for 37.2% of patients with muscle guarding or diffuse pain demonstrated diseased organ location compatible with final diagnosis showed. **Conclusion** The delimitation by APOM as a separation zone may allow positional recognition of the tenderness with decreased overlap of signs. In cases with muscle guarding or diffuse pain, APOM effectively located tenderness with OuDP induced with contralateral hand of the examiner by pressing the hand in a chopping gesture along a line from the subumbilicus to the femoral arterial canal of the inguinal area to induce a zone of alleviated pain under the hand.

### ISP-26-2

**Inhibitory Effects of *Lactobacillus* Culture Supernatants on *Candida albicans*** Yuko Matsuda<sup>1</sup>, Daiki Ogishima<sup>1</sup>, Satoru Takeda<sup>2</sup> *Juntendo University Nerima Hospital<sup>1</sup>, Juntendo University<sup>2</sup>*

**Objective** Vulvovaginal candidiasis (VVC) is an infection of the vaginal mucous membrane caused by *Candida albicans*. *C. albicans* exists as a yeast and/or in hyphal form, and forms a biofilm on the vaginal mucosa. The healthy vaginal microbiome comprises predominantly *Lactobacillus*, the presence of which inhibits pathogen invasion. In this study, we assessed the mechanisms underlying the inhibitory effects of *Lactobacillus* culture supernatants on *C. albicans* bud-to-hyphal form transition (BHT), biofilm formation, and adhesion to HeLa cells. **Methods** *C. albicans* cells were cultured with *L. gasseri* or *L. crispatus* supernatants under BHT- and biofilm formation-inducing conditions. Inhibitory effects on biofilm formation were determined by 2,3-bis (2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenyl-amino) carbonyl]-2H-tetrazolium hydroxide (XTT) reduction assay. The expression levels of BHT- and biofilm formation-associated genes were determined by RT-qPCR. Inhibition of *C. albicans* adhesion to HeLa cells by the supernatants was evaluated by enumerating viable *C. albicans* cells. **Results** *Lactobacillus* supernatants inhibited *C. albicans* hyphae and biofilm formation. The expression of BHT- and biofilm formation-associated genes was downregulated, and *C. albicans* adhesion to HeLa cells was inhibited, in the presence of *Lactobacillus* supernatants. **Conclusion** Culture supernatants of *L. gasseri* and *L. crispatus*, commonly found in the vaginas of healthy Japanese women, inhibit *C. albicans* biofilm formation by downregulating biofilm formation-related genes and *C. albicans* adhesion to HeLa cells. These findings support the notion that *Lactobacillus* metabolites may be useful alternatives to antifungal drugs for the management of VVC.

### ISP-26-3

**Successful treatment of *Candida glabrata* after infectious abortion and maternal fungemia resulting in the next normal pregnancy** Megumi Oh, Takahiro Yamashita, Haruka Mitsui, Eiji Shuri, Nobuko Akamata, Nagisa Yasumizu, Shinichiro Yabe, Yukiko Kawana, Yoshiharu Takeda, Tomoko Adachi, Takashi Okai, Masao Nakabayashi *Aiiku Hospital*

The case was 37 years old, G0P0. She conceived with intrauterine insemination (IUI), but the pregnancy ended in infectious abortion in 19 weeks gestation. *Candida glabrata* was detected on the surface of the placenta and in her blood. Following the JSMM Clinical Practice Guidelines for Diagnosis and Treatment

of Invasive Candidiasis 2013, four days of Fosfluconazole 400 mg/day were administered intravenously, followed by 14 days of Micafungin 50mg/day intravenously. Five months later, she conceived again with IUI. The culture of the vaginal discharge was performed at 7 weeks of pregnancy, followed by once a month of the culture. *Candida* species were not detected in all the examinations. A uterine cervical polyp causing bleeding was resected on 26 weeks of pregnancy. No other abnormal episodes were observed during pregnancy. Under epidural anesthesia, she delivered a female baby by vacuum extraction because of non-reassuring fetal status on 39 weeks 1 days of pregnancy. The birth weight was 2,504g and Apgar score was 9 (1 min) and 10 (5 min). Both the mother and the newborn were healthy and discharged from our hospital five days after the delivery. It should be thought that the treatment for *Candida glabrata* with Fosfluconazole and Micafungin was effective even after a serious infectious abortion and maternal fungemia.

### ISP-26-4

**Abdominal tuberculosis a major cause of infertility in developing countries** Sanjay Chaube, Mahendra Bhusari, Jyoti Chaube *St. Jude's Hospital, India*

Infertility a major social and psychological problem for women. Tuberculosis is a major health problem in developing countries due to poor socioeconomic status. The scenario of root cause is variable. A study of 128 patients of infertility over a period of seven years revealed pelvic tuberculosis leading to tubal block a major cause of infertility in the patients in developing country.

### ISP-26-5

**A case report of pelvic inflammatory disease due to *Streptococcus pneumoniae*** Miho Ando, Tatsuya Fukami, Sakiko Matsuoka, Sumie Nakamura, Takahiro Koyanagi, Yoko To, Maki Goto, Haruhiko Kondo, Hiroshi Tsujioka, Fuyuki Eguchi *Aso Iizuka Hospital*

*Streptococcus pneumoniae* is one of the normal bacterial floras of the upper respiratory tract. Peritonitis occurred by *streptococcus pneumoniae* is uncommon disease defined as the infection in the abdominal cavity despite the absence of an obvious source of infection. The occurrence of it in young healthy women is very rare. It occurs mostly in patients with portal hypertension such as liver cirrhosis and those with nephrotic syndrome and HIV infection. We experienced a case of 48-year-old woman with Tubo-Ovarian abscess. Although she had no particular history but hypertension and hyperlipidemia, it proved to be caused by *streptococcus pneumoniae*. The specimen was cultured inside blood, which means it was an invasive pneumococcal disease (IPD) so we made a report to the local health center. We started treating with a broad antibacterial drugs and the inflammatory reaction improved in two weeks of hospitalization. Peritonitis and pelvic inflammatory disease in adults are rare phenotype of symptoms for *streptococcus pneumoniae* related disease. *Streptococcus pneumoniae* represents a common pathogen associated with high morbidity and mortality around the world. There are only few studies about this infection and it is poorly understood. We suggest that everyone should take into consideration of pelvic inflammatory disease caused by *streptococcus pneumoniae* when we perform medical examinations. We will show the case with the review of the literature.

### ISP-26-6

**Human CD134 (OX40) expressed on T cells plays a key role for human herpesvirus 6B replication after umbilical cord blood transplantation** Satoshi Nagamata<sup>1</sup>, Yasuko Mori<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University<sup>1</sup>, Division of Clinical Virology, Kobe University Graduate School of Medicine<sup>2</sup>*

**Objective** CD134 (OX40), which is a cellular receptor for human herpesvirus-6B (HHV-6B) and expresses on activated T cells, may play a key role for HHV-6B replication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Several studies have shown that umbilical cord blood transplantation (UCBT) is a strong risk factor for HHV-6B reactivation and encephalitis. **Methods** We measured the percentage of CD134-positive cells within T cells and viral copy number of HHV-6B after allo-HSCT, including UCBT. The correlation between CD134 and HHV-6B viral load was then statistically analyzed. **Results** Twenty-three patients after allo-HSCT were enrolled. HHV-6B reactivation occurred in 11 of 23 patients (47.8%). CD134 expression was seen on T cells and was coincident with the time of peak viral load. The percentage of CD134-positive cells decreased significantly when HHV-6B DNA disappeared ( $p=0.005$  in CD4<sup>+</sup> T cells,  $p=0.02$  in CD8<sup>+</sup> T cells). In the patients after UCBT, the HHV-6B viral load varied with the percentage of CD134-positive cells. In the comparison between the HHV-6B reactivation group and non-reactivation group, maximum percentages of CD134-positive cells among CD4<sup>+</sup> T cells in reactivation group were significantly higher than those in non-reactivation group ( $p=0.04$ ). **Conclusion** This is the first study to show that a correlation of CD134 expression on T cells with HHV-6B replication after allo-HSCT. The results possibly indicate that CD134 on T cells plays a key role for HHV-6B replication after allo-HSCT, especially in UCBT.

## ISP-26-7

**Diagnosis and treatment of the adnexal actinomycosis mimicking an advanced epithelial ovarian cancer** Seok-Mo Kim, U Chul Ju, Woo Dae Kang *Chonnam National University, Korea*  
**Objectives** Adnexal actinomycosis can mimic advanced epithelial ovarian cancer (EOC). Although histopathologic confirmation is required for diagnosis, it is often impossible. **Methods** Among 79 cases suspected to actinomycosis more than EOC in pelvis MRI, 35 cases without histopathologic confirmation were included in this study. We compared those to 108 cases of stage II/III EOC. Patients with actinomycosis were treated with antibiotics for 6 months or more and took imaging every 3 months. **Results** The median age of patients with actinomycosis was 48 years (range, 27-68) and 74.3% were premenopausal. 91.4% had a history of intrauterine device (IUD) during a mean of 8.7 years (range, 3-20). The mean serum WBC, CRP, and CA-125 level were 14,330/mm<sup>3</sup> (range, 4,100-30,100), 9.7 mg/dL (range, 0-27), and 38.0 U/mL (range, 7-135), respectively. In MRI, the mean size of adnexal masses was 6.8 cm (range, 4-12) and all had no or small amount of ascites. Lymph node enlargement (> 0.5cm) and hydronephrosis were presented in 48.6% and 57.1%, respectively. After 6 months, 77.1% showed complete remission and the remaining also showed 3 to 4cm mass. Multivariate analysis revealed that IUD history (OR=15.055; 95% CI, 4.690-48.330;  $p<0.001$ ), WBC>10,800/mm<sup>3</sup> (6.566; 2.774-15.539;  $p<0.001$ ), CA-125<105 U/mL (19.171; 7.535-83.182;  $p<0.001$ ), size<10 cm (7.867; 1.080-57.294;  $p<0.001$ ), presence of hydronephrosis (5.182; 1.807-14.861;  $p=0.008$ ), and no or small amount of ascites (7.135; 1.681-30.291;  $p=0.002$ ) were predictive factors of adnexal actinomycosis compared to EOC. **Conclusion** If patients with adnexal actinomycosis mimicking EOC in MRI have IUD history, serum WBC beyond normal range, serum CA-125 within 3 times normal range, mass<10 cm, hydronephrosis, and no or small amount of ascites, antibiotics can be a proper treatment without surgical intervention.

## ISP-27-1

**Systemic and local status of myeloid-derived suppressor cells (MDSC) in endometriosis patients** Erina Satake, Kaori Koga,

Arisa Takeuchi, Tomoko Makabe, Ayumi Taguchi, Gentaro Izumi, Masashi Takamura, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Myeloid-derived suppressor cells (MDSC) are recently identified heterogeneous population of immature myeloid cells. They suppress both innate and adaptive immunity, thereby enhance various pathological settings such as inflammation and cancer. The main subsets of MDSC are mononuclear-MDSC (M-MDSC) and polymorphonuclear-MDSC (PMN-MDSC). In endometriosis, it has been previously shown that the depletion of PMN-MDSC in the mouse model reduced the number of lesions; however, the status of MDSC in endometriosis patients is not known. To determine the systemic and local status of MDSC in endometriosis patients, we conducted following studies. **Methods** Under IRB approval and informed consents, peripheral blood mononuclear cells (PBMC) and peritoneal fluid MC (PFMC) were collected from the control (n=13) and endometriosis patients (n=13), and the numbers of M-MDSC (CD33<sup>+</sup>, HLA-DR<sup>-low</sup>, CD14<sup>+</sup>, CD15<sup>-</sup>) and PMN-MDSC (CD33<sup>+</sup>, HLA-DR<sup>-low</sup>, CD14<sup>+</sup>, CD15<sup>+</sup>) were counted by flow cytometry. The percentages of M-MDSC, PMN-MDSC and total MDSC were compared between the groups. **Results** In PBMC, percentages of PMN-MDSC and total MDSC were significantly higher in endometriosis group (3.0% vs 7.9%, 9.9% vs 15.4%, the control vs endometriosis group, PMN-MDSC, total MDSC, respectively,  $p<0.05$ ), while the percentage of M-MDSC was not different between groups (7.0% vs 7.5%). In PFMC, the percentages of neither M-MDSC nor PMN-MDSC were different between groups. **Conclusion** Our study found that MDSC, especially PMN-MDSC were enhanced systemically in endometriosis patients. Together with our previous findings, PMN-MDSC may contribute to the pathogenesis of endometriosis, although further studies are warranted.

## ISP-27-2

**SR-16234, a novel selective estrogen receptor modulator, for pain symptoms with endometriosis: an open-label clinical trial** Tasuku Harada<sup>1</sup>, Ikuko Ota<sup>2</sup>, Fuminori Taniguchi<sup>1</sup> *Tottori University<sup>1</sup>, Kurashiki Heisei Hospital<sup>2</sup>*

**Objective** SR-16234 is a selective estrogen receptor modulator (SERM) structurally different from approved SERM and has reported to have estrogen receptor (ER)  $\alpha$  antagonistic activity and strong affinity with a weak partial agonistic activity to ER $\beta$ . SR-16234 showed strong inhibitory effects on transplanted endometrial cysts in endometriosis model of rat and mouse. In this clinical trial, efficacy and safety of SR-16234 have been evaluated in endometriosis patients. **Methods** This trial was an open-label single arm clinical trial. Ten patients with dysmenorrhea and pelvic pain associated with endometriosis and adenomyosis were enrolled in this trial with written informed consent, and received 40 mg of SR-16234 once a daily for 12 weeks. The primary endpoint was the visual analogue scale (VAS) of pelvic pain. The secondary endpoints included dysmenorrhea score, pelvic pain score, objective observations (stiffness of Douglas pouch, limitation of uterine movement, size of ovarian chocolate cysts, thickness of endometrium, and serum CA125 concentration) and safety. **Results** After oral administration of SR-16234 40 mg for 12 weeks, there were statistically significant decreases in pelvic pain VAS, total pelvic pain score, total dysmenorrhea score, stiffness of Douglas pouch, limitation of uterine movement comparing with the baseline values. **Conclusion** The present trial suggested that a selective estrogen receptor modulator could be used for treatment of pain associated with endometriosis for the first time.

## ISP-27-3

**Expression pattern of membrane proteins in endometrial stromal cells from women with endometriosis** Saya Yamashita<sup>1</sup>, Kae Hashimoto<sup>1</sup>, Akihiko Yoshimura<sup>1</sup>, Ikuko Sawada<sup>2</sup>, Yuri Matsumoto<sup>1</sup>, Michiko Kodama<sup>1</sup>, Seiji Mabuchi<sup>1</sup>, Kenjiro Sawada<sup>1</sup>, Tadashi Kimura<sup>1</sup> *Osaka University<sup>1</sup>, Itami City Hospital<sup>2</sup>*

**Objective** Endometriosis affects women during their reproductive years, and can impact all aspects of their lives. The transplantation of an endometrial fragment during menstruation to ectopic sites is probably the most widely accepted mechanism for endometriosis. However, how endometrial cells, although they are not cancer cells, can adhere to the peritoneal surface and invade the underlying tissues is not fully understood. In the current study, we have focused on the membrane proteins of endometrial stromal cells and investigated their role in the pathogenesis of endometriosis. **Methods** The eutopic endometrial stromal cells were collected from patients undergoing hysterectomy for endometriosis and for other benign reasons. The expression patterns of membrane proteins were compared, using iTRAQ. We identified the protein whose expression was higher in the eutopic endometrium of women with endometriosis than those without endometriosis. We also performed protein analysis by immunohistochemistry and western blotting. **Results** By iTRAQ comparison, the eutopic endometrium from patients with endometriosis showed stronger expression of several molecules including galectin-3. Immunohistochemical analysis revealed immunoreactive score according to Remmele was  $6.4 \pm 1.6$  and  $2.6 \pm 1.4$  respectively. Western blotting also showed a significantly higher expression of galectin-3 in the cells from endometriosis patients. **Conclusion** Expression of galectin-3 increased significantly in the eutopic endometrium of women with endometriosis. We are trying to demonstrate the function of galectin-3 to the endometrial stromal cell adhesion, as well as migration and proliferation.

## ISP-27-4

**CXCL12-CXCR4 axis is enhanced in endometriosis via prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)** Tomoko Makabe, Kaori Koga, Erina Satake, Arisa Takeuchi, Ayumi Taguchi, Fusako Sue, Mariko Miyashita, Gentaro Izumi, Masashi Takamura, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Chemokine CXCL12 and its receptor CXCR4 are known to play a role in cancer progression, both by activating cancer cells and inducing immunosuppressive cells. We hypothesized that CXCL12-CXCR4 axis is also enhanced in endometriosis, and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is involved in the enhancement. **Methods** Under informed consents, peritoneal fluids (PF) were collected from the control and endometriosis patients. 1) Concentrations of CXCL12 in PF were measured using ELISA (18 control, 31 endometriosis). 2) Peritoneal macrophages (PM) were isolated using CD14 MACS selection. mRNA was extracted and expressions of CXCR4 and PGE<sub>2</sub> receptors (EP2, EP4) were measured using qRT-PCR (11 control, 6 endometriosis). 3) PM were stimulated with PGE<sub>2</sub> (100 nM) in the absence or presence of EP2 antagonist (PF-0418948, 100 nM) or EP4 antagonist (CL-042794, 100 nM) for 24h, and CXCR4 mRNA expression was measured. **Results** 1) Concentration of CXCL12 in PF was significantly higher in endometriosis ( $p < 0.05$ ). 2) mRNA expressions of CXCR4 and EP2 in PM were significantly higher in endometriosis ( $p < 0.05$ ), whereas mRNA expression of EP4 was slightly but not significantly higher in endometriosis. 3) PGE<sub>2</sub> significantly increased CXCR4 mRNA expression in PM ( $15.0 \pm 3.0$  fold,  $p < 0.01$ ). Both EP2 and EP4 antagonist decreased PGE<sub>2</sub>-induced CXCR4 expression to  $87.7 \pm 15.4\%$  ( $p < 0.05$ ) and  $65.2 \pm 15.3\%$  ( $p < 0.01$ ), respectively. **Conclusion** CXCL12-CXCR4

axis is enhanced in the peritoneal cavity of endometriosis, and PGE<sub>2</sub> seems to be involved in this enhancement. Therefore, PGE<sub>2</sub> can be therapeutic targets for endometriosis.

## ISP-27-5

**Bradykinin system is involved in endometriosis-related pain through endothelin-1 production** Osamu Yoshino<sup>1</sup>, Mutsumi Kobayashi<sup>1</sup>, Yosuke Ono<sup>1</sup>, Akihisa Nakashima<sup>1</sup>, Akiko Hasegawa<sup>2</sup>, Yutaka Osuga<sup>2</sup>, Shigeru Saito<sup>1</sup> *University of Toyama<sup>1</sup>, The University of Tokyo<sup>2</sup>*

**Objective** The mechanism of pain production in endometriosis remains unknown. Bradykinin (BK), one of the most algogenic substances, is also known as an inflammatory mediator. In the present study, we evaluated whether BK is involved in endometriosis-related pain. **Methods** Endometriotic lesions were used for immunohistochemistry. Primary cultures of endometriotic stromal cells (ESC) were stimulated with IL-1 $\beta$  and/or BK. Quantitative-PCR was used to evaluate the mRNA expressions of BK receptors (BKR) and endothelin-1, which causes neuropathic pain. The concentration of endothelin-1 in cystic fluid of endometrioma or non-endometrioma was measured with ELISA. The conditioned medium of ESC stimulated with IL-1 $\beta$  and/or BK was injected intraplantarly in mice, and evaluated whether pain-related licking behavior was elicited. **Results** The expressions of BK and BKR in endometriotic lesions were observed by immunohistochemistry. In vitro experiments showed that IL-1 $\beta$  induced  $4 \pm 0.2$ -fold increase of BKR mRNA on ESC ( $P < 0.01$ ). Activation of these receptors by BK significantly induced endothelin-1 expression in ESC, which was negated completely by HOE-140, a BKR antagonist. The cystic fluid of endometrioma contained higher amount of endothelin-1 (median 22 pg/ml, range 0-324 pg/ml) compared to non-endometrioma (0 pg/ml, range 0-10 pg/ml) significantly ( $P < 0.01$ ). Intraplantar injection of the conditioned medium of ESC treated with IL-1 $\beta$  and BK significantly induced licking behavior, which was suppressed with BQ-123, an endothelin receptor antagonist. **Conclusion** The present study demonstrated the presence and the function of the BK axis in endometriosis, and established potential new therapy targets for endometriosis-related pain.

## ISP-27-6

**Dienogest improves decreased chemotaxis of peritoneal natural killer cells from women with endometriosis** Chiaki Izumiya<sup>1</sup>, Shimpei Yamamoto<sup>1</sup>, Takashi Ushiwaka<sup>1</sup>, Tamami Tsuzuki<sup>1</sup>, Kayo Taniguchi<sup>1</sup>, Masanori Nakakuki<sup>2</sup>, Nagamasa Maeda<sup>1</sup> *Kochi Medical School<sup>1</sup>, MOCHIDA PHARMACEUTICAL CO., LTD.<sup>2</sup>*

**Objective** The immunologic suppression is considered as one of the pathogenesis of endometriosis. We have been investigated the behavior of peritoneal natural killer (NK) cells from women with endometriosis by time-lapse imaging system. According to the previous investigation, in women with endometriosis, peritoneal NK cells function was decreased compared to without endometriosis. In this paper, we investigated the immunological effects of Dienogest (DNG), an oral anti-endometriosis progestin, on chemotaxis of peritoneal NK cells in women with endometriosis. **Methods** The effects of DNG on PF cells from women with endometriosis were compared to without endometriosis (control). We investigated cell movement speed and also pseudo-pod formation of peritoneal NK cells by time-lapse imaging under microscope incubator. The cell movement speeds were measured twice before and after administration of DNG ( $10^7$  mol/L). **Results** The cell movement speed and frequency of pseudo-pod formation of NK cells from women with endometriosis was significantly decreased compared to control. There was significantly positive correlation between cell move-

ment speeds and frequency of pseudo-pod formation of NK cells. The cell movement speeds of both macrophages and lymphocytes were not significantly difference between with and without endometriosis. After DNG administration, the cell movement speeds of only peritoneal NK cells from women with endometriosis were increased to the same level as in controls. **Conclusion** DNG may improve the cell movement speed of NK cells in women with endometriosis ; suggesting that DNG may improve the chemotaxis of NK cells and also improve the immunological peritoneal environment in women with endometriosis.

## ISP-28-1

**Epidemiology and Recent Treatment of Leiomyomas in Korean Women** Hyejin Hwang<sup>1</sup>, Minkyung Lee<sup>1</sup>, Hyunkyung Kim<sup>1</sup>, Younhee Chung<sup>1</sup>, Soohyun Sim<sup>1</sup>, Youngsin Han<sup>1</sup>, Kyunghee Chae<sup>2</sup>, Mira Kim<sup>2</sup>, Sukil Kim<sup>2</sup>, Meeran Kim<sup>1</sup> *The Catholic University of Korea, Korea<sup>1</sup>, Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Korea<sup>2</sup>*

**Objective** The purpose of this study is to investigate epidemiology of uterine leiomyoma in general population. **Methods** Korean National Health Insurance Service (KNHIS) sample cohort dataset which were collected during 2002–2013. Patients with uterine leiomyoma were identified by ICD–10 and intervention codes for the Korean health insurance. **Results** A total of 50,884 women aged 15–54 were selected from the KNHIS cohort database, which included approximately 1 million individuals. The incidence had increased all over the age. The age group 45–49 showed highest incidence for the years. In 2012, the incidence of age group 45–49 was 2.97%. The total number of surgical treatment and intervention was increased from 561 in 2002 to 1,137 in 2011. The treatment percentage of all diagnosed patient was decreased (28.51% in 2002 to 13.81% in 2013). Only the treatment percentage of 20–24 age group was increased (5.00% in 2002 to 7.10% in 2013). Of all treatment, the proportion of myomectomy was increased 2.22 fold (22% in 2002 to 49% in 2013) while the proportion of hysterectomy was decreased 0.57 fold (78% in 2002 to 45% in 2013) constantly. **Conclusion** This study showed a significant trend towards an increase in diagnosis for uterine leiomyoma in Korean women with time. Particularly, we found that the trend of surgical treatment moved to fertility preservation among Korean women. This study has meaningful in regard of general population based epidemiology study in asian women.

## ISP-28-2

**Disturbed WNT/ $\beta$ -catenin Signaling under Serum Starvation and Hypoxia Induces Adipocytic Transdifferentiation in Human Uterine Leiomyoma Cells** Hiroshi Harada, Taeko Ueda, Tomoko Kurita, Seiji Kagami, Toshinori Kawagoe, Yusuke Matsuura, Toru Hachisuga *University of Occupational and Environmental Health*

**Objective** Fatty metamorphosis is known as an uncommon alteration in uterine leiomyoma (i.e. lipoleiomyoma), the pathogenic mechanisms underlying this phenomenon remain poorly understood. Because a conditional deletion of  $\beta$ -catenin, a major transducer of the canonical Wingless/integrated (WNT) pathway, in the developing mouse uterus can induce adipogenesis in the myometrium, it is hypothesized that disrupted WNT/ $\beta$ -catenin signaling may be also involved in the development of fat cells within uterine leiomyoma. Our goal was to induce the adipocytic transdifferentiation in human leiomyoma cells by the inhibition of the WNT/ $\beta$ -catenin signaling. **Methods** Tumor samples were obtained from seven individuals at the time of surgery for uterine leiomyoma (range, 33 to 49 years). We treated cultured leiomyoma cells with a potent tankyrase inhibitor (XAV939) that can antagonize  $\beta$ -catenin by stimulating its degradation, in a serum-starved and hypoxic culture condition

without additional adipogenesis-inducing agents or supplements. After two weeks treatment, intracytoplasmic lipid droplets were detectable in cultured human leiomyoma cells, and showed increasing accumulation in a time-dependent manner. **Results** Using real-time reverse transcriptional PCR assays, the marker genes of differentiated fat cells such as ADIPOQ and PLIN were highly expressed in leiomyoma cells that were treated with XAV939 under hypoxia and serum starvation, whereas the immunohistochemical expression of desmin was down-regulated, which is in line with the switch in differentiation. **Conclusion** Our study demonstrates that the disturbance of canonical WNT/ $\beta$ -catenin signaling under the stress due to hypoxia and serum starvation can initiate adipocytic transdifferentiation or metaplasia in human uterine leiomyoma cells.

## ISP-28-3

**Diffuse type adenomyosis is associated with the high incidence of pregnancy complications** Ayako Hashimoto<sup>1</sup>, Takayuki Iriyama<sup>1</sup>, Rieko Shitara<sup>1</sup>, Hitomi Furuya<sup>1</sup>, Takahiro Seyama<sup>1</sup>, Toshio Nakayama<sup>1</sup>, Akito Miyauchi<sup>2</sup>, Osamu Nishii<sup>3</sup>, Takeshi Nagamatsu<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Japanese Red Cross Medical Center<sup>2</sup>, Teikyo University Hospital, Mizonokuchi<sup>3</sup>*

**Objective** It has been reported that adenomyosis is associated with the increased incidence of obstetrics complications, including hypertensive disorders of pregnancy (HDP), second-trimester miscarriage, placental malposition, and preterm birth. In this study, we aimed to examine the difference in the impact on pregnancy outcomes between adenomyosis subtypes, diffuse and focal types. **Methods** This study was conducted under approval of our facility ethical committee. Ninety-four singleton pregnancy cases complicated with adenomyosis that had been diagnosed by magnetic resonance imaging (MRI) and/or transvaginal ultrasonography (TVS) and were perinatally managed in three hospitals from 2000 to 2016 were included in this study. All cases were retrospectively subcategorized based on the findings of MRI and/or TVS as follows ; focal type : confined lesion which is embedded within the myometrium, diffuse type : extensive lesion reaching throughout the uterine musculature. The incidence of obstetrical complications was examined. **Results** Among a total 94 cases, 49 cases (52%) and 45 cases (48%) were subcategorized as diffuse and focal type respectively. Diffuse type cases were more likely to develop HDP with statistical significance when compared with focal type cases (34.6% vs. 15.5% ;  $p < 0.05$ , OR 2.8, chi-square test). The incidence of other obstetrical complications including second-trimester miscarriage and placental malposition exhibited increased tendency in diffuse type cases. **Conclusion** Among adenomyosis-complicated pregnant women who display increased risk for obstetrical complications, patients with diffuse type adenomyosis require even more careful and intensive perinatal management.

## ISP-28-4

**Hypoxia-induced gene expression profile of uterine leiomyoma under extracellular matrix-free conditions** Hiroshi Ishikawa<sup>1</sup>, Tetsuji Nishiwaki<sup>1</sup>, Makio Shozu<sup>1</sup> *Chiba University<sup>1</sup>, Chiba Aoba Municipal Hospital<sup>2</sup>*

**Objective** Uterine leiomyoma is characterized by large amounts of extracellular matrix (ECM) and broad avascular area, both of which may induce hypoxia in the leiomyoma cells. We recently identified hypoxia-induced hypoxia inducible factor-1  $\alpha$  (HIF-1  $\alpha$ ) expression in uterine leiomyoma cells. To further clarify hypoxic response in these cells, we explored hypoxia-induced gene expression profile of uterine leiomyoma in the absence of ECM, which is possible to modify microenvironment of this tumor. **Methods** IRB at our facility approved all experimen-



tal protocols, and written consents were obtained from participants. We cultured primary leiomyoma and myometrial cells obtained from surgical specimens under hypoxia (1% oxygen) and normoxia for 12 hours (n=3), and then extracted total RNA. We performed exhaustive cDNA microarray analysis using these specimens, and also performed qPCR for the validation of the microarray data using other specimens (n=10). **Results** Pathway analysis and subsequent validation qPCR revealed that hypoxia significantly up-regulated HIF-responsive gene expressions (*LDHA*, *SLC2A1*, *ENO1*, *ENO2*, *HK2*, *PDK1*, and *PFKFB3*) in uterine leiomyoma cells. Gene Ontology analysis revealed that hypoxia significantly up-regulated metabolic and catabolic process of glucose, hexose, and monosaccharide, glycolysis, and glucose binding in these cells. **Conclusion** Hypoxia significantly up-regulated HIF-responsive gene expressions and glycolysis-related biological process in uterine leiomyoma cells under ECM-free conditions. These results may indicate fundamental hypoxic response in uterine leiomyoma.

### ISP-28-5

**The use of the apparent diffusion coefficient (ADC) value for differentiating leiomyosarcoma from leiomyoma variants** Mai Nishimura, Sachiko Matsumoto, Yasuhiro Ohara, Kaoru Minowa, Risa Tsunematsu, Kanako Takimoto, Kazuaki Imai, Yoko Tsuzuki, Hajime Ota, Yoshiyuki Fukushi, Shinichiro Wada, Takafumi Fujino *Teine Keijinkai Hospital*

**Objective** Most of leiomyosarcoma (LMS) and leiomyoma variants (LMV) display high intensity on diffuse weighted imaging of magnetic resonance imaging (MRI), however, differentiating LMS from LMV preoperatively is sometimes difficult. The objective of our study was to investigate the clinical usefulness of the apparent diffusion coefficient (ADC) value for preoperative differentiation between uterine LMS and LMV. **Methods** Thirty-five patients were diagnosed with LMS or LMV pathologically in our hospital from 2013 to 2016. Twenty-eight patients were LMV and 7 patients were LMS. All patients underwent 1.5-T MRI preoperatively. **Results** The mean ADC value of the patients with LMV was  $1.173 \pm 0.231$  ( $\times 10^{-3} \text{mm}^2/\text{s}$ ) and that of the LMS was  $0.880 \pm 0.1222$  ( $\times 10^{-3} \text{mm}^2/\text{s}$ ). The mean ADC value was significantly lower in LMS than LMV ( $p=0.0029$ ). With the exclusion of 3 apparently advanced-stage LMS patients, the highest ADC value of the LMS was 0.829 and the lowest ADC value of the LMV was 0.849. Based on the receiver operation characteristic (ROC) curve analysis, the optimal ADC value for minimizing the false negative rate was 1.092 (sensitivity; 100%, specificity; 53.6%). **Conclusion** Preoperative measurement of the ADC value is useful for differentiating LMS from LMV.

### ISP-29-1

**Three cases of retained products of conception treated with hysteroscopic surgery following uterine artery embolization** Teppei Ichikawa<sup>1</sup>, Yoshinobu Hamada<sup>1</sup>, Kohei Nemoto<sup>1</sup>, Mao Hisamatsu<sup>1</sup>, Nobuhiko Yamashita<sup>1</sup>, Shin Onoto<sup>2</sup>, Atsushi Yamamoto<sup>2</sup>, Akiko Fujii<sup>3</sup>, Manabu Nakata<sup>4</sup>, Kouhei Sugimoto<sup>2</sup>, Shuichi Sakamoto<sup>1</sup>, Satoshi Takakura<sup>1</sup> *Dokkyo Medical University Saitama Medical Center<sup>1</sup>, Dokkyo Medical University Reproduction Center<sup>2</sup>, Department of Pathology, Dokkyo Medical University<sup>3</sup>, Department of Radiology, Dokkyo Medical University<sup>4</sup>*

**Introduction** Retained products of conception (RPOC) are intrauterine tissues that persist after miscarriage or pregnancy termination. Hysteroscopic transcervical resection (TCR) is effective for RPOC. However, in cases of hypervascular RPOC, TCR may cause massive bleeding. We report three cases of hypervascular RPOC treated with TCR following uterine artery

embolization (UAE) for preventing massive bleeding. **Case1** Forty years old woman G1P1 (vaginal delivery1) underwent artificial abortion at 19 weeks of pregnancy. Ultrasonography showed intrauterine mass 45mm size 41 days after that, suggestive of RPOC. Curettage was performed but massive bleeding occurred. Bleeding was controlled with UAE. TCR was performed 2 days after UAE. **Case2** Thirty three years old woman G3P2 (vaginal delivery2, miscarriage1) presented with irregular vaginal bleeding for more 2 months after vaginal delivery at 40 weeks of pregnancy. Ultrasonography and color doppler showed intrauterine mass 17 mm size with hypervascularity, suggestive of hypervascular RPOC. After expectant management, RPOC was unchanged. TCR was performed 1 day after UAE. **Case3** Thirty-one year-old woman G2P1 (vaginal delivery1, miscarriage1) presented with irregular vaginal bleeding for more 3 months after curettage for miscarriage at 7 weeks of pregnancy. Ultrasonography and color doppler showed intrauterine mass 20 mm size with hypervascularity, suggestive of either hypervascular RPOC or trophoblastic diseases. TCR was performed on the day of UAE. In all three cases, RPOC were removed by TCR without massive bleeding and pathologically diagnosed chorionic villi, and postoperative periods were uneventful. **Conclusion** TCR following UAE may be effective in treatment of hypervascular RPOC.

### ISP-29-2

**Laparoscopic Hysterectomy in Large Myoma Uteri by Using Lee-Huang Point** Mayuko Komori, Takehiko Tsuchiya, Eijiro Hayata, Yuko Hayashi, Tomoko Taniguchi, Yusuke Fukuda, Toshimitsu Maemura, Yukiko Katagiri, Masahiko Nakata, Mineto Morita *Toho University Omori Medical Center*

**Objective** The Lee-Huang point was developed as the site for insertion of the primary trocar midway between the xiphoid process and the umbilicus. Its location provided the laparoscopist a central anatomical view compatible with the practice of head-to-foot orientation of laparoscopic surgery. Since then, the application of the Lee-Huang point has expanded to various gynecologic laparoscopic surgeries. To present cases of laparoscopic hysterectomy in large myoma uteri by using Lee-Huang point. **Methods** In five patients with large myoma uteri, Lee-Huang point was used as primary 12mm trocar. Patients were placed in a dorsal lithotomy position. The arms are tucked at the sides and a foam mattress is situated directly under the patient to prevent sliding during steep Trendelenburg. **Results** The average value of amount of bleeding was 370 ml (120-680 ml). The average of surgical time was 161 minutes (138-198 minutes). The average weight of the specimen was 1,125 gram (847-1,468 gram). The postoperative course of all patients was good. Pathology anatomy results were fit with leiomyoma. **Conclusion** Lee-Huang point approach offers wide access to abdominal cavity, proper visual angle and increase work space. Lee-Huang Point was very useful in laparoscopic surgery of patients with large myoma uteri.

### ISP-29-3

**Six ideas to provide accurate histopathological diagnosis for specimens extracted by power morcellation during total laparoscopic hysterectomy** Yoji Hisamatsu, Akiko Ikuta, Takeharu Kido, Naoko Kida, Maiko Kobayashi, Hiromi Murata, Hideharu Kanzaki, Masato Kita, Hidetaka Okada *Kansai Medical University*

Because surgical specimens extracted by power morcellation during total laparoscopic hysterectomy (TLH) are small, anatomical location of uterus is macroscopically indistinct. Histopathological diagnosis of specimens is obtained by power morcellation is difficult to confirm compare with that by total abdomi-

nal hysterectomy or by vaginal manual morcellation. To improve this problem, we take 6 ideas for the perioperative period. Our procedures are as follows : 1. Cytological examination for the cervix and endometrium are performed before operation to eliminate the presence of malignancy. If the result of that is not negative, histopathological examination by cervical biopsy or endometrial curettage is added. 2. The bilateral fallopian tubes are amputated from uterus and are extracted subsequently. 3. The endometrium is curetted. 4. Indigocarmine is injected in the uterine cavity aim to stain endometrium indigoblue. 3 and 4 of procedure will occasionally reveal the unsuspected presence of malignant neoplasm of cervix and endometrium. 5. The cervix is amputated from uterine body in vaginal canal. 6. The uterine body is morcellated by power morcellation in abdominal cavity. The extracted specimens are separated staining indigoblue or not ; former can be considered as the specimens around endometrium, and later can be as the other, including myometrium or uterine serosa. The procedures from 3 to 5 take less than 10 minutes, and the technique is very easy. Even if occult uterus malignant tumor is confirmed after operation, we can prevent the oversight of malignancy. This procedure may be useful for increasing the accuracy of histopathological examination for morcellated specimens.

### ISP-29-4

**Spray type adhesion prevention barrier, how to use and short-term report** Masato Kita, Yusuke Butsuhara, Takuya Yokoe, Takeharu Kido, Hiromi Murata, Tomomi Mizokami, Tomoo Yoshimura, Hidetaka Okada *Kansai Medical University*  
**Objective** From January 2017, spray-type adhesion prevention barrier, developed in Japan became clinically available. **Methods** We used this barrier in total 81 cases, including 55 Laparoscopies and 26 open surgeries. Mean age was 47.5 years old. And average period of postoperative monitoring was 6 months. **Results** Postoperative complications included no intraabdominal infections and no surgical wound dehiscence. One case of subileus occurred but it was ovarian cancer case with peritonitis carcinomatosa, received neoadjuvant chemotherapy and tumor debulking surgery. She was treated with nothing per os and gastric tube for 3days. She fully recovered and no recurrence occurred. We checked postoperative uterine-intestines adhesion of some cases by transvaginal sonography. In these cases, we usually had observed postoperative adhesion if treated by conventional sheet type adhesion preventing materials. But by this barrier, almost all cases had no postoperative adhesion, and ileus or subileus case were decreasing in our institute. **Conclusion** This barrier may compensate for shortcomings, including difficult to apply, easily removed, cannot cover wide area, of previous adhesion prevention agents No remarkable postoperative complication Clinical outcome of postoperative adhesion prevention was satisfactory.

### ISP-29-5

**Utility of continuous sutures by STRATAFIX® for closing vaginal stump in total laparoscopic hysterectomy** Shintaro Yanazume<sup>1</sup>, Shinichi Togami<sup>1</sup>, Mika Fukuda<sup>1</sup>, Masaki Kamio<sup>1</sup>, Noriko Karakida<sup>2</sup>, Shunichiro Ota<sup>2</sup> *Kagoshima University Hospital<sup>1</sup>, Kagoshima Medical Center<sup>2</sup>*  
**Objective** STRATAFIX® (SF) is an antibacterial monofilament absorbable suture which has multiple small anchors on the string surface. We report the application of SF on the closure of vaginal stump in TLH, and compare it to conventional sutures. **Methods** SF suture procedures were as follows. The needle was inserted into the 6 o'clock position of the vaginal wall and exited from the right vaginal cuff to affix its tab at the tail end. Reverse handlings of the needle from vesical side to dorsal side were

performed from the 3 to 9 o'clock position. For duplicated stump closure, backstitching from 9 to 3 o'clock were similarly added. We evaluated the procedure difficulties and complications of SF (n=14), compared with conventional sutures (n=21) from August, 2016. **Results** SF and conventional sutures were enrolled. Characteristics were almost even in each group. The median time of closing vaginal cuff was 12.5 minutes and 14.8 minutes, respectively (p=0.373). Particularly, closure by operators without experience using SF was 6.3 minutes shorter than using conventional sutures. Complications including organ injury, bleeding, wound separation, and pain did not occur in both groups. **Conclusion** SF has the potential benefits of stronger and faster closure than conventional sutures in closing vaginal cuff during TLH. Beginners particularly can obtain benefit from its easier procedure.

### ISP-29-6

**Hand-Assisted In-Bag Morcellation with the Inside Retractor Technique** Yoichi Aoki, Hiroyuki Kanao, Kohei Omatsu, Maki Matoda, Terumi Tanigawa, Tsuyoshi Hisa, Syuhei Okamoto, Takeru Sugihara, Makiko Omi, Nobuhiro Takeshima *Cancer Institute Hospital*  
**Objective** Electromechanical morcellation is familiar to laparoscopic gynecologic surgeons. Several in-bag morcellation techniques were developed, but there is a risk of leakage with the trocar piercing method. We introduced a new technique for safe Hand-Assisted In-Bag Morcellation with the Inside Retractor. **Methods** The method of hand-assisted morcellation has been reported in various literature. However, bag damage caused by slicing the scalpel is considered a problem. Many method introduced use retractors on outside of the bag. However, we introduce a method of installing a retractor inside the bag. This method is highly likely to prevent the bag from being damaged by the scalpel. **Results** Hand assisted in-bag morcellation was performed in 2 patients undergoing laparoscopic myomectomy and in 2 patients undergoing total laparoscopic hysterectomy. Median patient age was 44 years (range : 30-71 years), median BMI was 21.6 (range : 19.8-30.7), Mean operation time was 187.2 min (range, 164-220 min), mean estimated blood loss was 246.2 ml (range, 10-575 ml), mean specimen weight was 217 g (range, 42-546 g). Upon physiological saline testing, no bag leakage was discovered in any case. No postoperative complications were noted during follow-up at the outpatient clinic, and no patient required re-operation. **Conclusion** Preventing specimen leakage from the bag is the most important purpose of our novel technique because bag breakage should be avoided at all costs. Our method may allow the safe collection of specimens with the use of conventional equipment. We plan to accumulate cases in the future and aim to generalize the technique.

### ISP-29-7

**Proper device usage in total laparoscopic hysterectomy : A retrospective analysis in single institute** Kenro Chikazawa, Ken Imai, Yuko Irie, Shigetane Sasaki, Junko Ushijima, Sachiko Netsu, Isao Horiuchi, Tomoyuki Kuwata, Kenjiro Takagi, Ryo Konno *Jichi Medical University Saitama Medical Center*  
**Objective** We retrospectively reviewed the usage of advanced bipolar/ultrasonic scalpel for laparoscopic hysterectomy to identify the most useful device and to understand how to properly use it. **Methods** The medical records of 341 women who underwent total laparoscopic hysterectomy (TLH) at our institute, between October 2014 and November 2016 were retrospectively reviewed. Data on operating times, bleeding, and uterine weight were collected. **Results** Devices used were the Ligasure Blunt tip (Medtronic, Tokyo, Japan), ENSEAL TRIO/G2, (Johnson & Johnson, Tokyo, Japan), HARMONIC ACE/ACE+ (Johnson &



Johnson, Tokyo, Japan), and THUNDERBEAT<sup>®</sup> (OLYMPUS, Tokyo, Japan). Bleeding was similar in each group, but tended to be higher with the HARMONIC. There were no significant differences among the 4 devices regarding the operating time, but the THUNDERBEAT tended towards a shorter operative time. Finally, LIGASURE was associated with significantly heavier uterine weight, which was preselected based on pelvic examination. **Conclusion** This study suggests that LIGASURE is safe devices to use for TLH of large uteri. Moreover, THUNDERBEAT might shorten the operative time in TLH.

### ISP-29-8

**Contained Morcellation for laparoscopic surgery Using a Tissue Isolation Bag (MorSafe)** Atsuko Yamada, Iwaho Kikuchi, Wakako Mouri, Yasuho Yanagihara, Kyoko Oshina, Akari Koizumi, Izumi Suzuki, Takafumi Ujihira, Yuka Yamamoto, Tsuyoshi Ota, Michio Nojima, Koyo Yoshida *Juntendo University Urayasu Hospital*

In April 2014, the FDA released a statement discouraging the use of laparoscopic morcellation during hysterectomy and myomectomy. Morcellation has come fragmentation and intraperitoneal dissemination of leiomyosarcomas, with upstaging of the disease and worsened outcomes. We describe the use of a tissue isolation bag designed for a 2-port morcellation technique. Nine patients underwent in-bag morcellation of myomas with a tissue isolation bag (MorSafe) between November 2016 and August 2017. This technique involved placing the myomas into the isolation bag within the abdomen, exteriorizing the tail end of the bag, insufflating the bag within the peritoneal cavity, and morcellating the myomas under vision. The mean operative time was LM 112.6 minutes (range 64–187 minutes), TLH 173 minutes (range 159–190 minutes). The average specimen weight was 320.5 g (range 70–490 g), the mean time for specimen introduction into the bag was 17.6 minutes (range 10–22 minutes), and mean time for morcellation and bag removal was 15.8 minute (range 5–23 minutes). Our morcellation within a bag performed no bag-related complications. This method of morcellation is safe technique and feasible, reliable, reproducible.

### ISP-29-9

**Examination of the Efficacy of Combination Therapy with DOAC and Fondaparinux in Gynecology Patients with Venous Thromboembolism** Norihito Yoshioka, Noriyuki Yokomichi, Takahiro Akama, Haruka Imai, Yuko Nagasawa, Shiho Kuji, Imari Deura, Tatsuru Ohara, Akiko Tozawa, Junichi Hasegawa, Nao Suzuki *St. Marianna University School of Medicine*

**Objective** In recent years, several researchers have conducted studies on the effectiveness of combination therapy with fondaparinux (FPX) and direct oral anticoagulant (DOAC) for the treatment of venous thromboembolism (VTE). We performed the examination about the utility of the VTE treatment by FPX and DOAC. **Methods** The subjects were divided into three groups according to their treatment period and method. Group A of 39 gynecology patients received heparin treatment for VTE between February 2009 and December 2011, and initiated warfarin from day four. Group B of 64 patients received FPX 7.5 mg/day for seven days between January 2012 and March 2016, and initiated warfarin from day four. Group C of 25 patients received FPX 7.5 mg/day for four days between April 2016 and July 2017, and started oral DOAC treatment. We conducted D-dimer tests on the day of discovery, day three, and day seven to compare the changes in values. **Results** The D-dimer values of day three reduced from the day of discovery are significantly different between groups A and B and between groups A and C. The D-dimer values of day seven reduced from day three are significantly different between groups A and C. In addition, the

D-dimer values of day seven reduced from the day of discovery are significantly different between groups A and B and between groups A and C. **Conclusion** This results showed that FPX and DOAC are sufficiently effective for the treatment of VTE in the field of gynecology compared with other existing anticoagulants.

### ISP-30-1

**Long-term oncologic and reproductive outcomes of a fertility-sparing management using high-dose medroxyprogesterone acetate (MPA) for endometrial adenocarcinoma or atypical endometrial hyperplasia** Emi Yokoyama, Naomi Shiga, Takashi Kuno, Shoko Sakurada, Masumi Ishibashi, Zen Watanabe, Hideki Tokunaga, Masahito Tachibana, Hitoshi Niikura, Kiyoshi Ito, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** High-dose medroxyprogesterone acetate (MPA) therapy is a fertility-sparing treatment, for well-differentiated endometrioid adenocarcinoma (EA) or atypical endometrial hyperplasia (AEH). Even though it is aimed to a fertility-sparing treatment, little is known of its relationship in their oncologic outcomes and fertility. To verify the current strategy, we retrospectively analyzed the long-term oncologic and reproductive outcomes of high-dose MPA therapy for EA or AEH. **Methods** We analyzed 22 patients with stage IA, grade 1, EA (EA group), and 20 patients with AEH (AEH group) who underwent fertility-sparing management using MPA (600mg/day) at our hospital from April 1998 to August 2017. **Results** In EA group, 13 patients (59.1%) achieved complete response (CR), and 7 patients (53.8%) of them experienced recurrence after median follow-up time of 14.3 months. 7 patients (31.8%) who failed to achieve CR underwent surgical management. 4 patients of EA group underwent fertility treatment and 2 patients of them become pregnant. 1 patient had one live birth and 1 patient is during pregnancy. In AEH group, 17 patients (85%) achieved CR, and 12 patients (70.6%) of them experienced recurrence after median follow-up time of 16.9 months. 1 patients (5%) who failed to achieve CR underwent surgical management. 3 patients of AEH group become pregnant. 2 patients had two live births and 1 patient had a spontaneous abortion. **Conclusion** High-dose MPA therapy can be considered for the purpose of enabling patients to preserve their fertility. However, the rate of recurrence was considerably high. Early intervention of fertility specialist is recommended for the purpose of pregnancy.

### ISP-30-2

**Fertility-sparing surgery of malignant transformation arising from mature cystic teratoma of the ovary** Nobuhisa Yoshikawa<sup>1</sup>, Toshiya Teshigawara<sup>2</sup>, Kimihiro Nishino<sup>1</sup>, Jun Sakata<sup>1</sup>, Fumi Utsumi<sup>1</sup>, Kaoru Niimi<sup>1</sup>, Shiro Suzuki<sup>1</sup>, Hiroaki Kajiyama<sup>1</sup>, Fumitaka Kikkawa<sup>1</sup> *Nagoya University<sup>1</sup>, Ogaki Municipal Hospital<sup>2</sup>*

**Objective** The purpose of this study was to evaluate the long-term clinical outcome of young women with malignant transformation arising from mature cystic teratoma of the ovary (MT-MCT) by comparing radical surgery and fertility-sparing surgery (FSS). **Methods** All patients treated with radical surgery or FSS for MT-MCT in multiple institutions were registered in this analysis. Univariate and multivariate analyses were performed to evaluate clinical outcome, including overall survival (OS) and disease-free survival (DFS). **Results** From 1986 to 2016, 62 patients with MT-MCT were treated in our group. The median follow-up period was 38.0 (2.0–227.9) months, and the median age was 54 (17–82) years old. Multivariate analysis revealed that only advanced stage was significantly correlated with poorer prognosis of patients [hazard ratio (HR) for death :

6.58, 95% confidence interval (CI) : 1.82–24.78,  $P=0.0048$  ; HR for recurrence : 5.59, 95% CI : 1.52–21.83,  $P=0.01$ ]. Of a total of 13 women with stage I–II disease at less than 45 years old, 7 were treated with FSS, and there was no recurrence except for in one woman with stage II MT–MCT. There was no significant difference in long-term oncological outcome between radical surgery and FSS. Of patients treated with FSS, 2 (29%) were successfully pregnant. **Conclusion** FSS may be indicated for patients with stage I MT–MCT, who hope to preserve fertility, as no relapse was found after FSS. However, FSS should not be recommended for patients with stage II disease.

### ISP-30-3

**A questionnaire study of awareness of the foster care system and adoption for the young cancer survivor in Japan** Kouhei Sugimoto<sup>1</sup>, Eriko Shiraishi<sup>2</sup>, Yodo Sugishita<sup>3</sup>, Nao Suzuki<sup>3</sup> *Dokkyo Medical University Saitama Medical Center<sup>1</sup>, The Jikei University Hospital<sup>2</sup>, St. Marianna University School of Medicine<sup>3</sup>*

**Objective** To objective this study was to elucidate the criteria for the young cancer survivors to be the foster parents and the adopted parents in each child guidance offices and adoption agencies in Japan. **Methods** We researched the criteria for the young cancer survivors to be the foster parents and the adopted parents in sixty-nine each child guidance offices and twenty-three adoption agencies by a questionnaire. **Results** Five child guidance offices or adoption agencies answered that it is hard for the young cancer survivors during the period of cancer treatments to be the foster parents or the adopted parents. No one answered it hard for the young cancer survivors in follow-up duration after cancer treatments to be the foster parents or the adopted parents. Almost of all answered that it is possible after they confirm the health status of cancer survivors. This trend was same as the young cancer survivors fully healed after cancer treatments. More than eighty percent answered that they will use the consultation service for the health status of the foster parents or the adopted parents, if The Japan Society for Fertility Preservation will set up that. Many mentioned individual correspondence was important in free comment. **Conclusion** This study showed that child guidance offices or adoption agencies did not eliminate the young cancer survivors, however, they paid attention to the health status of them. These results enhanced that healthcare providers should advance great partnership with child guidance office or adoption agencies.

### ISP-30-4

**Evaluation of fertility preservation in 25 patients with hematologic malignancies at our hospital** Yuta Kasahara, Eriko Shiraishi, Keiko Kamoshita, Takayuki Haino, Aikou Okamoto *The Jikei University Hospital*

**Objective** Hematologic malignancies present an acute challenge for fertility preservation due to the need for rapid chemotherapeutic intervention. Although more and more patients are referred for fertility preservation, it is unclear whether fertility preservation and assisted reproductive therapies (ART) are effective once chemotherapy has begun. **Methods** We retrospectively examined medical records of 25 female patients with hematologic malignancies who visited our hospital between June 2014 and August 2017. We analyzed for outcomes of fertility preservation and ART. **Results** Of the 25 patients who were referred to our clinic, 14 (56%) wished to receive fertility preservation or ART. Of these patients, 6 had not yet received initial treatment for their malignancy, while 8 had already begun treatment. Of the patients who thought fertility preservation therapy before initial treatment, we were able to preserve fertility in 1 patient via embryo freezing. Among patients who had already received chemotherapy, 2 patients became pregnant natu-

rally and delivered healthy babies. 1 patient became pregnant five years after chemotherapy and peripheral stem cell transplantation. Finally, 1 patient became pregnant via intrauterine insemination, fifteen years after chemotherapy. **Conclusion** In patients with acute hematologic malignancies where rapid intervention is necessary, preserving fertility before treatment is seldom possible. In some patients, a viable pregnancy via natural means or ART is possible despite previous treatment with chemotherapy. We speculate that, for hematologic malignancies, the appropriate timing for fertility preservation is not limited to the period before initial treatment.

### ISP-30-5

**The best and safest strategy for fertility preservation for cancer patients in Japan** Koichi Kyono<sup>1</sup>, Tomoko Hashimoto<sup>2</sup>, Masae Koizumi<sup>1</sup>, Mayumi Toya<sup>1</sup>, Hideki Igarashi<sup>1</sup> *Kyono ART Clinic<sup>1</sup>, Kyono ART Clinic Takanawa<sup>2</sup>, Human Ovarian-tissue Preservation Enterprise<sup>3</sup>*

**Objective** To investigate the best and safest strategy of fertility preservation (FP) for cancer patients in Japan. **Methods** PubMed and reference lists were searched for papers of "cryopreservation, transplantation, transportation, pregnancy, and birth using human ovarian tissue (HOT)." **Results** It is estimated that the number of new FP patients using HOT is around 400 at most in Japan each year. Ninety-three out of 95 children have been born from HOT cryopreservation by slow freezing (SF) worldwide. In vitrification methods (VF), residual cryoprotectants (RC) remained in HOT after warming just before transplantation. However, in SF, RC were washed out after thawing. The concentration of cryoprotectants is four times higher and warming time is four times shorter in VF compared with SF. A transportation system using a special box at 4–8 degrees Celsius for 24h has been established. It costs 5 million euros for to establish and maintain one cryopreservation center for 30 years. Quality control and assessment, including detection of minimal residual disease are important keys to a successful safe birth by transplantation of frozen-thawed HOT. **Conclusion** SF is the safest proven method at present. A transportation network with a few cryopreservation centers is an ideal strategy to lighten the burden of patients, medical staff, and the Government. It has the potential to increase the number of patients and local medical staff who are in geographic areas that lack an oncofertility program to have ovarian tissue preserved for later use in transplantation or other emerging FP options. Further studies are needed.

### ISP-30-6

**Fertility preservation by ovarian tissue cryopreservation for adolescent and young adult patients in our department** Yuta Fujii, Yu Wakimoto, Ryu Takeyama, Naoharu Morimoto, Kayo Inoue, Hiroshi Tsubamoto, Akiko Hasegawa, Hiroaki Shibahara *Hyogo College of Medicine*

**Objective** Fertility preservation by ovarian tissue cryopreservation for adolescent and young adult (AYA) patients with cancer has been performed, and many cases of pregnancy and delivery after warming and transplantation have been reported. In our department, the number of ovarian tissue cryopreservation cases has been increasing after Hyogo oncofertility network (Hyogo-OFN) was established. Here we evaluated the current status of fertility preservation by ovarian tissue cryopreservation. **Methods** We preserved fertility using ovarian tissue cryopreservation for seven patients between February 2017 and August 2017. We collected data retrospectively from medical records. **Results** Patient ages ranged from 11 to 42 years and all patients were nulligravida. Among these patients, 2 had breast cancer, 2 had leukemia, 1 had Ewing sarcoma, 1 had vulvar sarcoma, and 1 had a mediastinal tumor. 4 of 7 patients were per-

formed ovarian tissue cryopreservation following chemotherapy. The average value of Anti-Müllerian hormone (AMH) was 0.87 ng/ml. One of seven patients was initially cryopreserved oocytes, then ovarian tissue cryopreservation was performed. In 4 of 7 patients, oocyte pick up without controlled ovarian stimulation was carried out simultaneously from ipsilateral ovary when removal of one ovary under laparoscopic surgery. The total number of oocytes collected was 10 from 4 patients. However, only one oocyte matured in vitro could be cryopreserved. **Conclusion** Fertility preservation will help AYA patients fight cancer by providing hope that they can conceive in the future. Further accumulation of cases and consideration will be needed to yield any findings about its usefulness.

### ISP-30-7

**Two cases of the fertility preservation for ovarian malignant tumor to reconfirm the importance of the oncofertility network** Naoko Kida, Tomoko Tsuzuki, Mio Matsumoto, Takeharu Kido, Maiko Kobayashi, Yoji Hisamatsu, Hiromi Murata, Toshiko Ono, Sonoko Okada, Hidetaka Okada *Kansai Medical University*

The number of the consultation for the fertility preservation is a tendency to increase in our hospital. As the fertility preservation is generally known, the cases which were consulted by medical doctors, health care providers, and patients themselves increase. However, the confusion sometimes happens because of the insufficient correspondence of management. We report 2 cases that reconfirmed the importance of the oncofertility network. The first case is 41-year-old woman. She had right ovarian tumor pointed out at reproduction clinic in Osaka city. She introduced other hospital and diagnosed of the ovarian cancer, and radical operation was recommended. She refused the radical operation and consulted other hospital in Tokyo. The laparotomy right adnexa resection was performed at the hospital. The diagnosis was clear cell carcinoma, Stage IA. After that she came to our hospital for fertility preservation and the adjuvant chemotherapy. We obtained a fertilized egg with random-start controlled ovarian stimulation before chemotherapy. The second case is 32-year-old woman. She had both sides ovarian tumor pointed out at reproduction clinic. She had laparoscopic surgery in other hospital. The laparoscopic finding was Stage IIIB. Only the biopsy was performed and the diagnosis was serous borderline tumor. She wished for fertility preservation in our hospital. However, we decided the fertility preservation is inappropriate at that time and started chemotherapy and plan to operation again. We started to setup oncofertility network and want to contribute patient referral system and provide the appropriate information.

### ISP-30-8

**A case of retroperitoneal Ewing sarcoma in early pregnancy** Masashi Noguchi<sup>1</sup>, Kiyonori Miura<sup>2</sup>, Michio Kitajima<sup>1</sup>, Yuri Hasegawa<sup>1</sup>, Daisuke Hamaguchi<sup>1</sup>, Naoko Murakami<sup>1</sup>, Naoki Fuchi<sup>1</sup>, Nahoko Komatsu<sup>1</sup>, Kouichi Hiraki<sup>2</sup>, Akira Fujishita<sup>2</sup>, Hideaki Masuzaki<sup>1</sup> *Nagasaki University Hospital<sup>1</sup>, Saiseikai Nagasaki Hospital<sup>2</sup>*

The patient was a 33-year-old female, gravida 1 para 0. As she was diagnosed to have an 8cm tumor lesion with a solid part in the right adnexal region in early pregnancy, laparoscopic surgery was conducted at 12 weeks of gestation. The tumor was present engulfed in the ureter from the right posterior broad ligament through Douglas' fossa and was suspected of being a tumor outside the gynecologic region; therefore, she was referred to our hospital at 13 weeks of gestation. At 15 weeks of gestation, laparoscopic surgery was jointly conducted by the Surgical Oncology Department and the Urology Department. It

was diagnosed as Ewing's sarcoma by histopathologic and genetic tests. In our cancer joint conference, chemotherapy (VAC-IE therapy) was planned and we explained the effects on the mother and fetus associated with VAC-IE therapy if the pregnancy was continued, leading to the patient and her family choosing artificial termination of her pregnancy at 18 weeks of gestation. Moreover, because VAC-IE therapy significantly impairs the ovarian function irreversibly, the patient and her family requested to freeze a fertilized embryo prior to the initiation of chemotherapy, and succeeded in freezing one fertilized embryo, after which we immediately initiated the VAC-IE therapy over a total of 12 scheduled courses.

### ISP-30-9

**Fertility Preservation before treatment of malignant disease** Shiho Takeuchi, Takashi Nakasuji, Nobuyuki Kidera, Yuki Iwahara, Tomonori Ishikawa, Naoyuki Miyasaka *Tokyo Medical and Dental University*

**Objective** Fertility Preservation for the patients who survive from malignant disease has become more important, because the treatment of the malignant disease has progressed and the number of malignant disease survivor has increased recently. Here we report our study of fertility preservation. **Methods** This is a retrospective analysis of patient records who underwent ovarian stimulation and oocyte retrieval for the purpose of to prevent depression of fertility induced from cancer treatment or any other drug which decrease fertility. The study was done at our Hospital from June 2015 to September 2017. **Results** Twenty-four women were evaluated who were before or undergoing treatment for malignant disease; breast cancer, 18; hematologic disease, 4; atypical endometrial hyperplasia, 1; collagen disease, 1. Average age of the patients was 34.2 years (22-45). 23 patient preserved oocytes or embryos in 33 cycles. Peak estradiol levels ranged from 135 to 4,239pg/ml. Average AMH was 3.17 (0.22-11.6). The average number of the frozen oocytes and the embryos per cycle was 11 (2.5-26) and 1.3 (0-6). **Conclusion** We found that we could get sufficient number of oocyte or embryo in short period before malignant treatment. Continued research is needed to investigate the pregnancy rate after treatment of malignant disease.

### ISP-31-1

**Diagnostic value of bioactive factors from blood sample for the early detection of uterine sarcoma** Hideaki Tsuyoshi, Yoshio Yoshida *University of Fukui*

**Objective** The reliable biomarker of uterine sarcoma for the early diagnosis can enable to achieve early and complete resection, leading to improving the prognosis. The comprehensive study of bioactive factors based on genome data has been reported the potential biomarker for the early diagnosis of cancer. The aim of our study is to clarify the role of the bioactive factor for the early diagnostic biomarker in uterine sarcoma. **Methods** To identify the candidates for the early detection of uterine sarcoma, the genome-wide expression data from 57 uterine sarcoma, 23 leiomyoma and 23 myometrium were used. Four candidate genes were identified as the uterine sarcoma specific-bioactive factors and these concentrations were measured by ELISA from blood sample of 41 patients with gynecologic tumors (leiomyoma, ovarian, cervical, endometrial cancer and uterine sarcoma). **Results** A comprehensive analysis of genome data identified four candidate gene, Midkine, Osteopontin, GDF-15 and Granulin. Uterine sarcoma revealed higher concentrations of Midkine (6,732 ± 4,500 pg/ml) than leiomyoma (2,634 ± 1,585 pg/ml) (P>0.05). Uterine sarcoma showed significantly higher concentration of Osteopontin, GDF-15 and Granulin (5058 ± 1,173, 1,152 ± 610.7 and 16,508 ± 2,890 pg/ml) than leiomyoma

( $2,226 \pm 200.6$ ,  $165.3 \pm 16.56$  and  $9,065 \pm 608.3$  pg/ml) ( $P < 0.01$ ). GDF-15 was bioactive factor which uterine sarcoma revealed significantly higher concentration than all gynecologic tumors ( $P < 0.01$ ). **Conclusion** We demonstrated that the measurement of bioactive factors based on genome data can offer the high diagnostic performance for the early diagnosis of uterine sarcoma. The combined analysis of bioactive factors might improve the diagnostic accuracy.

### ISP-31-2

**Survival impact of reduction surgery for elderly or obese patients with endometrial cancer** Junko Minato, Hitoshi Niikura, Yusuke Shibuya, Shoko Sakurada, Chiaki Hashimoto, Tomoyuki Nagai, Michiko Kaiho, Masafumi Toyoshima, Hideki Tokunaga, Muneaki Shimada, Nobuo Yaegashi *Tohoku University Hospital*  
**Objective** Conservative surgery without systematic lymphadenectomy is a treatment option for patients with endometrial cancer who are elderly or obese. In our institution, conservative surgery has been performed for patients 70 years of age or older and those with a body mass index (BMI)  $> 32$  kg/m<sup>2</sup>. The aim of this study is to evaluate the survival impact of conservative surgery for elderly or obese patients with endometrial cancer retrospectively. **Methods** From 2007 to 2012, 215 patients underwent standard surgery and 183 patients received conservative surgery as initial treatment. The subjects for analysis were 59 patients undergoing conservative surgery due to old age (elderly group) and 40 undergoing conservative surgery due to obesity (obese group). The clinical and histological characteristics and survival of these patients were analyzed and compared with those of the standard surgery group. Univariate analysis was performed to determine prognostic factors. **Results** A large proportion of elderly group had type2 endometrial cancers, whereas most of obese group had stage I endometrioid carcinoma (G1/G2). The disease-free survival (DFS) rate were 68.1% in the elderly group, 94.6% in the obese group, and 84.5% in the standard surgery group. The 5-year DFS rate was significantly shorter in the elderly group than in the standard surgery and obese group ( $p=0.0018$ ). In univariate analysis, advanced stage and type2 histology correlated with poor prognosis in both the elderly group and the obese group. **Conclusion** Standard surgery can also be a treatment option in patients who are elderly and obese when they have advanced stage disease or type2 histology.

### ISP-31-3

**Introduction of transperitoneal paraaortic lymphadenectomy for endometrial cancer** Eiji Kobayashi<sup>1</sup>, Mamoru Kakuda<sup>2</sup>, Tsuyoshi Takiuchi<sup>1</sup>, Yuri Matsumoto<sup>1</sup>, Michiko Kodama<sup>1</sup>, Kae Hashimoto<sup>1</sup>, Seiji Mabuchi<sup>1</sup>, Yutaka Ueda<sup>1</sup>, Kenjiro Sawada<sup>1</sup>, Takuji Tomimatsu<sup>1</sup>, Kiyoshi Yoshino<sup>1</sup>, Tadashi Kimura<sup>1</sup> *Osaka University<sup>1</sup>, Sakai City Medical Center<sup>2</sup>*  
**Objective** Lymphadenectomy is an integral part of staging and treatment of gynecologic malignancies. The aim of this study is to evaluate the feasibility and perioperative outcome of laparoscopic surgery including paraaortic lymphadenectomy for endometrial cancer in the early learning curve of this procedure. **Methods** From December 2015, surgery including laparoscopic hysterectomy, bilateral salpingo-oophorectomy, pelvic and transperitoneal paraaortic laparoscopic lymphadenectomy was performed in 15 patients at our institute as a clinical study. We evaluated the clinical characteristics, surgical outcomes, surgery-related complications, and hospital stays. **Results** The study included 15 consecutive patients. Median length of operation was 445 min (range, 345–546). Median blood loss was 80 ml (range, 20–1,600). The median number of harvested lymph node was 63 (range, 46–120). Among the 15 patients, one patient expe-

rienced conversion from laparoscopy to laparotomy. The overall complication rate was 53% with 13.3% intraoperative (one transfusion and one organ residue) and 40% postoperative complications (six chylous ascites and one surgical site infection). All postoperative chylous ascites resolved conservative treatment. Median duration postoperative hospital stay was 7 days (range, 7–23). **Conclusion** By transperitoneal laparoscopic lymphadenectomy, an adequate number of lymph nodes can be removed in an adequate time. The rate of chylous ascites was higher than expected and will be minimized by standardization of the procedure.

### ISP-31-4

**Germline BRCA1/2 mutations in patients with epithelial ovarian cancer** Akiko Abe, Masato Nishimura, Minoru Irahara *Tokushima University*  
**Objective** In Japan, the number of BRCA testing is increasing annually. But, till recently, genetic counselling for epithelial ovarian cancer (EOC) has not been generalized according to hereditary breast and ovarian cancer (HBOC). We investigated the awareness survey and the rate of gBRCA1/2 mutation with EOC, regardless of their family histories. **Methods** 105 patients with EOC who had treated at our hospital were enrolled for 2 years. After genetic counselling, four patients refused gBRCA1/2 test because of no relatives or depression. For 101 patients, analyses for gBRCA1/2 test were performed. DNA was extracted from whole blood, and all coding exons and their flanking intron regions of BRCA1 and BRCA2 were sequenced with next-generation sequencing in our laboratory. **Results** 83 patients (82%) wished for gBRCA1/2 result disclosure, and other 18 patients did not wish to know that result because of worrying. Thirteen of the 107 patients (12.8%); 5 patients in gBRCA1 mutation and 8 patients in gBRCA2 mutation. 8 of 13 with gBRCA1/2 mutation were serous carcinoma, three; adenocarcinoma, one; poorly differentiated adenocarcinoma, and one clear cell carcinoma. **Conclusion** Almost patients with EOC wanted to know genetic risk after genetic counselling. The rate of gBRCA1/2 mutation in tested Japanese EOC patients with an inherited risk, regardless of a family history, was 12.8%. This finding indicates that the cooperation of genetic counselling with other department would be important for patients with ovarian cancers.

### ISP-31-5

**The refractoriness to anti-VEGF therapy in ovarian cancer is mediated via infiltration of GM-CSF-induced MDSCs** Naoki Horikawa<sup>1</sup>, Kaoru Abiko<sup>2</sup>, Noriomi Matsumura<sup>3</sup>, Junzo Hamanishi<sup>2</sup>, Tsukasa Baba<sup>2</sup>, Ryusuke Murakami<sup>2</sup>, Ikuo Konishi<sup>1</sup>, Masaki Mandai<sup>2</sup> *Shiga Medical Center for Adults<sup>1</sup>, Kyoto University<sup>2</sup>, Kindai University<sup>3</sup>, Kyoto Medical Center<sup>4</sup>*  
**Objective** Although bevacizumab has been used to treat ovarian cancer, few cases achieve complete response. The mechanism of resistance to anti-VEGF therapy is unknown. Myeloid Derived Suppressor Cells (MDSCs) are immunosuppressive cells composed of myeloid lineage cells at various stages of differentiation that expand in the tumor sites. Herein, we elucidated the alteration of immune condition in anti-VEGF antibody (a-VEGF abs)-resistant tumor. **Methods** HM-1, mouse ovarian cancer cell line, exhibited resistance to a-VEGF abs (B20-4.1.1) in mouse model. The resistant tumors were collected and analyzed by immunohistochemistry for Gr-1, CD8 and Pimonidazole as a hypoxic marker. Membrane-based cytokine array of tumor lysates was performed. Expression of GM-CSF in ovarian cancer cells cultured under hypoxic conditions was analyzed. The impact of GM-CSF on MDSC function was analyzed. The combination therapy of anti-VEGF antibody and anti-GM-CSF anti-



body was performed. **Results** Increased Gr-1+ MDSC and decreased CD8+ lymphocytes were observed in a-VEGF abs-resistant tumors. Pimonidazole+ area was increased in a-VEGF abs-resistant tumor. MDSCs were preferentially infiltrated into hypoxic lesions. Protein array exhibited increased GM-CSF in a-VEGF abs-resistant tumors. The expression level of GM-CSF was up-regulated in HM-1 cells cultured under hypoxic condition. The migration assay showed hypoxia promoted MDSC recruitment through GM-CSF signal. The combination therapy with anti-GM-CSF abs significantly inhibited the tumor growth compared with a-VEGF abs only. Tumor-infiltrating MDSC were reduced and CD8+ lymphocytes were increased by combination therapy. **Conclusion** Anti-VEGF therapy induced tumor hypoxia and up-regulated GM-CSF expression. Anti-GM-CSF abs improve the efficacy of a-VEGF abs through blockade of MDSC influx into tumor.

### ISP-31-6

**Overexpression of cyclase-associated protein 2 (CAP2) is a new prognostic indicator in Type II ovarian cancer** Masataka Adachi<sup>1</sup>, Kouji Banno<sup>1</sup>, Mayuka Anko<sup>1</sup>, Takayuki Takahashi<sup>1</sup>, Moito Iijima<sup>1</sup>, Takashi Takeda<sup>1</sup>, Miho Iida<sup>1</sup>, Yusuke Kobayashi<sup>1</sup>, Eiichiro Tominaga<sup>1</sup>, Mamoru Tanaka<sup>1</sup>, Michiie Sakamoto<sup>2</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Department of Pathology, Keio University<sup>2</sup>*

**Objective** The cyclase-associated protein 2 (CAP2) is protein that regulates actin dynamics and known as cell cycle regulator or carcinogenic factor. Although CAP2 expression is associated with progression of hepatocellular carcinoma, CAP2 expression in other malignancies remains unclear. The aim of this study was to assess the clinicopathological significance of CAP2 expression in ovarian cancer. **Methods** The subjects were 518 patients with ovarian cancer who underwent surgical resection in our institute between 2000 and 2016. The study included 336 cases of Type I (low-grade serous, well-differentiated endometrioid, clear cell and mucinous carcinoma) and 182 of Type II (high-grade serous, poorly-differentiated endometrioid and undifferentiated carcinoma) ovarian cancer. CAP2 immunohistochemistry was performed and staining criteria was defined based on its intensity and area. Each case was classified in overexpression or low expression of CAP2. Correlation analyses of CAP2 and clinicopathological factors were performed by Chi-square test. The log-rank test and univariate and multivariate Cox regression analysis were performed to assess the prognostic significance of CAP2. This study was approved by our ethical committee. **Results** CAP2 overexpression was observed in 59 (11.4%) cases and significantly related to Type II histology (4.8% of Type I vs 23.6% of Type II,  $p < 0.001$ ), decreased progression free survival (PFS) (67.4 vs 157.2 months,  $p < 0.001$ ) and overall survival (98.9 vs 166.4 months,  $p = 0.009$ ) compared with low expression. Amongst Type II ovarian cancer, CAP2 expression was an independent prognostic factor for PFS [HR, 2.077 ; 95% CI, 1.297-3.324 ;  $p = 0.002$ ]. **Conclusion** This study suggests that CAP2 is a new prognostic indicator in Type II ovarian cancer.

### ISP-31-7

**The histone methyltransferase, SUV39H2, involved in resistance to anti-cancer treatment with  $\gamma$ -H2AX production, is a potent therapeutic target in high-grade serous ovarian carcinoma** Kenbun Sone<sup>1</sup>, Katsutoshi Oda<sup>2</sup>, Asako Kukita<sup>1</sup>, Hidenori Machino<sup>1</sup>, Machiko Kojima<sup>1</sup>, Shinya Oki<sup>1</sup>, Michihiro Tanikawa<sup>1</sup>, Kazunori Nagasaka<sup>1</sup>, Yoko Matsumoto<sup>1</sup>, Osamu Hiraikae<sup>2</sup>, Yutaka Osuga<sup>2</sup>, Tomoyuki Fujii<sup>2</sup> *The University of Tokyo Hospital<sup>1</sup>, The University of Tokyo<sup>2</sup>*

**Objective** Dysregulation of histone modification, especially the

process of histone methylation, has been considered as one of key regulators for human carcinogenesis. Overexpression of various histone methyltransferases has been reported in multiple cancers. However, there are no reports about SUV39H2 in high-grade serous ovarian carcinomas (HGSC). The aim of this study is to clarify expression and functions of SUV39H2 in HGSC. **Methods** We analyzed 39 clinical HGSC specimens under informed consent and approval of our ethics committee. We performed quantitative real-time PCR (q-PCR) to evaluate expression of SUV39H2. The functional analysis of SUV39H2 was examined with in vitro methylation assay, mass spectrometry, in vitro kinase assay, and dominant negative experiments. **Results** The q-PCR revealed that SUV39H2 was overexpressed in clinical HGSC specimens ( $P = 0.006$ ), compared with normal ovarian tissues. In vitro methylation assay and mass spectrometry revealed that SUV39H2 methylated histone H2AX on lysine 134. In vitro kinase assay indicated that lysine 134 methylation on histone H2AX enhanced H2AX serine 139 phosphorylation ( $\gamma$ -H2AX). Introduction of K134-substituted histone H2AX, which is not methylated by SUV39H2, increased the sensitivity of cancer cells to ionizing radiation and chemotherapeutic agents (doxorubicin and cisplatin). **Conclusion** SUV39H2 inhibition may reduce  $\gamma$ -H2AX production and sensitize the cancer cells to radiotherapy and chemotherapy. Inhibition of SUV39H2, in combination with DNA-damaging agents, may be a novel therapeutic strategy in HGSC

### ISP-31-8

**Safety and efficacy of neoadjuvant chemotherapy with bevacizumab in advanced-stage peritoneal/ovarian cancer patients** Kazunari Fujino<sup>1</sup>, Soshi Kusunoki<sup>1</sup>, Takashi Hirayama<sup>1</sup>, Takafumi Ujihira<sup>2</sup>, Tsuyoshi Ota<sup>2</sup>, Yasuhisa Terao<sup>1</sup>, Atsuo Itakura<sup>1</sup>, Satoru Takeda<sup>1</sup> *Juntendo University Hospital<sup>1</sup>, Juntendo University Urayasu Hospital<sup>2</sup>*

**Objective** The aim of this study was to evaluate the outcomes of neoadjuvant chemotherapy (NAC) with bevacizumab (Bev) at our institute. **Methods** Eleven patients with stage IIIC or IV peritoneal/ovarian cancer who underwent interval debulking surgery (IDS) after NAC with Bev between December 2014 and December 2016 were enrolled retrospectively (TCB group). As a control group, we enrolled 13 patients evaluated between December 2012 and December 2014 who underwent IDS and received NAC without Bev (TC group). Both the TCB and TC groups received combination chemotherapy consisting of paclitaxel (175 mg/m<sup>2</sup>) or docetaxel (70 mg/m<sup>2</sup>) and carboplatin (area under the curve 6 mg/mL/min) administered intravenously every 3 weeks (cycles 3 - 6). **Results** All patients in both groups underwent IDS. There were 7 (63.6%) and 8 (61.5%) cases with stage IIIC disease and 4 (36.3%) and 5 (30.7%) with stage IV disease in the TCB and TC groups, respectively. The complete resection rate was 81.8% in the TCB group and 69.2% in the TC group. The rate of achieving either complete or optimal resection was 100% in the TCB group and 69.2% in the TC group ( $p = 0.043$ ). Hematoxicity (grade 3 or higher) was observed in 9 patients (81.8%) in the TCB group and 12 (92.3%) patients in the TC group. One patient (9%) experienced abdominal incisional hernia due to a fascial defect in the TCB group. **Conclusion** IDS after NAC with Bev is safe, with a similar efficacy as that after NAC without Bev.

### ISP-32-1

**Differential requirement of amino acids on cell survival of ovarian cancer cells** Akiko Furusawa<sup>1</sup>, Jun Inoue<sup>2</sup>, Hitoshi Tsuda<sup>3</sup>, Naoyuki Miyasaka<sup>1</sup>, Johji Inazawa<sup>2</sup> *Tokyo Medical and Dental University<sup>1</sup>, Medical Research Institute, Tokyo Medical and Dental University<sup>2</sup>, National Defense Medical College Hospi-*

tal<sup>3</sup>

**Objective** Amino acids (AAs) play an important role on cellular metabolism in cancer cells. However, which AAs are indispensable the survival of which cancer cells has not been elucidated. Here, we examined the indispensable AAs for ovarian cancer (OVC) cells and the relationship between the AAs synthetase and cancer cell survival. **Methods** To validate the requirement of each AA on cell survival in 14 OVC cell lines, we examined the effect of cultivation in single AA depleted conditioned medium on OVC cells. **Results** By cultivating for 14 OVC cell lines in different medium in which a single AA was depleted, we found that the requirement of AAs was cell type dependent. Next, we focused on the relationship between the sensitivity to glutamine deprivation and glutamine synthetase (GS). The expression level of GS protein was found to positively correlate with the cell survival rate under glutamine-depleted condition. GS overexpression in GS downregulated OVC cells induced decreased sensitivity to glutamine deprivation and induced inhibition of in vivo tumor growth, suggesting that OVC cells with GS downregulation require extracellular glutamine for cell survival. Furthermore, we showed that expression of GS protein was negative in 10 of 316 primary OVC tumors (3.2%). **Conclusion** Our finding suggest that the therapeutic reduction of extracellular glutamine may be effective against OVCs with GS downregulation.

### ISP-32-2

**Serum CA125 level after neoadjuvant chemotherapy is predictive of prognosis and surgical outcomes in advanced epithelial ovarian cancer** Tomohiko Matsuhashi<sup>1</sup>, Hisamori Kato<sup>2</sup>, Kazuho Nakanishi<sup>1</sup>, Takashi Yamada<sup>1</sup>, Gen Ishikawa<sup>1</sup>, Seiryu Kamo<sup>1</sup>, Toshiyuki Takeshita<sup>1</sup> *Nippon Medical School<sup>1</sup>, Kana-gawa Cancer Center<sup>2</sup>*

**Objective** Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) has recently been recommended for selected patients with advanced epithelial ovarian cancer (EOC) because NACT-IDS was shown to have fewer complications compared to conventional primary debulking surgery (PDS), without any significant difference in therapeutic efficacy. Reductions in cancer antigen 125 (CA125) levels before and after primary treatment have been known to predict the prognosis of advanced EOC patients. However, the correlation between post-NACT CA125 levels and successful IDS remains controversial. The objective of this study was to evaluate associations between post-NACT serum CA125 levels, surgical outcomes, and clinical outcomes in advanced EOC. **Methods** We retrospectively analyzed 107 patients with FIGO stage III or IV ovarian cancer who were treated with NACT-IDS between January 2001 and December 2012. All patients provided verbal and written informed consent for the use of their anonymized clinical records for the research. **Results** Serum CA125 levels after NACT were significantly lower in the complete/optimal IDS group (n=77) compared to the suboptimal IDS group (n=30, mean  $\pm$  standard deviation : 48.1  $\pm$  27.6 vs. 346.5  $\pm$  295.2 U/mL,  $p < 0.01$ ). Patients with low preoperative CA125 levels (<35 U/mL) had a higher probability of optimal IDS (78.1  $\pm$  41.9% vs. 33.3  $\pm$  19.2%,  $p < 0.01$ ) and longer progression-free survival (mean  $\pm$  standard deviation : 30.4  $\pm$  14.3 months vs. 21.3  $\pm$  7.3 months,  $p < 0.05$ ) than patients with high CA125 levels (>100 U/mL). **Conclusion** Patients with low CA125 levels (<35 U/mL) had a higher probability of complete/optimal IDS and longer progression-free survival compared to patients with high CA125 levels (>100 U/mL).

### ISP-32-3

**Investigation for characteristics of clear cell carcinoma be-**

**tween developing and non-developing endometriosis** Yu Horibe, Toshiyuki Kanno, Junna Taguchi, Yuri Itai, Fumika Tsuchiyama, Nobuko Takahashi, Yoshika Akizawa, Akira Nakabayashi, Kazunori Hashimoto, Jun Kumakiri, Hideo Matsui, Shoko Inokuchi *Tokyo Women's Medical University Hospital*

**Objective** Clear cell carcinoma (CCC) is a rare subtype of epithelial ovarian cancer. However, in Japan, 20% of ovarian cancer is CCC. CCC is well-known as adverse prognosis clinically because of low chemosensitivity and high rate of recurrence. For long term investigation, part of CCC has developed from endometriosis. If characteristics of CCC with or without endometriosis are pointed out, it would reflect to finding patient under high-risk developing CCC, estimating prognosis and strategy for surgery. **Methods** We investigated 19 patients who underwent primary surgery due to CCC in our institution from 2016 to 2017. Patients were divided into two groups which developed endometriosis or not. Each group assessed by age weight, height, elevation of CA125 and CA199, maximum size of ovary, surgery completeness, pelvic and para-aorta lymphadenectomy, peritoneal washing, FIGO classification, content and length of chemotherapy, recurrence after six months, gravidity and parity. Data was examined by Box-and-whisker plot and Fisher's exact test. **Results** As a results, we couldn't find any significant difference statistically on pelvic and para-aorta lymphadenectomy, gravidity, parity, elevation of CA125 and CA199 between two groups. In box plot, patient with endometriosis, tumor marker and maximum size of ovary were wide-ranged and weight and height were high value. **Conclusion** This study couldn't point statistical significant difference out. Whereas we found characteristics from graphical data. To obtain accurate result, further investigation and increasing parameter would be required.

### ISP-32-4

**Clinical impact of routine DNA genotyping on the management of suspected early hydatidiform mole** Yoko Aoyagi<sup>1</sup>, Kentaro Kai<sup>2</sup>, Takao Matsuda<sup>3</sup>, Shimpei Sato<sup>1</sup>, Kanetoshi Takebayashi<sup>1</sup>, Naoko Oyama<sup>1</sup>, Kaei Nasu<sup>1</sup>, Hisashi Narahara<sup>1</sup> *Oita University Hospital<sup>1</sup>, Nakatsu Municipal Hospital<sup>2</sup>, Nishibeppu National Hospital<sup>3</sup>, Oita Red Cross Hospital<sup>4</sup>*

**Objective** The widespread use of transvaginal ultrasonography and the high-sensitive human chorionic gonadotropin (hCG) test makes the pathological differentiation of partial or complete hydatidiform mole (HM) and hydrops abortus difficult. We compared the utility of a combined routine use of DNA genotyping with that of a conventional diagnostic evaluation in women with suspected HM. **Methods** We analyzed the cases of 44 consecutive women with suspected HM who underwent a routine DNA genotyping in addition to a conventional diagnostic evaluation (combination group, n=29) or a conventional diagnostic evaluation only (conventional group, n=15). The primary endpoint was the diagnostic yield for DNA genotyping. The secondary endpoints were the diagnostic concordance rate in the combination group and the percentage of re-evacuation and definite diagnostic yield in both groups. We compared the allelic pattern of maternal peripheral blood and chorionic villus by short tandem repeat typing. Approval for the study was obtained from the institutional review board. **Results** The diagnostic yield for DNA genotyping was 96.6%. The diagnostic concordance rate in the combination group was 58.6%. The re-evacuation rate was significantly lower in the combination group than the conventional group (44.8% vs. 86.7%;  $p=0.008$ ). The definite diagnostic yield was obtained in all patients in the combination group, but in only 73.3% in the conventional group ( $p=0.01$ ). **Conclusion** Routine DNA genotyping combined with a conventional diagnostic evaluation provided a decreased re-evacuation rate and



an increased definite diagnostic yield, and will be of benefit to the clinical management of patients with suspected HM.

### ISP-32-5

**Second curettage as initial treatment for molar pregnancy : who can skip it?** Shingo Miyamoto<sup>1</sup>, Yasushi Sasaki<sup>2</sup>, Mitsuyoshi Ichihara<sup>3</sup>, Makoto Nakabayashi<sup>1</sup>, Yoshiyuki Okada<sup>1</sup>, Yuka Asami<sup>1</sup>, Kanae Shimada<sup>1</sup>, Chiaki Iitsuka<sup>1</sup>, Mamiko Onuki<sup>1</sup>, Tetsuya Ishikawa<sup>1</sup>, Koji Matsumoto<sup>1</sup>, Akihiko Sekizawa<sup>1</sup> *Showa University<sup>1</sup>, Showa University Fujioka Hospital<sup>2</sup>, Showa University Northern Yokohama Hospital<sup>3</sup>*

**Objective** The therapeutic role of routine second curettage in patients after first evacuation of molar pregnancy is still controversial. The aim of the present study was to clarify candidates who could skip the second curettage as an initial treatment for molar pregnancy. **Methods** A retrospective cohort study was conducted on 80 patients of hydatidiform mole (56 of complete, and 25 of partial), who received routine second curettage at one week after the first curettage between 2007 and 2016. The levels of serum hCG and the thickness of uterine cavity measured by ultrasound sonography before second curettage were obtained from medical records. **Results** There were 16 cases with residual molar tissues and 64 cases with no residual molar tissues, analyzed respectively. The incidence of persistent gestational trophoblast neoplasia was significantly higher in residual cases. The levels of hCG was significantly higher in residual cases (median : 9,455mIU/ml [2,359-41,500] vs. 2,228mIU/ml [64-12,400],  $p < 0.0001$ ). Furthermore, the thickness of uterine cavity was also significantly greater in cases with residual molar tissues (median : 15mm [9-23] vs. 7mm [1-15],  $p < 0.0001$ ). Cut-offs of 10 mm of the thickness and 2,000 mIU/ml of hCG at one week after first curettage gave a sensitivity of 100% to detect a residual condition. **Conclusion** Our data suggested that the levels of hCG and the thickness of uterine cavity before second curettage were related to residual molar tissues. Therefore, the second curettage might be skipped for those patients with the hCG levels of less than 2,000 mIU/ml and the thickness of less than 10 mm at one week after first curettage.

### ISP-32-6

**Limitations of hormonal therapy in adenomyosis patients** Chiho Miyagawa, Takako Tobiume, Yasushi Kotani, Kiko Yamamoto, Risa Fujishima, Masato Aoki, Yoshie Yo, Kosuke Murakami, Hisamitsu Takaya, Hidekatsu Nakai, Ayako Suzuki, Noriomi Matsumura *Kindai University Hospital*

**Objective** Recently hormone therapy made it possible for adenomyosis patients to keep their uteruses intact. However, there is no consensus about which patients require hysterectomies. The purpose of this study is to define the limitations of hormone therapy for, evaluate the efficacy of hormonal treatment for and the necessity of hysterectomies for adenomyosis patients. **Methods** From January 2008 to September 2017, a total of 96 patients with adenomyosis had their uterine sizes measured before receiving treatment. From this data, we performed a retrospective study. We define the hormone therapy as GnRH analogs, dienogest, low dose estrogen-progestin and levonorgestrel-releasing intrauterine systems that are used by themselves or in combination. **Results** The average uterine length was 98.22 mm. 28 patients (29%) were treated by hysterectomy. The remaining 68 patients (71%) were first treated with hormone therapy only. A total of 52 patients (54%) were successful. The remaining sixteen patients (17%) required a hysterectomy. A significant number of patients that had larger sized uterus eventually required hysterectomies ( $P=0.01$ ). An ROC analysis was taken, it found a cut off value for uterine lengths of 86mm for heightened risk of requiring a hysterectomy. For uterine lengths greater than 86

mm, the percentage of patients requiring hysterectomies was 58%, compared to 17% for these with uterine lengths less than 86mm. **Conclusion** About half of cases of adenomyosis patients treated with hormone therapy were successful. However, patients with uterine lengths more than 86mm had a higher chance of requiring hysterectomy.

### ISP-32-7

**The frequencies of peripheral blood regulatory T cells and activated lymphocytes of the premature ovarian insufficiency** Mutsumi Kobayashi<sup>1</sup>, Akemi Ushijima<sup>1</sup>, Masami Ito<sup>1</sup>, Yosuke Ono<sup>1</sup>, Daisuke Matsui<sup>2</sup>, Kazuhiro Kawamura<sup>2</sup>, Osamu Yoshino<sup>1</sup>, Bunpei Ishizuka<sup>2</sup>, Shigeru Saito<sup>1</sup> *Toyama University Hospital<sup>1</sup>, Rose Ladies Clinic<sup>2</sup>*

**Objective** Premature ovarian insufficiency (POI) is not rare that 1% of the population are affected. Approximately 50% of patients with POI have some autoantibodies. It is suggesting that POI is one of the autoimmune diseases. Decreased regulatory T (Treg) cells and activated T cells are observed in autoimmune diseases. Thus we studied the immune system in POI. **Methods** Peripheral blood was collected from patients with POI (POI group, n=35) and normal menstruation women (control group, n=8). Using flow cytometry we analyzed the proportion of monocytes, CD4/8 ratio, Treg and activation marker ; CD69, on these cells. And in POI group, We analyzed correlation between autoantibody titer and immune cells. **Results** CD14<sup>+</sup> cells were low proportion in POI group compared to control group (median 7.0% vs 16.8%,  $p=0.00167$ ), and there was no change in the CD4/8 ratio and Treg between two groups (median 1.53 vs 1.45,  $p=0.343$ , 1.27% vs 1.14%  $p=0.673$ ). CD69<sup>+</sup> CD4/8 ratio were significantly higher in POI group (0.24 vs 0.096,  $p=0.032$ ). There were negative correlations between the anti - thyroglobulin antibody titer and the proportion of Treg ( $r=-0.519$ ,  $p=0.039$ ) and between the proportion of CD69<sup>+</sup>CD4<sup>+</sup> and Treg ( $r=-0.497$ ,  $p=0.00236$ ). **Conclusion** We firstly showed that activated CD4<sup>+</sup> T cells were increased in POI. And there is a possibility decreasing Treg increase autoantibody titer and activated CD4<sup>+</sup> cells. These data suggest immunological dysfunction may be one of the cause of POI.

### ISP-32-8

**Validity of assisted reproductive technology after laparoscopic myomectomy** Takashi Nakasuji, Tomonori Ishikawa, Nobuyuki Kidera, Yuki Iwahara, Naoyuki Miyasaka *Tokyo Medical and Dental University*

**Objective** Infertile patients in late reproductive age have a risk of developing uterine myoma. Recently, many uterine myoma have been treated by laparoscopic surgery instead of laparotomy. In general, 3 to 6 months contraceptive period after laparoscopic myomectomy for healing of uterine wound were recommended. So called surgery-assisted reproductive technology hybrid therapy were often performed to use the contraceptive periods effectively. Ovum pick up and embryo freezing is performed during the contraceptive period and frozen-thawed embryo transfer is performed after contraceptive periods in the hybrid therapy. In this presentation, we report effectiveness of the hybrid therapy in our hospital. **Methods** We retrospectively investigated six infertile patients with uterine myoma who underwent the hybrid therapy in our hospital between October 2011 and June 2017. **Results** The mean age of the patients was 39 years-old. The mean maximum diameter of enucleated myoma was 6.7 cm, and endometrium was deformed due to uterine myoma in 5 of 6 patients. The average number of cryopreserved embryos in the pre or postoperative period was 2.3. The average clinical pregnancy rate per embryo transfer after the contraceptive periods was 50%. **Conclusion** Though contraceptive period

after myomectomy can decrease fertility especially in late reproductive age, the hybrid therapy can preserve embryo without oocyte aging in the contraceptive periods. As clinical pregnancy rate of hybrid therapy for infertile patient with myoma was as high as general assisted reproductive technology for infertile patients, the hybrid therapy is a strong strategy for infertile patients with myoma.

### ISP-33-1

**Prevention of postpartum depression by the intake of omega-3 polyunsaturated fatty acids (PUFAs)** Yoko Nagayasu, Daisuke Fujita, Atsushi Daimon, Misa Nunode, Saori Ota, Atsuko Okamoto, Sayaka Taga, Takumi Sano, Yusuke Suzuki, Masami Hayashi, Yoshito Terai, Masahide Ohmichi *Osaka Medical College*

**Objective** Omega-3 PUFAs, including EPA, are known to have protective effects on depression. However, there is no consensus as to whether this applies to postpartum depression as well. The aim of this study is to examine whether the intake of omega-3 PUFAs prevents postpartum depression. **Methods** Under the approval by our ethics committee and informed consent, we measured the EPA, EPA/AA and conducted a dietary questionnaire survey on 50 singleton pregnant women. The questionnaire was about how often they eat fish. It was performed at the first trimester, second trimester and postpartum. EPDS (Edinburgh Postnatal Depression Scale) was tested postpartum after one month. **Results** The frequency of eating fish was correlated with EPA in the first trimester ( $r=0.555, p<0.001$ ) and postpartum ( $r=0.522, p<0.001$ ). Moreover, it was also correlated with EPA/AA in the first trimester ( $r=0.527, p<0.001$ ), second trimester ( $r=0.524, p<0.001$ ) and postpartum ( $r=0.528, p<0.001$ ). The levels of EPA and EPA/AA in EPDS $>7$  were lower than the levels in EPDS $<7$  ( $p<0.05$ ). **Conclusion** A lower diet intake of omega-3 PUFAs during pregnancy correlated to the occurrence of postpartum depression. Sufficient intake of omega-3 PUFAs may provide pregnant women a way to prevent postpartum depression.

### ISP-33-2

**Are treatment interventions for early onset gestational diabetes based on the International Association of Diabetes and Pregnancy Study Groups criteria effective?** Yuko Hagiwara<sup>1</sup>, Junko Kasai<sup>1</sup>, Sayuri Nakanishi<sup>1</sup>, Etsuko Miyagi<sup>2</sup>, Shigeru Aoki<sup>1</sup> *Yokohama City University Medical Center<sup>1</sup>, Yokohama City University Hospital<sup>2</sup>*

**Objective** To investigate whether the broad interpretation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria with application to the early pregnancy (adopted as the standard in Japan) is appropriate. **Methods** We conducted this investigation by comparing diabetes-related adverse pregnancy outcomes among women treated for Gestational diabetes mellitus (GDM) following an early-pregnancy diagnosis (early-onset GDM,  $n=528$ ) and those treated for GDM following a mid-pregnancy diagnosis, which is the international standard (Mid-term-onset GDM,  $n=147$ ). **Results** Gestational weight gain was significantly lower in the early-onset GDM group (7.5 kg) than the mid-term-onset GDM group (8.4 kg). The frequency of hypertensive disorders of pregnancy tended to be lower in the early-onset GDM group (5.6% vs. 8.8%,  $p=0.085$ ), but infant birth weight did not differ significantly between the groups. No between-group difference was observed in macrosomia, large-for-gestational-age (LGA), small-for-gestational age (SGA), low Apgar score, shoulder dystocia, cesarean delivery, NICU admission, hyperbilirubinemia, neonatal hypoglycemia, or respiratory distress syndrome. The frequency of LGA showed a significant association with pre-pregnancy body

mass index but did not differ according to the timing of therapy initiation. **Conclusion** We could not find the effectiveness of therapeutic interventions initiated after GDM diagnosis in the early pregnancy based on the IADPSG criteria compared to therapeutic interventions after a mid-pregnancy GDM diagnosis. It was suggested that the IADPSG criteria for diagnosing GDM at 24 to 28 weeks gestation should not be applied to Japanese women in the early pregnancy by a broader interpretation.

### ISP-33-3

**Three cases of cesarean scar pregnancy treated with conservative surgery** Haruka Ueda, Kosuke Yoshihara, Makoto Chihara, Tatsuya Ishiguro, Sosuke Adachi, Masanori Isobe, Akiko Kobayashi, Koji Nishino, Nobumichi Nishikawa, Masayuki Sekine, Takayuki Enomoto *Niigata University Medical and Dental Hospital*

Cesarean Scar Pregnancy (CSP) is a rare life-threatening type of ectopic pregnancy in which implantation occurs in the previous cesarean-section scar. However, optimal treatment strategy for CSP is unclear. We report three cases of CSP treated with conservative surgery. **Case1** A 29-years-old woman with a past history of previous cesarean section was diagnosed with CSP at five weeks of gestation via ultrasound examination. She complained continual vaginal bleeding and lower abdominal pain since six weeks and we performed uterine artery embolization (UAE) followed by dilatation and curettage (D&C) at eight weeks. **Case2** A 40-years-old woman with a past history of previous cesarean section and adenomyomectomy was suspected with hydatidiform mole based on ultrasound findings at six weeks of gestation. She was referred to our hospital by ambulance due to massive vaginal bleeding, and we performed UAE followed by D&C at 10 weeks, and diagnosed no molar change pathologically. **Case3** A 33-years-old woman with a past history of previous cesarean section was diagnosed with CSP at five weeks of gestation through ultrasound examination. She had abnormal vaginal bleeding appeared at 6 weeks of gestation and was referred for the management of CSP. When she arrived at our hospital, massive blood flow but not gestational sac was detected around the scar. We performed only UAE. She was diagnosed with clinical invasive mole due to the elevated hCG level (6 days after UAE). UAE combined with D&C might be an effective uterine conservative treatment for CSP and useful for histological diagnosis of CSP.

### ISP-33-4

**Non-invasive positive pressure ventilation for preeclamptic women ; 4 case reports** Kohei Hamada, Yoshitsugu Chigusa, Eiji Kondoh, Yusuke Ueda, Shunsuke Kawahara, Haruta Mogami, Masaki Mandai *Kyoto University Hospital*

**Objective** Pleural effusion or pulmonary edema caused by preeclampsia could be an indication for termination of pregnancy. Taking the mortality and morbidity of neonates into account, however, the decision of early preterm delivery is a clinical dilemma for obstetricians. Although non-invasive positive pressure ventilation (NPPV) has been widely used in patients with respiratory failure, there has been limited data and evidence regarding NPPV during pregnancy thus far. Therefore the aim of this study was to evaluate the clinical outcome of NPPV management for respiratory distress in pregnancy due to preeclampsia. **Methods** The medical record of cases managed with NPPV during pregnancy in our institution was reviewed, and patients' characteristics, background, pregnancy outcome, and complications of NPPV were analyzed retrospectively. **Results** NPPV was employed in four pregnant women between 2011 and 2016 in our hospital, and all cases were diagnosed with severe preeclampsia. In three cases, pleural effusion was de-

ected and the other case was complicated with sleep apnea syndrome. NPPV was initiated at 20, 23, 24, and 30 weeks of gestation, respectively. In all cases NPPV alleviated respiratory distress, and succeeded in delaying the termination of pregnancy for 17 days on average. Maternal outcome was uneventful and no intubation was required. No complication such as aspiration caused by NPPV was observed. **Conclusion** NPPV might contribute to prolongation of pregnancy in patients with poor oxygenation due to preeclampsia.

### ISP-33-5

**Study on the Kinetics of Pregnancy-Related Proteins in Primates** Hirofumi Kashiwagi, Shunichiro Izumi, Kanako Mitsuzuka, Atsuko Togo, Hitoshi Ishimoto, Mikio Mikami *Tokai University*

**Objective** Decidual membrane forms the environment to inhibit that fetus and placenta were excluded as allografts. There are proteins to suppress the cytotoxic activity of T cells and NK cells which are called pregnancy-related proteins. In this study, it is important to clarify the role of these proteins to contribute to the acceptance of allografts in the pregnancy. We examined what proteins and functions were preserved evolutionarily and important for maintaining placental function through comparing the difference between human and Common Marmoset (CM) pregnant kinetics. **Methods** Plasma were collected in each trimester and non-pregnancy cycle, and analyzed by LC/MS. We predicted the homology and domain structure of these proteins. Finally, expression in placenta was analyzed by IHC and RT-PCR. **Results** In our LC/MS study, protease inhibitors that showed the most prominent changes were PZP in human and A2ML1 in CM. These proteins belong to the same A2M family as protease inhibitors capable of inhibiting multiple proteases. Sequence analysis of BAIT REGION which determines the specificity to the proteases showed that this very limited region had very low homology compared to all amino acid sequences which had high homology. These proteases common to PZP in human and A2ML1 in CM were predicted to be MMP9 and PE. In IHC, PZP and A2ML1 were accumulated in maternal-fetal interface in placenta. **Conclusion** PZP in human and A2ML1 in CM showed prominent changes during pregnancy. These molecules work for the maintenance of pregnancy through inhibitory action against a common protease.

### ISP-33-6

**Change in fetal cardiac output distribution to the placenta with ritodrine tocolysis** Ryuichi Shimaoka, Tomomi Shiga, Tatsuro Furui, Kenichiro Morishige *Gifu University*

**Objective** To define the normal range of fetal blood flow distribution to the placenta estimated from the ratio of fetal combined cardiac output (CCO) and umbilical vein flow volume (UVFV), and to investigate the change in the distribution with ritodrine tocolysis. **Methods** This was a single center cross-sectional study of 189 singleton and appropriate for gestational age (AGA) pregnancies with a gestation of 19–39 weeks. Fetal CCO and UVFV were measured and the distribution was calculated in every pregnancy checkup. Ritodrine group was defined as cases with ritodrine therapy more than 50 µg/min for premature labor (n=43), and non-ritodrine group (n=43) was extracted with propensity score matching for estimated fetal body weight (EFBW) and gestational age at measurement. **Results** Fetal CCO and UVFV increased linearly with gestation ( $r=0.86$ ,  $p<0.01$  and  $r=0.58$ ,  $p<0.01$  respectively), and they were almost unchanged in corrected by EFBW. The normal CCO/kg, UVFV/kg and distribution were on average  $1,009 \pm 200$  ml/min/kg,  $115 \pm 36$  ml/min/kg and  $11.8 \pm 4.1\%$  respectively. Ritodrine group was significantly higher than non-ritodrine group in CCO/kg

( $1,025 \pm 189$  vs  $913 \pm 170$  ml/min/kg,  $p<0.05$ ), UVFV/kg ( $136 \pm 51$  vs  $103 \pm 30$  ml/min/kg,  $p<0.05$ ) and Distribution ( $13.4 \pm 4.5$  vs  $11.6 \pm 3.6\%$ ,  $p<0.05$ ). Ritodrine infusion caused increase in fetal heart rate and the right cardiac output relating to CCO, and diameter of intrahepatic umbilical vein and mean umbilical vein flow velocity relating to UVFV. **Conclusion** Ritodrine infusion increases fetal cardiac distribution to the placenta in AGA with a gestation of 19–39 weeks.

### ISP-34-1

**Post-surgical maintenance of cardiac function in an ex vivo premature lamb model** Yusaku Kumagai, Masatoshi Saito, Nobuo Yaegashi *Tohoku University*

**Objective** Ex vivo uterine environment (EVE) therapy is an experimental neonatal intensive care model which involves surgical cannulation of umbilical vessels to connect parallel membranous oxygenators for fetal gas exchange. The aim of the current study was to evaluate the impact of the cannulation on fetal circulation and cardiac function using ultrasound measurements. **Methods** The study was performed on preterm lambs at gestational age (GA) of  $115 \pm 3$  days. Fetuses received either 8 Fr arterial and 10 Fr venous catheters (n=5, Group A) or 10 Fr arterial 10 Fr venous catheters (n=5, Group B), which were placed into umbilical vessels. Fetal circulation (flow direction of DA and FO) and cardiac function (MV/TV-E/A, MPI, Ao-Vmax and PLI) were measured after surgery and in ewes of corresponding GA (n=6, Controls). Data were assessed by ANOVA and Tukey's test. **Results** Blood flow at DA and FO was kept right to left direction in all groups. Regarding MV-E/A and TV-E/A, Group A had a significantly higher value than Group B or Controls. There was no significant difference between Group B and Controls. For MPI and Ao-Vmax, both Group A and B were significantly different from controls. There was no significant difference between group A and B. No difference was observed for PLI among the three groups. **Conclusion** Fetal circulation was maintained immediately after surgery in both catheter groups. Enlargement of catheter diameter contributed to improvement in cardiac function as a result of decreasing in afterload. However, further improvement is necessary to fill the gap between natural and EVE animals.

### ISP-34-2

**What is useful ultrasound screening for congenital heart disease in the first trimester?** Mayumi Tokunaka, Ryu Matsuoka, Hiroko Takita, Tatsuya Arakaki, Tomohiro Oba, Masamitsu Nakamura, Akihiko Sekizawa *Showa University Hospital*

**Objective** To evaluate the methods of ultrasound screening for fetal congenital heart disease (CHD) in the first trimester. **Methods** A prospective cohort study was conducted at a single university hospital in the period from January 2012 to February 2017. Patients who had first trimester screening and diagnosed as CHD ant- and postnatally were enrolled. All cases were undergoing ultrasound screening by four-chamber views (4CV) using B mode at 11 to 13+6 weeks gestation (1stTS) and by 4CV and outflow tracts views using B and color Dopplar mode at 18 to 20 weeks gestation (2ndTS). The accuracy of detection in this screening protocol for CHD was investigated. **Results** There were 5,015 cases which were singleton pregnancy and undertaken 1stTS. Overall, CHD were detected 45 cases. In 15 cases, the findings suspected for CHD were observed at 1stTS. In these cases, 9 cases were terminated, 5 cases were intrauterine death, and one case was confirmed as CHD after delivery. There were 17 cases which were not suspected at 1stTS and diagnosed as CHD at 2ndTS. In those cases, 12 cases had possibilities to detect CHD at 1stTS if we assessed not only by 4CV using B mode, but by 4CV and outflow tracts views using color Dopplar. Addi-

tionally, 13 cases were diagnosed postnatally as CHD, and most of those had ventricular septal defect. **Conclusion** It could be possible to detect CHD in the first trimester with a higher detection rate if both 4CV and outflow tract views were assessed.

### ISP-34-3

**Analysis of fetal gross movements in light for date infants by a fetal movement acceleration measurement recorder** Masayoshi Morita, Eiji Ryo, Youhei Nagaya, Michiharu Seto, Hideo Kamata, Yasuhiro Matsumoto, Masahiro Shiba, Yukifumi Sasamori, Koichiro Kido, Takuya Ayabe *Teikyo University Hospital*

**Objective** The purpose of this study was to investigate the fetal gross movements (FGM) of fetal growth restriction (FGR) using fetal movement acceleration measurement recorder (FMAM recorder). **Methods** (Subject) Study group : A total of 17 pregnant women who delivered light for date (LFD) single infant. Control group : A total of 60 pregnant women who delivered appropriate for date (AFD) single infant at term. (Recording) The pregnant women themselves recorded FGM by FMAM recorder weekly from 28 weeks to term. (Assessment) The records which could be obtained more than 4 hours per night were assessed by a newly developed software. The following numbers were calculated. (1) The ratio of 10-second epoch with FGM to total epoch on the number basis per night. (2) The numbers of FGM per hours. (3) (a) The average number (per hours) of non-FGM periods which were more than 5 min, 10 min, 15 min, and 20 min, and (b) the average duration and (c) the longest duration of non-FGM periods through night. (Statistical analysis) Linear regression analysis was conducted with the FGM numbers as response variable and explanatory variables (LFD or AFD, gestational weeks, maternal height, and body mass index). **Results** Study group vs Control group : (1) 13.57 vs 14.73% ( $p=0.0118$ ). (2) 58.64 vs 66.63 times/h ( $p=0.0017$ ). (3) (a) 5min 2.34 vs 1.85 times/h ( $p=0.0002$ ), 10min 0.69 vs 0.51 times/h ( $p=0.0025$ ), 15min 0.32 vs 0.23 times/h ( $p=0.0085$ ), 20 min 0.17 vs 0.12 times/h ( $p=0.0020$ ). (b) 9.34 vs 8.73 min ( $p=0.0072$ ). (c) 25.3min vs 19.05 min ( $p<0.0001$ ). **Conclusion** FGR fetuses decreased FGM and increased non-FGM periods.

### ISP-34-4

**Elastography for predicting time to delivery at third trimester** Yoshie Yo, Masao Shimaoka, Ayako Suzuki, Hanako Sato, Kiko Yamamoto, Risa Fujishima, Shiro Takamatsu, Akiko Kanto, Yasushi Kotani, Hidekatsu Nakai, Isao Tsuji, Noriomi Matsumura *Kindai University Hospital*

**Objective** The Bishop score has been widely used to evaluate how much the pregnant woman is ready for vaginal delivery. Although ripening of the uterine cervix is a major component of the Bishop score, it is subjectively determined, and therefore, not reproducible among different obstetricians. Elastography is an ultrasound-based modality to evaluate stiffness of tissues. The aim of the study was to test whether elastography could evaluate cervical stiffness and predict delivery at third trimester. **Methods** A total of 43 women who experienced spontaneous vaginal delivery of singleton babies at our hospital were analyzed with written consent of the individuals under the approval of the institutional ethics committee. We assessed cervical ripening of pregnant women every week after 36 weeks of gestation using both digital examination and ultrasonography. The stiffness of internal ostium of uterus was classified into three : hard, middle, and soft. **Results** The average Bishop score of women who delivered within 7 days was higher than women who delivered over 7 days after the examinations (3.5 vs. 2.6,  $p<0.001$ ). The average cervical length was also different between them (24 mm vs. 29mm,  $p=0.011$ ). The soft internal

ostium was correlated with deliveries within 7 days ( $p=0.027$ ), whereas the hard internal ostium was correlated with deliveries later than 7 days ( $p=0.0038$ ). A multivariate analysis indicated elastography was an independent predictor of delivery within 7 days. **Conclusion** Elastography may be useful to predict time to delivery.

### ISP-34-5

**Timing of birth for women with a twin pregnancy in the past three years** Aya Yoshida, Atsushi Kasamatsu, Chikako Soejima, Shuhei Nishibata, Yuki Yasuhara, Takuya Yokoe, Yumi Kuroda, Naoko Kobayashi, Mio Matsumoto, Tomomi Okano, Susumu Sawaragi, Hidetaka Okada *Kansai Medical University*

**Objective** The optimal gestational duration for twin pregnancy is unknown. The aim of this study was to evaluate the incidence of serious complications for both maternal women and infants of a twin pregnancy. **Methods** From 2014 through 2016, we retrospectively reviewed medical records of 130 women with a twin pregnancy (monochorionic diamniotic twins 47cases, Dichorionic diamniotic twins 83 cases) delivered at 36 weeks or after gestation at our institution. We examined maternal serious complications (severe pregnancy induced hypertension, eclampsia, abruptio placentae, HELLP syndrome, cerebrovascular disease), delivery outcomes, infants' complications (respiratory distress, nasal continuous positive air-way pressure or intubation, need for neonatal intensive care (NICU)), and outcomes. The chi-square test or Fisher's exact test was used for categorical variables. **Results** The success rate of cesarean delivery was 82% (41/50) in the planned-cesarean-delivery, and that of vaginal delivery was 79% (63/80) in the planned-vaginal-delivery. And that of the cesarean delivery of the second twin after vaginal birth of the first was 4 cases. The rate of maternal serious complications in women at 36, 37, 38 and 39 weeks' gestation, was 1.5%, 13.9%, 2.4% and 16.7%, respectively. There were significant differences in the respiratory distress and NICU between infants born at 36 weeks and 37 weeks or after (22% and 5%, 33% and 13%, respectively). **Conclusion** Delivery of twins at 37 weeks or after gestation decreases infants' complications without maternal complications increases, as compared with 36 weeks' gestation.

### ISP-34-6

**Outcomes of placental abruption in 75 patients** Kazuma Onishi, Hiroyuki Tsuda, Masatoshi Esaki, Akiko Kimura, Keiko Sakata, Kazuya Fuma, Yoshiaki Maseki, Atsuko Tezuka, Tomoko Ando, Kimio Mizuno *Japanese Red Cross Nagoya Dai-ichi Hospital*

**Objective** In pregnancies complicated with placental abruption (PA), a negative correlation was revealed between the onset-to-delivery time and neonatal and maternal outcomes. We investigated the differences in neonatal and maternal outcomes between patients with and without maternal transfer from other clinics. **Methods** We retrospectively reviewed patients with PA from January 2009 to September 2017. We investigated 75 patients with PA excluding 7 intrauterine fetal deaths, 2 vaginal deliveries, and 1 chronic PA. We examined the correlation between the onset-to-delivery time and neonatal and maternal outcomes. We also compared these outcomes between transferred and non-transferred patients. **Results** The average umbilical artery pH of neonates delivered <45 minutes from onset was significantly higher than those delivered  $\geq 45$  minutes from onset (7.211 vs. 7.027 ;  $p=0.02$ ). The average onset-to-delivery time of patients transferred from other clinics was significantly longer than non-transferred patients (284 vs. 135 minutes ;  $p<0.0001$ ). No significant differences were noted in the umbilical artery pH or DIC score between transferred patients and non-



transferred patients. **Conclusion** PA is an important cause of perinatal mortality and morbidity, so prompt delivery should be performed after a diagnosis. However, diagnosing PA exactly is difficult, and its severity varies. We detected no significant differences in neonatal and maternal outcomes between transferred and non-transferred patients. In Aichi Prefecture, a unique maternal transfer system using the iPhone was established, and most patients can transfer from clinics to our hospital smoothly and promptly. This system may have affected the results of our study.

### ISP-34-7

**Hyperfibrinolysis with Consumptive Coagulopathy in Amniotic Fluid Embolism** Tomoaki Oda, Naoaki Tamura, Yukiko Kohmura, Naomi Furuta, Toshiyuki Uchida, Kazunao Suzuki, Hiroaki Itoh, Kazuhiro Sugihara, Naohiro Kanayama *Hama-matsu University School of Medicine*

**Objective** Amniotic fluid embolism (AFE) induces an abrupt and severe disseminated intravascular coagulation (DIC). Although consumptive coagulopathy has been considered as the cause of DIC, the details are still unknown. Considering the role of fibrinolysis, fibrin is degraded mainly by plasmin along with neutrophil elastase (NE). Our objective is to investigate hyperfibrinolysis at the onset of AFE. **Methods** We have collected many blood specimens suspected as AFE from all over Japan. We investigated plasma from patients of AFE and atonic bleeding collected within 2 hours from the onset without blood transfusion since the year 2009 up to 2017. Diagnosis of AFE was based on the Japanese criteria, which also required fibrinogen value below 2.0 g/l at the onset. Plasmin- $\alpha$ 2 plasmin inhibitor complex (PIC), fibrin degradation product by elastase (EXDP), fibrin degradation product (FDP), D-dimer, and NE were compared. The data was described as median with minimum to maximum. Chi-square and Mann-Whitney *U* test were used for statistical analysis. **Results** The number of the patients were 13 in both the two groups. There was no difference in blood loss at plasma collection. The number of AFE patients with fibrinogen below 1.0 g/l were significantly more than that of atonic bleeding patients (n=7 vs. 0). PIC ( $\mu$ g/ml) (42.7 [0.3–143] vs. 4.9 [1.0–33.9]), FDP ( $\mu$ g/ml) (667 [304–1,111] vs. 80 [27–119]), and D-dimer ( $\mu$ g/ml) (117 [45.7–687] vs. 16.6 [3.99–57.0]) were significantly higher in the AFE group. EXDP and NE had no significant differences. **Conclusion** AFE patients had hyperfibrinolysis due to excessive plasmin along with consumptive coagulopathy at the onset.

### ISP-35-1

**Identification of risk factors in patients with positive lymph node after radical hysterectomy for early stage cervical cancer** Soyi Lim<sup>1</sup>, Yoon-Jin Cho<sup>1</sup>, Kwang-Beom Lee<sup>1</sup>, Jong-Min Lee<sup>2</sup> *Gachon University Gil Medical Center, Korea<sup>1</sup>, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Korea<sup>2</sup>*

**Objective** To identify risk factors in patients with lymph node metastasis after radical hysterectomy for early stage cervical cancer. **Methods** The medical records of patients with early-stage cervical cancer with lymph node metastasis after radical hysterectomy and lymph node dissection conducted from March 2006 to December 2015 at the Gil Medical Center were retrospectively analyzed. Patients that received chemotherapy, radiation therapy or concurrent chemoradiotherapy before surgery and patients with neuroendocrine or sarcoma histology were excluded. Histological tumor type, tumor size, lymph-vascular space invasion, parametrial involvement, number of positive nodes, and involvements of common iliac nodes and paraaortic lymph nodes were assessed and correlations with tu-

mor recurrence were sought. **Results** We analyzed 523 patients with FIGO stage IB to IIA cervical carcinoma that underwent radical hysterectomy with lymph node dissection. Pathological analyses of surgical specimens showed positive lymph nodes in 127 patients (24.3%). When the above-mentioned variables were subjected to Cox proportional regression analysis, parametrial infiltration and metastatic lymph nodes ( $\geq 5$ ) were found to be significantly correlated with disease-specific survival. Using these two factors, node-positive patients were divided into low-risk (n=57), intermediate-risk (n=47), and high-risk (n=23) groups. Disease specific survival for the high-risk group was significantly poorer than for the intermediate and low-risk groups. **Conclusion** The prognosis of node positive patients after radical hysterectomy was found to be different according to clinicopathologic risk factors. Current adjuvant therapy strategies after surgery may not be sufficient for patient with positive nodes. New strategies that improve survival should be considered for such patients.

### ISP-35-2

**Sentinel lymph node mapping using indocyanine green in cervical cancer** Sahori Kakuda, Eiji Kobayashi, Tsuyoshi Takiuchi, Yuri Matsumoto, Michiko Kodama, Kae Kashimoto, Seiji Mabuchi, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** Sentinel lymph node (SLN) biopsy technique is gradually applied for gynecologic malignancies although its reliability is unclear. Near-infrared (NIR) imaging appears to be a beneficial new technique for SLN biopsy. The objective of this study was to evaluate the detection rate, sensitivity, and negative predictive value (NPV) of laparoscopic NIR fluorescence imaging for early-stage cervical cancer. **Methods** From January 2013 to August 2017, 36 early-stage (FIGO2008, stage1A–2B) cervical cancer patients undergoing SLN biopsy were retrospectively analyzed. All patients had undergone laparoscopic radical hysterectomy with pelvic lymphadenectomy after SLN biopsy. **Results** The overall and bilateral detection rate was 100% (36/36) and 86.1% (31/36). Positive SLNs were found in 11.1% (4/36). The sensitivity and negative predictive value for SLN were 100% respectively. The average SLN count was 3.7 (0–9). All procedures were successfully completed without conversion to open laparotomy, and no intraoperative or postoperative complications occurred. **Conclusion** Laparoscopic SLN mapping with ICG for cervical cancer patients revealed high detection rate, sensitivity and NPV. Prospective studies are needed to determine if SLN mapping can replace lymphadenectomy in this setting.

### ISP-35-3

**Extraperitoneal Radical Trachelectomy With Pelvic Lymphadenectomy: A Novel Fertility-Preserving Option for Early Stage Cervical Cancer Patients** Kazunobu Yagi, Seiji Mabuchi, Tsuyoshi Takiuchi, Yuri Matsumoto, Michiko Kodama, Eiji Kobayashi, Kae Hashimoto, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** Radical trachelectomy combined with pelvic lymphadenectomy has been used to treat early stage cervical cancer patients who wish to preserve their fertility. Although vaginal, abdominal, laparoscopic, and robotic approaches have been used during this procedure, all of these approaches cause peritoneal damage, which could result in periaidnexal adhesion. The aim of the present study was to introduce and discuss a novel fertility-preserving option, extraperitoneal radical trachelectomy with pelvic lymphadenectomy. **Methods** To minimize peritoneal damage, we developed a new surgical approach for

radical trachelectomy combined with pelvic lymphadenectomy. All surgical procedures associated with radical trachelectomy and pelvic lymphadenectomy were performed via an extraperitoneal approach. During this procedure, the uterine arteries, inferior hypogastric nerve, and pelvic splanchnic nerve were preserved. **Results** Extraperitoneal nerve-sparing radical trachelectomy with pelvic lymphadenectomy was performed in 3 Japanese women with FIGO stage IA2 and IB1 cervical cancers. In all patients, complete resection of the disease was achieved without causing any intraoperative complications. Although an infected lymphocele developed in a patient that was managed conservatively, no severe postoperative complications were noted. No adjuvant treatments were given, and the patients are currently free of disease. **Conclusion** This is the first report about extraperitoneal radical trachelectomy in patients with early stage cervical cancer. Extraperitoneal radical trachelectomy combined with pelvic lymphadenectomy can be safely performed. Because peritoneal damages, which can cause peritoneal adhesion, could be avoided, we consider that this surgical approach may be an ideal treatment option for women with early stage cervical cancer who wish to preserve their fertility.

### ISP-35-4

**Identifying a candidate population for ovarian conservation in young women with clinical stage IB-IIB cervical cancer** Imari Deura<sup>1</sup>, Muneaki Shimada<sup>2</sup>, Koji Matsuo<sup>3</sup>, Satoshi Yamaguchi<sup>4</sup>, Hiroyuki Kanao<sup>5</sup>, Toru Nakanishi<sup>6</sup>, Toshiaki Saito<sup>7</sup>, Shoji Kamiura<sup>8</sup>, Takashi Iwata<sup>9</sup>, Nao Suzuki<sup>1</sup>, Mikio Mikami<sup>10</sup>, Toru Sugiyama<sup>11</sup>. *St. Marianna University School of Medicine<sup>1</sup>, Tohoku University Hospital<sup>2</sup>, University of Southern California, USA<sup>3</sup>, Hyogo Cancer Center<sup>4</sup>, Cancer Institute Hospital<sup>5</sup>, Tohoku Medical and Pharmaceutical University<sup>6</sup>, Kyushu Cancer Center<sup>7</sup>, Osaka International Cancer Institute<sup>8</sup>, Keio University<sup>9</sup>, Tokai University<sup>10</sup>, Iwate Medical University<sup>11</sup>*

**Objective** To identify risk factors associated with ovarian metastasis and to characterize a population with minimum risk of ovarian metastasis in young women with stage IB-IIB cervical cancer. **Methods** This was a nation-wide multicenter retrospective study in Japan examining consecutive cases of surgically-treated women with clinical stage IB-IIB cervical cancer who had oophorectomy at radical hysterectomy (n=5,697). Multivariable analysis was performed to identify independent risk factors for ovarian metastasis. **Results** Ovarian metastasis was seen in 70 (1.2%) cases. In the entire cohort, adenocarcinoma, lymphovascular space invasion, uterine corpus tumor invasion, and pelvic/para-aortic nodal metastases remained independent risk factors for ovarian metastasis (all, adjusted-P<0.05). In a sensitivity analysis of 3,165 women aged<50 years (ovarian metastasis, 1.0%), adenocarcinoma, parametrial tumor involvement, uterine corpus tumor involvement, and pelvic/para-aortic nodal metastases remained independent risk factors for ovarian metastasis (all, adjusted-P<0.05). In the absence of these five risk factors (representing 46.1% of women aged<50 years), the incidence of ovarian metastasis was 0.14%. With the presence of adenocarcinoma alone (representing 18.9% of women aged<50 years), the incidence of ovarian metastasis was 0.17% and was not associated with increased risk of ovarian metastasis compared to the subgroup without any risk factors (P=0.87). **Conclusion** Nearly two thirds of women aged<50 years with clinical stage IB-IIB cervical cancer had no risk factor for ovarian metastasis or had adenocarcinoma alone: these subgroups had ovarian metastasis rates of around 0.1% and may be a candidate population for ovarian conservation at surgical treatment.

### ISP-35-5

**Salvage hysterectomy after concurrent chemoradiotherapy**

**for advanced cervical cancer** Natsuko Kamiya, Yuichi Imai, Tatsuya Matsunaga, Yukihide Ota, Yukio Suzuki, Naho Ruiz Yokota, Mikiko Sato, Etsuko Miyagi *Yokohama City University Hospital*

**Objective** Chemotherapy, salvage hysterectomy, and follow-up are options for patients with residual tumor after concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer. We have conducted hysterectomy on such patients since 2009. Here, we retrospectively evaluated selection of patients, and effectiveness and safety of the salvage hysterectomy. **Methods** We conducted hysterectomy on 26 patients suspected to have residual tumor after CCRT as primary treatment of advanced cervical cancer between January 2009 and March 2017. We retrospectively assessed the preoperative examinations, presence of residual tumor in resected uterus, adverse events and local tumor control rate. **Results** The median age was 49.5 (29-75) years. The histo-pathological diagnosis before CCRT was squamous cell carcinoma (SCC) in 6 cases and non-SCC in 20 cases. Nineteen patients had pathological residual tumor in resected uterus (group A) and seven had no tumor (group B). The sensitivity and specificity of preoperative MRI for detecting residual tumor were 90.5% and 71.4%, and those of pathological examination were 77.8% and 42.9%, respectively. Using both measures, the sensitivity and specificity were 73.7% and 100%, respectively. Moreover, tumor markers were higher in group A. The local recurrence rate was 23.1% and the complication rate was 38.5%. **Conclusion** Combination of imaging and pathological examination after CCRT may be useful for evaluation of residual tumor. Tumor markers also may be helpful for it. Salvage hysterectomy could be an effective strategy for advanced cervical cancer, but the indication should be assessed carefully because of surgical complications and it will be shown based on the further prospective study.

### ISP-35-6

**Efficacy of neoadjuvant chemotherapy plus radical hysterectomy for stage IB2, IIA2 and IIB cervical cancer** Takahito Ashihara, Masahiro Sumitomo, Naoki Horikawa, Hirofumi Nonogaki *Shiga Medical Center for Adults*

**Objective** In Japan Society of Gynecologic Oncology guidelines 2017 for the treatment of uterine cervical cancer, the efficacy of NAC for stage IB2, IIA2 and IIB cervical cancer is restrictively recognized. Nevertheless, NAC therapy has disadvantages tumor progress before surgery if tumor has not responded, and intraoperative blood transfusion increase due to chemotherapy induced anemia. The aim of this single institution study was to evaluate the disadvantage of NAC plus radical hysterectomy. **Methods** We performed a retrospective analysis of patients with stage IB2, IIA2, IIB cervical cancer started therapy at our hospital from January 1, 2009 to January 1, 2016. They were received either neoadjuvant chemotherapy (NAC) plus radical hysterectomy (NAC group) or radical hysterectomy alone (RH group) or concurrent chemoradiation therapy (CCRT group). **Results** A total of 56 patients were enrolled, 17 of whom were underwent NAC plus radical hysterectomy. Twelve patients (70.6%) had more than 30% decrease in tumor size and 16 patients (94.1%) had underwent planned radical hysterectomy after NAC. The NAC group did not show unacceptable toxicity and increase significant intraoperative blood transfusion. On the other hand, although tumor size in NAC group was significantly larger than in RH group and patients with stage IIB in NAC group and CCRT group were significantly more than in RH group, there was no significant difference in overall survival (OS) and disease-free survival (DFS) among these three groups. **Conclusion** This study confirmed that NAC plus radical hysterectomy is acceptable treatment option for stage IB2, IIA2 and IIB cervical cancer.



## ISP-35-7

**Comparison of laparoscopic and open radical hysterectomies in the surgical treatment of stage IB1 cervical cancer in a single institute in Japan** Tsuyoshi Takiuchi, Eiji Kobayashi, Yuri Matsumoto, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** In many countries, the two common ways of surgical technique of stage IB1 cervical cancer are the laparoscopy and the laparotomy. Our aim is to compare the intra- and postoperative results of laparoscopic radical hysterectomy (LRH) and abdominal radical hysterectomy (ARH) in a single institute in Japan. **Methods** Twelve LRH and 11 ARH were performed from January 2015 until December 2016 because of stage IB1 cervical cancer. Results were analyzed retrospectively. The surgical outcomes include operating time, blood loss, pelvic lymph node yield, hospitalization days, and intraoperative and postoperative complications. Follow-up results were also analyzed for all patients. **Results** Both groups have similar patient and tumor characteristics. Median follow-up time was 17 months (range 8–30 months). There was no significant difference between the two groups in pelvic lymph node yield, intra- and postoperative complications and length of hospitalization. The operating time was significantly shorter in the ARH group. The treatment with LRH was generally superior to ARH with respect to blood loss. No conversion of laparotomy occurred in the LRH group. On follow-up of patients, there was one relapse reported in both groups, respectively. **Conclusion** Results of LRH are comparable and not worse than ARH. LRH may pose a safe and feasible alternative to ARH and have a priority because of the general advantages of laparoscopic surgery in the surgical treatment of stage IB1 cervical cancer in Japan.

## ISP-35-8

**A retrospective study of uterine arterial neoadjuvant chemotherapy plus radical hysterectomy versus radical hysterectomy alone in patients with stage IB2 to IIB uterine cervical cancer** Takashi Suzuki, Hiroshi Adachi, Hiroharu Kobayashi, Misa Kobayashi, Hiroko Konno, Shuhei Terada, Naoko Inaoka, Ayumi Yasuda, Keiichiro Kato, Kentaro Iga, Satoru Nakayama, Takeshi Murakoshi *Seirei Hamamatsu General Hospital*

**Objective** To evaluate the effectiveness and adverse events of uterine arterial neoadjuvant chemotherapy (UAI-NAC) plus radical hysterectomy (RH) compared to RH alone in the stage IB2 to IIB patients. **Methods** Patients diagnosed cervical cancer and treated with both UAI-NAC and RH in our facility from January 2009 through August 2016 with informed consent were enrolled. Indications of UAI-NAC in our facility are : RH could not be scheduled within 8 weeks since first visit, staging between IB2 and IIB, histopathologies with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma. RH would be appropriate if the tumor size is reduced. Intraarterial cisplatin (60 mg/m<sup>2</sup>) on day 1 followed by intravenous paclitaxel (80 mg/m<sup>2</sup>) on days 2, 9 and 16 of a 28-day cycle, maximum of 3 courses. We assessed overall survival (OS) with the log-rank test, estimating hazard ratio (HR) with a Cox proportional hazards model. Furthermore, surgical time and blood loss were assessed with Mann-Whitney U-test. **Results** Total of 22 cases of UAI-NAC plus RH and 28 cases of RH alone with stage IB2 to IIB were enrolled. Median ages were 47.5 and 44.5 (p=0.463) years, respectively. p-value of OS were 0.882, HR 1.138 (95% CI 0.21 - 6.3). Surgical time (p=0.123) and blood loss (p=0.984) were not statistically significant. **Conclusion** UAI-NAC plus RH might be another option for those who had to wait for RH more than 8 weeks in stage IB2 to IIB cervical cancer patients.

## ISP-35-9

**Radical hysterectomy after radiotherapy for recurrent or persistent cervical cancer** Seiji Mabuchi, Tsuyoshi Takiuchi, Yuri Matsumoto, Michiko Kodama, Eiji Kobayashi, Kae Hashimoto, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** To evaluate the safety and efficacy of radical hysterectomy after radiotherapy (RH-AR) for recurrent or persistent cervical cancer. **Methods** The present retrospective study included patients who underwent RH-AR for recurrent or persistent cervical cancer between May 1, 2010 and September 30, 2016. Patient characteristics, intraoperative and postoperative adverse events, and surgical outcomes were investigated to identify patients at increased risk of recurrence or severe surgical adverse events. **Results** There were 31 patients scheduled for treatment with RH-AR ; one hysterectomy procedure was aborted. No intraoperative adverse events or treatment-related deaths occurred, and 8 (27%) patients experienced severe postoperative adverse events. After a median 34 months of follow-up, 13 (43%) patients had developed recurrent disease, predominantly at distant sites. The estimated 3-year overall survival rate was 53.8%. Positive surgical margins, nodal metastasis, parametrial invasion, and no adjuvant treatment after RH-AR were found to be predictors of increased risk of recurrence. No predictors of severe surgical adverse events were identified. **Conclusion** RH-AR was a safe, curative treatment for patients with recurrent or persistent cervical cancer. However, considering the significant risk of surgical adverse events, RH-AR should only be performed for a select group of patients.

## ISP-36-1

**The efficacy of national HPV vaccination program against cervical cancer in Japanese young women** Risa Kudo<sup>1</sup>, Masayuki Sekine<sup>1</sup>, Manako Yamaguchi<sup>1</sup>, Sosuke Adachi<sup>1</sup>, Asami Yagi<sup>2</sup>, Yutaka Ueda<sup>2</sup>, Sharon Hanley<sup>3</sup>, Etsuko Miyagi<sup>1</sup>, Takayuki Enomoto<sup>1</sup> *Niigata University<sup>1</sup>, Osaka University<sup>2</sup>, Department of Women's Health Medicine, Hokkaido University<sup>3</sup>, Yokohama City University<sup>4</sup>*

**Objective** To investigate the effectiveness of national HPV vaccination program against cervical cancer for Japanese young women. **Methods** We recruited 20–22 years old females who attended the public cervical cancer screening program from April 2014 to March 2017 in Niigata, Japan. HPV testing was performed using HCII (Qiagen) and TM HPV kit (MEBGEN) and questionnaire about HPV vaccination was conducted. A Chi-square test was used in this statistical analysis. Additionally, we counted prevalence ratios (PR) and vaccine effectiveness (VE), their 95% confidence intervals. **Results** HPV testing was performed to a total of 2,197 registrants and 2005 women were eligible for this study. A total of 1,546 (77.1%) participants were vaccinated, and 459 (22.9%) were unvaccinated. High risk HPV infection rate was 12.0% in vaccinated group and 15.3% in unvaccinated group, respectively (p=0.08). The prevalence of vaccine types 16 and 18 was significantly lower in vaccinated group (0.2%) than in unvaccinated group (2.2% ; p<0.001). Similarly, the prevalence of HPV 31, 33 and 45 which are cross-protected by HPV bivalent and quadrivalent vaccination was significantly lower in vaccinated group (0.8%) than in unvaccinated group (1.7% ; p=0.11). PR and VE against HPV 16/18 was 0.09 (95%CI 0.03 to 0.32) and 91% (95% CI 68% to 98%). **Conclusion** Our study demonstrates evidence of high effectiveness of national HPV vaccination program in Japanese young women.

## ISP-36-2

**Correlation among HPV-derived transcriptomes, HPV types and CIN grades** Satoshi Baba<sup>1</sup>, Ayumi Taguchi<sup>1</sup>, Akira Kawata<sup>1</sup>,

Satoko Eguchi<sup>1</sup>, Kensuke Tomio<sup>1</sup>, Katsuyuki Adachi<sup>1</sup>, Takashi Iwata<sup>2</sup>, Akira Mitsuhashi<sup>3</sup>, Katsutoshi Oda<sup>1</sup>, Kei Kawana<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Keio University Hospital<sup>2</sup>, Chiba University Hospital<sup>3</sup>, Nihon University Hospital<sup>4</sup>*

**Objective** High risk-HPV (HR-HPV) infection is a main cause of cervical cancer. Expression patterns of HPV-derived transcriptomes change with epithelial differentiation and/or CIN progression. Previous reports suggested that E7 modulates CIN progression, and that E1^E4 is expressed along with epithelial differentiation. We herein investigated characteristics of HPV-derived transcriptomes in CIN lesions according to HPV types and CIN grades. **Methods** After obtaining IRB approvals of our institutions, 174 CIN subjects were prospectively enrolled. HPV subtypes were confirmed by the PGMY-PCR-based genotyping assay. Expressions of HPV E7 and E1^E4 were analyzed by real-time PCR, especially focusing on four major HR-HPV types (HPV16, 18, 52 and 58). **Results** HPV subtypes comprised : HPV16 in 37 patients (Infection rate of 174 CIN patients in this trial=21.3%) ; HPV18 in 7 (4.0%) ; HPV52 in 43 (24.7%) ; and HPV58 in 38 (21.8%), respectively. In HPV16 or in total analysis, detection rate of E7 was increased along with the CIN progression (Cochran-Armitage test,  $p=0.0257$  and  $p=0.0015$ , respectively). Detection rate of E1^E4 was also increased along with the CIN progression in HPV58 or in total analysis (Cochran-Armitage test,  $p=0.0111$  and  $p=0.0031$ , respectively), whereas HPV 18-positive samples did not express E1^E4 mRNA regardless of CIN grades. **Conclusion** HPV-derived transcriptomes may reflect the degree of CIN in HPV-type dependent manner.

### ISP-36-3

**Phase I/IIa study of photodynamic therapy using talaporfin sodium and diode laser (L-PDT) for Cervical Intraepithelial Neoplasia** Masaru Sakamoto<sup>1</sup>, Kiyohiko Miyake<sup>1</sup>, Hiroshi Tanabe<sup>1</sup>, Yasuko Koyamatsu<sup>1</sup>, Kenji Umayahara<sup>1</sup>, Tadao Tanaka<sup>1</sup>, Aikou Okamoto<sup>2</sup> *Sasaki Foundation Kyoundo Hospital<sup>1</sup>, The Jikei University Hospital<sup>2</sup>*

**Objective** PDT using Photofrin (P-PDT) is considered to be a treatment modality with higher fertility sparing capacity than cone resection as uterine preservation therapy for CIN3. However, P-PDT has a high efficacy, and despite the low obstetric risk such as premature birth, side effects of photosensitivity are strong and the hospitalization period is long, so it has not reached standard treatment. Therefore, in order to investigate the safety and effectiveness of the next generation L-PDT using semiconductor laser and Laserphyrin with less half-life in blood, we started Phase I/IIa study of L-PDT after registration to UMIN. **Methods** After approval of the ethical committee, phase I study of L-PDT was performed on nine cases of CIN2-3 with IC. In order to investigate the optimal dose of laser irradiation, 3 cases were performed for each step of 50, 75 and 100 J/cm<sup>2</sup>. **Results** Phase I study was performed in 9 cases in total. Intra-tumor accumulation of Laserphyrin was confirmed by Fluorescence microscopy. Dose Limiting Toxicity was not observed, suggesting safety. The main side effects were lower abdominal pain of G1-2 and fever of G1-2. Photosensitivity was G1 in only one case. Histological disappearance of CIN2-3 was observed in all 9 cases. Recommended Dose for CIN3 was considered to be 100 J/cm<sup>2</sup>. **Conclusion** In L-PDT, photosensitivity was hardly seen unlike P-PDT, temporary lower abdominal pain and fever were observed, suggesting safety. All nine cases showed CR after L-PDT, suggesting efficacy. We have started phase II study in order to further investigate safety and effectiveness of L-PDT.

### ISP-36-4

**Posttreatment human papillomavirus testing for residual or recurrent high-grade cervical intraepithelial neoplasia : a pooled analysis** Mamiko Onuki, Koji Matsumoto *Showa University*

**Objective** We conducted a pooled analysis of published studies to compare the performance of human papillomavirus (HPV) testing and cytology in detecting residual or recurrent diseases after treatment for cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3). **Methods** Source articles presenting data on post-treatment HPV testing were identified from the National Library of Medicine (PubMed) database. We included 5,319 cases from 33articles published between 1996 and 2013. **Results** The pooled sensitivity of high-risk HPV testing (0.92 ; 95% confidence interval [CI], 0.90 to 0.94) for detecting posttreatment CIN 2 or worse (CIN 2+) was much higher than that of cytology (0.76 ; 95% CI, 0.71 to 0.80). Co-testing of HPV testing and cytology maximized the sensitivity (0.93 ; 95% CI, 0.87 to 0.96), while HPV genotyping (detection of the same genotype between pre- and posttreatments) did not improve the sensitivity (0.89 ; 95% CI, 0.82 to 0.94) compared with high-risk HPV testing alone. The specificity of high-risk HPV testing (0.83 ; 95% CI, 0.82 to 0.84) was similar to that of cytology (0.85 ; 95% CI, 0.84 to 0.87) and HPV genotyping (0.83 ; 95% CI, 0.81 to 0.85), while co-testing had reduced specificity (0.76 ; 95% CI, 0.75 to 0.78). For women with positive surgical margins, high-risk HPV testing provided remarkable risk discrimination between test-positives and test-negatives (absolute risk of residual CIN 2+ 74.4% [95% CI, 64.0 to 82.6] vs. 0.8% [95% CI, 0.15 to 4.6] ;  $pp<0.001$ ). **Conclusion** Our findings recommend the addition of high-risk HPV testing, either alone or in conjunction with cytology, to post-treatment surveillance strategies.

### ISP-36-5

**Conservative management for cervical intraepithelial neoplasia during pregnancy** Misato Ogino, Yasuhiko Ebina, Mizuki Uenaka, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

**Objective** To assess the safety and efficacy of conservative management for intraepithelial neoplasia (CIN) during pregnancy. **Methods** In this prospective study, 60 pregnant women who were diagnosed as having abnormal cervical cytology underwent colposcopy between 2010 and 2016. A punch biopsy was performed in cases with abnormal colposcopy findings. Conservative management was performed in women without invasive cancer. All women underwent cervical cytology every 4 months during pregnancy, and cervical cytology as well as colposcopy 2 months postpartum. Rates of persistence, progression and regression of CIN were assessed. Whether the delivery mode affected the regression of CIN was also assessed. **Results** The age of women was median 30 (range 20-39) years old. A punch biopsy was performed in 48 (80%) of the 60 women, and demonstrated CIN1 (n=7), CIN2 (n=8) and CIN3 (n=25). Postpartum regression, persistence and progression of lesions were observed in 12 (30.0%), 25 (62.5%), and 3 (7.5%) of the 40 women with CIN, respectively. No progression to invasive cancer was observed. Women who had CIN3 lesion showed high persistence/progression rates (80.0% versus 46.7%,  $p=0.041$ ) when compared with women who had CIN1/2. The regression rate in women who delivered vaginally was not different (32.0% versus 33.3%,  $p=0.93$ ) from that in women who underwent cesarean section. **Conclusion** Conservative management for CIN during pregnancy was found to be relevant for pregnant women with CIN. The delivery mode did not affect the regression of CIN.

## ISP-36-6

**Decision-making with fathers should influence the acceptance of HPV vaccine for their daughters** Mariko Shindo, Sahori Kakuda, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

**Objective** In Japan, HPV vaccination rate has remained low since the suspension of the governmental recommendation in 2013. A previous survey showed that mothers decided not to vaccinate their daughters under the present condition without talking with fathers. The objective of the present study was to assess father's role in HPV vaccination of their daughters for improvement of HPV immunization coverage in Japan. **Methods** We conducted an internet survey with Japanese fathers of 18-22-year-old girls who could have HPV vaccination under the governmental recommendation (n=2,472). We assessed father's attitude toward HPV vaccine and investigated how they were involved in decision-making of their daughters' inoculation. **Results** A total of 1177 fathers knew their daughter's HPV vaccination status (48%), and among them, 1012 fathers were involved in family council (41%). Father's participation in decision-making was associated with increased odds of vaccination of their daughters (odds ratio : 3.9, 95%CI : 2.35-6.46). When fathers had positive attitude to HPV vaccine, the relationship between father's participation in decision-making and their daughter's inoculation was enhanced (odds ratio : 10.51, 95%CI : 5.16-21.62). **Conclusion** In order to facilitate HPV vaccination, especially after resumption of the governmental recommendation, we should inform not only mother's but should focus on further's education. The health providers need to fill the knowledge gap between husband and wife, and promote a positive father's participation in decision-making.

## ISP-36-7

**Human papilloma virus (HPV) vaccination in Japan : An estrangement between self-reported information and municipal personal record of HPV vaccination in Japanese young women** Manako Yamaguchi<sup>1</sup>, Masayuki Sekine<sup>1</sup>, Risa Kudo<sup>1</sup>, Sosuke Adachi<sup>1</sup>, Asami Yagi<sup>2</sup>, Yutaka Ueda<sup>2</sup>, Sharon Hanley<sup>3</sup>, Etsuko Miyagi<sup>1</sup>, Takayuki Enomoto<sup>1</sup> *Niigata University<sup>1</sup>, Osaka University<sup>2</sup>, Hokkaido University<sup>3</sup>, Yokohama City University<sup>1</sup>*

**Objective** The national routine vaccination program against uterine cervical cancer began from April 2013 in Japan and approximately 1,700 municipalities has managed the immunization records. However, all of the published clinical studies about the efficacy of in HPV vaccination based on self-reported vaccination information in Japan. The present study was aimed to examine the accuracy of self-reported information. **Methods** We recruited 20 to 22-year old young women, target generation of HPV vaccination with public aid, when they had uterine cervical cancer screening in Niigata city. The period of recruitment was from April 2014 to March 2017. We examined past medical history of HPV vaccination from questionnaires (self-reported information) and compared those with the municipal immunization records in Niigata city. **Results** Of 1,230 eligible registrants, the vaccination rate by self-reported information and municipal records was 75.0% (922/1,230) and 77.2% (949/1,230), respectively. The accuracy rate of self-reported information was as follows : positive predictive value was 87.7% ; negative predictive value was 54.5% ; sensitivity was 85.2% ; and specificity was 59.8%. A Kappa statistic was 0.44 (95% confidence interval 0.37-0.50). Approximately 11.4% (140/1,230) of all registrants have not recollected that they had received vaccination at adolescence and they comprised 45% (140/308) of unvaccinated group in self-reported information. **Conclusion** Our study demonstrates that there was an unignorable estrangement between self-reported vaccination status and municipal personal records

in HPV vaccination with public aid in Japan. About 10% of women of 20 to 22-year old have ambiguous memory whether they received HPV vaccination at adolescence.

## ISP-36-8

**Management of cervical high-grade squamous intraepithelial lesions (HSIL) during pregnancy** Yusuke Matsuura<sup>1</sup>, Satoshi Aramaki<sup>2</sup>, Hiroshi Mori<sup>2</sup>, Chiho Koi<sup>3</sup>, Taeko Ueda<sup>3</sup>, Tomoko Kurita<sup>3</sup>, Seiji Kagami<sup>3</sup>, Toshinori Kawagoe<sup>3</sup>, Toru Hachisuga<sup>3</sup> *Nursing of Human Broad Development, University of Occupational and Environmental Health<sup>1</sup>, Hospital of the University of Occupational and Environmental Health<sup>2</sup>, University of Occupational and Environmental Health<sup>3</sup>*

**Objective** Early uterine cervical neoplasms and invasive cancers have been increasing gradually in young women. The women with cervical neoplasia are often diagnosed in early gestation. We studied the management of women diagnosed with HSIL during pregnancy. **Methods** During the five years from 2010 to 2014, 1,326 pregnant women came to our University Hospital, and the routine Papanicolaou test with cotton swab was performed in 89% (625 of 705). Thirty-five (5.6%) showed abnormal cytologic results. HSILs were seen in 28 patients (17 moderate dysplasia and 11 severe dysplasia), and were compared to 92 non-pregnant women with moderate dysplasia below the age of 50 around the same period. **Results** Underestimation by cervical Pap test in pregnancy occurred in 18% and overestimation in 28%. Underestimation of cytology were encountered in 25% (7 of 28) pregnant women with HSIL, and were detected in 45% (41 of 92) non-pregnant women with moderate dysplasia by brush. Moderate dysplasia had disappeared in 3 of 17 cases, progression was noted in 7 patients. Conization was performed in 6 patients, and radical abdominal hysterectomy was performed in one patient. Persistent disease was noted in 9 of 11 patients with severe dysplasia. Regression, persistence and progression were detected in 35%, 35%, and 30%, respectively, and conization was performed in 37 of 92 non-pregnant patients with moderate dysplasia. **Conclusion** The incidence of abnormal Pap test is the same in pregnant and nonpregnant women. Moderate dysplasia during pregnancy should be followed carefully as non-pregnant women after delivery.

## ISP-36-9

**Physicians' skill may be a prognostic factor of cervical intraepithelial neoplasia after CO<sub>2</sub> laser vaporization** Koichiro Kawano, Jongmyung Park, Hiroki Nasu, Ken Matsukuma, Atsumu Terada, Shin Nishio, Naotake Tsuda, Kimio Ushijima *Kurume University*

**Objective** To confirm whether physicians' skill may affect the recurrence rate of cervical intraepithelial neoplasia (CIN) 2/3 after CO<sub>2</sub> laser vaporization. **Methods** Women who underwent vaporization in diagnosis of CIN2/3 among 2001 and 2014 and followed longer than 1 year were enrolled in this study. Recurrence was defined as histologically confirmed CIN2/3 within 2-year of vaporization. We examined the recurrence rate of top 15 operators. Factors related to physicians were discriminated by the years of experience and the number of vaporizations. Recurrence risk factors were analyzed by logistic regression analysis. Recurrence rate by physician was analyzed according to the risk factor and the number of vaporization. **Results** In total, 381 patients were enrolled. Mean age was 32.9±6.7 years old. Median number of vaporization by each physician was 18 (range : 14-56). Recurrence rate of CIN was 13.6%. Recurrence rate in each physician was 0 to 37.5%, which was statistically significant difference (p<0.001). Years of experience of physicians did not correlate with recurrence. Three-quadrant disease (TD) was identified as a risk factor of recurrence (p<0.001). Recur-

rence rate in TD and non TD was 24.6% and 8.8%, respectively. In non TD, recurrence tended to decrease with the number of vaporization, but not in TD. However, recurrence did not decrease with the number of vaporization in 3 physicians who had more than 14% of recurrence rate in non TD. **Conclusion** Recurrence rate of CIN2/3 after vaporization differs depending on physician. Physicians who had more than 14% of recurrence will need re-education.

### ISP-36-10

**Interim results of a cohort study assessing efficacy of cervical cytology and HPV testing as modalities for population-based cervical cancer screening** Tohru Morisada<sup>1</sup>, Kumiko Saika<sup>2</sup>, Eiko Saitou<sup>3</sup>, Kanako Kono<sup>2</sup>, Masaru Nakamura<sup>1</sup>, Takashi Iwata<sup>1</sup>, Kyoko Tanaka<sup>1</sup>, Hiroshi Saito<sup>2</sup>, Mamoru Tanaka<sup>1</sup>, Daisuke Aoki<sup>1</sup> *Keio University<sup>1</sup>, Center for Public Health Sciences, National Cancer Center<sup>2</sup>, IUHW Mita Hospital<sup>3</sup>*

**Objective** Introduction of HPV testing in cervical cancer screening has been studied from the viewpoint that HPV testing is a more sensitive modality. This study was launched as a cohort study evaluating the HPV testing and verification project conducted in the Ministry of Health, Labor and Welfare's cancer screening promotion project. The morbidity rate of cervical intraepithelial lesion grade 3 or worse (CIN3+) and benefits and harms of introduction of HPV testing into cervical cancer screening will be examined. We aimed to provide the results of first round screening and the compliance rates for a detailed examination and subsequent screening. **Methods** The project was conducted in population-based cervical cancer screening program in local governments. Subjects were tested using cytology alone (control group) or cytology and HPV testing (intervention group). The results of first round screening and the compliance rates for a detailed examination and subsequent screening were examined. **Results** This study included 25,078 women in 39 local governments. For participants in the initial registration, the compliance rate for a detailed examination in cases referred for immediate check-up was 89.3%, whereas in newly appearing cases in the intervention group who were referred for cytology after 12 months, the compliance rate was only 53.0% and the compliance rate for subsequent screening was 48.1%. **Conclusion** The results of this study show the importance of establishing a system that adjusts the interval of consultation based on individual screening results and encouraging participants to have continuous screening when considering introduction of the HPV testing into population-based cervical cancer screening.

### ISP-37-1

**Introduction of HPV test for cervical cancer screening in Cambodia as low resource setting** Maryan Chhit<sup>1</sup>, Kanal Koun<sup>2</sup>, Chansoeung Sann<sup>2</sup>, Kyna Uy<sup>1</sup>, Yoshiko Nishigaya<sup>3</sup>, Sari Nakao<sup>4</sup>, Yasuyo Matsumoto<sup>5</sup>, Yutaka Ueda<sup>6</sup>, Kouji Banno<sup>7</sup>, Ruriko Nishino<sup>8</sup>, Noriko Fujita<sup>9</sup>, Tadashi Kimura<sup>6</sup> *Khmer-Soviet Friendship Hospital, Cambodia<sup>1</sup>, Cambodian Society of Gynecology and Obstetrics, Cambodia<sup>2</sup>, Kyorin University<sup>3</sup>, University of Tsukuba<sup>4</sup>, Omori Ladies' Clinic<sup>5</sup>, Osaka University<sup>6</sup>, Keio University<sup>7</sup>, All Japan Labour and Welfare Foundation<sup>8</sup>, National Center for Global Health and Medicine<sup>9</sup>*

**Objective** In Cambodia, female factory workers are valuable group to support their family and Cambodian economy, but are difficult to consult the doctors because of their sift working and lack of knowledge. We conducted the first cervical cancer screening in the factory to find out the feasible method with quality in low resource setting. **Methods** In January 2017, SCGO project started preparation by advise of JSOG and decided to use hybrid capture HPV detection for the screening because of its simple procedure and cost benefit. Also we made the stan-

dard procedures, trained human resources to examine HPV test and managed bar code registration for screening. The target factory was with 1,000 female workers, average age of 24 years old and about 20% married. In June 2017, the implementer team composed of 2 doctors, 3 nurses, and 2 secretaries conducted the screening at Phnom Penh Special Economic Zone. All samples were double checked by two laboratories. **Results** Forty-four female factory workers, rage of age are 20 years old to 44 years old (median 29 years old) ever married or with partners were applied for the screening and 31 was screened. Four cases are HPV positive, but no one came for secondary check till September 2017. The first cervical cancer screening among Cambodian factory workers showed HPV positive rate of 12%. The registered female workers were about 20% of targeted people. **Conclusion** Challenges are to promote cervical cancer screening and to connect first screening and secondary check.

### ISP-37-2

**Comparative Study of the effect of cervical cancer screening by Liquid-Based Cytology and High-Risk Human Papillomavirus detection in Inner Mongolia** Xianzhi Duan<sup>1</sup>, Yanbo Song<sup>2</sup>, Shaoming Wang<sup>3</sup>, Dan Dong<sup>1</sup>, Yongdong Zhang<sup>1</sup> *Tongren Hospital of Beijing, China<sup>1</sup>, Yizhuang Hospital of Beijing, China<sup>2</sup>, Cancer Hospital of Chinese Academy of Medical Sciences, China<sup>3</sup>, Population and Family Planning Bureau of Zhungeer of Inner Mongolia, Mongolia<sup>4</sup>*

**Objective** To investigate the effect of cervical cancer screening by liquid-based cytology and high-risk human papillomavirus (HPV) detection in Inner Mongolia, and to provide scientific data for the selection of primary screening technologies of cervical cancer in Inner Mongolia. **Methods** From 2012 to 2014, 30,118 women aged 20~70 were screened by the Thinprep liquid-based cytology (TCT) and the Cervista HPV detective method for cervical cancer in Inner Mongolia. Those with abnormal cytological results or HPV infection were referred to colposcopy examination, and biopsy was taken for pathological confirmation. **Results** The rate of positive cytology result and HPV infection was 5.54% and 23.18%, respectively. A9 group was the most common HPV types with a positive rate of 7.77%. The predominated HPV types were the same for the Han nationality and Mongolian. Both the total HPV infection rate and A9 group HPV infection rate were positively associated with the grade of cytological abnormality. The positivity of A9 HPV type was increased by the pathological grades. The consistence (84.71%) between TCT and Cervista for the detection of high grade cervical intraepithelial neoplasia (CIN2+) was high. The two methods worked as supplementary for each other. Twenty-six cases were detected by the HPV test while missed by the TCT, and 19 cases with negative HPV results were found by TCT. The combination of the two methods increased the detective rate of CIN 2+ from 84.71% to 98.47% (P<0.05). **Conclusion** The consistence of TCT and Cervista for the detection of CIN2+ was good. TCT and Cervista can be used as effective methods for cervical cancer screening in various areas with different health resources, and their combination can increase the accuracy.

### ISP-37-3

**Cervical Cancer in Women with Squamous Cell Carcinoma Cytology** Chumnan Kietpeerakool, Kaniknun Noonlamtong, Amornrat Temtanakitpaisan, Pilaiwan Kleebkaow, Apiwat Aue-Aungkul, Bundit Chumworathayi, Sanguanchoke Luanrananakorn *Khon Kaen University, Thailand*

**Objective** To determine rate of cervical cancer among women with squamous cell carcinoma (SCCA) cytology and associated risk factors. Results were pooled with previously reported findings. **Methods** We reviewed data regarding women with SCCA



cytology undergoing colposcopy at Khon Kaen University Hospital between October 2008 and March 2016. We also performed a meta-analysis incorporating this study and previous studies retrieved in order to provide the pooled rate of cervical cancer among women with SCCA cytology. A random-effects model was applied for meta-analysis. **Results** Data of 69 patients were reviewed. After colposcopy, 64 patients underwent cervical conization and/or hysterectomy and the five remaining patients underwent colposcopically-directed biopsy only. Thirty-six patients (52.2% ; 95% CI, 40.1% to 64.3%) had invasive lesions, all of which were cervical cancer. There were no significant associations between the patients' age, level of education, menopausal status, parity status, infection with human immunodeficiency virus, or symptoms presented during the cervical smear and the rate of invasive cervical cancer. After combining the data from this study with data from six other eligible studies, which were retrieved from a search of standard bibliographic databases, the pooled rate of cervical cancer among women with SCCA cytology was 56% (95% CI, 36% to 77%). **Conclusion** Approximately half of women with SCCA cytology in this study harbored cervical cancer. No significant factors predicting underlying cervical cancer were noted. By means of meta-analysis, the pooled rate of cervical cancer among women with SCCA cytology was found to be 56%.

#### ISP-37-4

##### **A study of the effectiveness and safety of Bevacizumab combination therapy for advanced or recurrent cervical cancer**

Satomi Kameda, Masafumi Toyoshima, Yoshiko Oyama, Asami Toki, Tomoyuki Nagai, Michiko Kaiho, Hideki Tokunaga, Muneaki Shimada, Hitoshi Niikura, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** Bevacizumab (Bev), an angiogenesis inhibitor, has been used for the treatment of advanced or recurrent cervical cancer, but there are only few reports in Japan. In order to investigate the efficacy and safety of Bev-combination therapy, we retrospectively studied the experiences in our hospital. **Methods** This study was approved by our institute. We examined the clinical data of the patients who underwent Bev-combined therapy during May 2016 and July 2017 in our hospital. **Results** The subjects were 10 cases and median age was 58.3 years. The number of stage I/II/III/IV were 3/1/1/5, respectively. Initial and recurrence treatment was 4 and 6, respectively. Administration regimen was TP-Bev (5) and TC-Bev (5), and 3 patients were changed to Bev single-maintenance therapy because of side effects. The median number of administrations was 8.2. The response rates were 25% (CR : 0, PR : 1, SD : 2, PD : 1) in initial treatment group and 83% (CR : 2, PR : 3, SD : 0, PD : 1) in recurrence treatment group, respectively. The common side effects were neutropenia, hypertension, nose bleeding and thrombocytopenia. However, there were no serious side effects such as gastrointestinal perforation and fistulas. There were 4 patients who have a risk factor such as hypertension history (1), DVT history (1) and brain metastasis (2), but these patients could continue Bev-combination therapy without serious side effects. **Conclusion** The response rate of Bev-combination therapy for advanced or recurrent cervical cancer patients was 60%, indicating very high effectiveness. Side effects were acceptable even in cases with a risk factor, and treatment continuation was possible in many cases.

#### ISP-37-5

**Examination of adverse gastrointestinal tract events in cases using Bevacizumab for cervical cancer in our department**  
Satoshi Nishiyama, Takako Hikari, Asako Fukuda, Satoko Tsuda, Makiko Kurihara, Maiko Kato, Misako Hideshima,

Hiroshi Watanabe, Yukihiko Nakayama, Mariko Hashiguchi, Yoshifumi Nakao, Masatoshi Yokoyama *Saga University*

**Objective** Bevacizumab (Bev), a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is indicated for advanced cervical cancer or recurrence of cervical cancer. Some serious adverse events, including gastrointestinal perforation, vesicovaginal/rectovaginal fistulas, and arteriovenous thrombosis were reported. In particular, adverse gastrointestinal tract events can deteriorate activities of daily living (ADL). Therefore, we must be careful when we use Bev. We examined adverse gastrointestinal tract events in cases using Bev for cervical cancer in our department. **Methods** A retrospective review of patients who received chemotherapy including Bev was performed. **Results** Between December 2016 and March 2017, nine patients received chemotherapy include Bev. All patients received cisplatin (50mg/m<sup>2</sup>) and paclitaxel (135mg/m<sup>2</sup> infused over 24 hour) and Bev (15mg/kg). Serious adverse events (more than G3 in CTCAE) included one gastrointestinal perforation, two vesicovaginal/rectovaginal fistulas, one paralytic ileus, and one arteriovenous thrombosis. In all cases, radiotherapy was administered before Bev therapy. Gastrointestinal perforation or fistula cases were irradiated by 30-55.8Gy extrapelvic irradiation and 24-30Gy Intracavitary irradiation. The ileus case resulted from hysterectomy as first therapy, and concurrent chemoradiotherapy as adjuvant therapy, although the patient was not irradiated to the para-aortic lymph nodes region. **Conclusion** In our study, radiation dose, hysterectomy, and the site of the active lesion may be associated with the onset of adverse gastrointestinal tract events. However, we could not determine clear tendencies due to the limited number of cases. Further studies are needed in order to provide safer Bev therapy.

#### ISP-37-6

**Clinical outcomes of bevacizumab in five recurrent patients with uterine cervical cancer after concurrent chemoradiotherapy**  
Takashi Ushiwaka, Yayoi Higuchi, Yusuke Ujihara, Ruriko Yamada, Nagamasa Maeda *Kochi Medical School*

**Background** Bevacizumab (Bev) has been approved to the recurrent uterine cervical cancer. We accessed the clinical outcome of Bev in 5 patients with recurrent cervical cancer performed CCRT. **Cases** Mean age was 58 years old. FIGO stage of 2 cases was 3B and 3 were 4B. Histological type of 4 cases was squamous cell carcinoma and 1 was adenosquamous cell carcinoma. All patients were received CCRT for primary therapy. 4 patients had lymph nodes recurrence and 1 had lung metastasis. 4 patients were received other chemotherapy before Bev because of previous recurrence after CCRT. Conventional chemotherapy was performed with Bev ; TC, weekly TC, DC, and CPT-11. Mean cycle of Bev administration was 4.6. Clinical outcome was 2 CR, 2 PR, and 1 PD after Bev. Adverse effects were 3 hypertension, 3 proteinurias, 1 intestinal perforation, 1 recto-vaginal fistula, and 1 ileus. Administration of Bev was discontinued in 2 patients with intestinal perforation and recto-vaginal fistula. **Discussion** Though the chemotherapy with Bev for recurrent cervical cancer may be effective, but there are severe adverse effects. According to our investigation, after CCRT, 2 patients with intestinal perforation and recto-vaginal fistula started Bev earlier than other patients without severe complications. **Conclusion** When applying Bev for recurrent cervical cancer, we have to obtain sufficient informed consent for possibility of severe adverse effects. We conclude that it is necessary to establish the application criteria to predict and prevent severe adverse effects such as intestinal perforation and recto-vaginal fistula by Bev.

## ISP-37-7

**Radiation therapy for para-aortic lymph node metastasis diagnosed by various imaging modalities and prognosis for advanced uterine cervical cancer** Kaho Suzuki, Yasuhiko Ebina, Yoshiya Miyahara, Senn Wakahashi, Hideto Yamada *Kobe University*

**Objective** Various imaging modalities are used to define radiation field before primary therapy in Japan. If we detected metastasis to para-aortic lymph node (PAN) in patients with advanced uterine cervical cancer, adequate treatment leads to prevent a recurrence. This study aimed to evaluate the association between para-aortic metastasis lymph node metastasis diagnosed by various imaging modalities and prognosis. **Methods** We conducted a retrospective study for women who were diagnosed as having stage IB-IVA cervical cancer between January 2010 and December 2016. A total of 46 patients were enrolled. All patients underwent various imaging modalities prior to radiation therapy (CCRT or RT). Patients were divided into two groups according to diagnostic imaging. The patients in group A had positive pelvic lymph node (PLN) and negative PAN. The patients in group B had positive PLN and positive PAN. The survival and recurrence rate of each group were assessed. **Results** The median age of all patients was 64 years (range 24-89). The median follow-up time for all patients was 18 months (range 2-84). Significant differences of prognosis (PFS, OS) were observed between Group A and B ( $p < 0.05$ ). Significant differences in rates of recurrence were observed between Group A and B ( $p < 0.05$ ). **Conclusion** For patients who had positive PLN and positive PAN, adjuvant chemotherapy might be considered because of the high rate of recurrence.

## ISP-37-8

**Treatment outcome of the definitive high-dose-rate brachytherapy combined with external beam pelvic radiotherapy for patients with uterine cervical cancer** Hiroshi Matsushima<sup>1</sup>, Taisuke Mori<sup>1</sup>, Morio Sawada<sup>1</sup>, Haruo Kuroboshi<sup>1</sup>, Hiroshi Tatsumi<sup>1</sup>, Shiori Umemura<sup>1</sup>, Kaori Yoriki<sup>1</sup>, Tetsuya Kokabu<sup>1</sup>, Jo Kitawaki<sup>1</sup> *Kyoto Prefectural University of Medicine<sup>1</sup>, Department of Radiology, Kyoto Prefectural University of Medicine<sup>2</sup>*

**Objective** The objective is to assess the efficacy and tolerance of high-dose-rate brachytherapy (HDR-BT) combined with external beam pelvic radiotherapy (EBRT) for patients with cervical cancer. **Methods** A total of 35 patients with uterine cervical cancer, treated with the definitive HDR-BT with or without cisplatin (40 mg/m<sup>2</sup>, q 1 week) from April 2009 to August 2015, were retrospectively analyzed. Toxicities were evaluated according to Common Terminology Criteria for Adverse Events version 4.0 and the responses by the treatment were examined according to RECIST-criteria. The primary and the secondary endpoints were 2-year OS and 2-year PFS, respectively. **Results** The median age was 61 year-old (range 35-89). Median follow-up period was 33.7 months (range 4.0-100.6). Of the 35 patients, one patient was classified as stage I (FIGO 2009), 15 were as stage II (42.8%), 12 were as stage III (34.2%), 7 were as stage IV (20%). Twenty-five patients (71.4%) had pelvic lymph nodes metastasis. The complete response (CR) rate was 72.7%. The 2-year OS rate was 79%, 2-year PFS rate was 50.8%. Local control rate was 87.2%. The mild (grade 1/2) late complications was observed in 14 patients (40%), and the severe (grade 3) complication was seen in 2 patients (5.7%). Vesico-vaginal fistula and rectovaginal fistula were observed in the 2 patients. No grade 4 complication was observed. **Conclusion** HDR-BT combined with EBRT will be considered as a treatment option for patients with locally advanced uterine cancer.

## ISP-37-9

**Two cases of uterine cervical adenocarcinoma with successful systemic chemotherapy** Hiroshi Kaneda, Shun Masaoka, Saki Ito, Sachi Sukeyawa, Shiori Nishizawa, Norikazu Ueki, Yoshiko Murase, Satomi Tanaka, Shotaro Yata, Yuka Yamamoto, Toshitaka Tanaka, Naoki Mitsushashi *Juntendo University Shizuoka Hospital*

Cervical adenocarcinoma is less frequent than cervical squamous cell carcinoma, progress is faster and chemotherapy is more difficult to be successful, so early treatment is important and surgical therapy is primarily chosen. We report two cases in which systemic chemotherapy was successful against cervical adenocarcinoma. **Case 1** 72-year-old woman with liver and pulmonary metastasis, diagnosed as FIGO I V B, was performed 6 courses of systemic chemotherapy of DC therapy (docetaxel and carboplatin). CA125 was under normal value in addition pulmonary and liver metastasis were disappeared, but ovarian tumor was found about 1 year later and therefore surgery were performed as total hysterectomy and bilateral salpingo-oophorectomy. Pathological diagnosis of ovary was carcinosarcoma and there was no cancer lesion in the uterine cervix. **Case 2** 82-year-old woman diagnosed as FIGO I I B performed six courses of systemic chemotherapy of DC therapy because of elderly. After chemotherapy total hysterectomy was performed because loss of measurable lesion was obtained. Systemic chemotherapy and concurrent chemoradiotherapy are main methods of treatment other than surgery for cervical cancer, and platinum drug is mainly selected for chemotherapy. Cervical adenocarcinoma is considered to have lower response rate of chemotherapy than squamous cell carcinoma, but I would like to report on two cases that have been effective with systemic chemotherapy for future treatment method.

## ISP-37-10

**Limitation of postoperative adjuvant chemotherapy (paclitaxel and carboplatin) for treatment of cervical cancer stage I/II patients at high risk of recurrence** Yuki Okuma, Takehiro Nakao, Erina Hashimoto, Remi Hasegawa, Akiko Kasuga, Hiromitsu Azuma, Chuyu Hayashi, Atsushi Komatsu, Yasuji Miyagawa, Shinichi Takada, Fumihisa Chishima, Kei Kawana *Nihon University*

**Objective** Postoperative adjuvant therapy is recommended for cervical cancer patients at high-risk and intermediate-risk of recurrence. While concurrent chemo-radiotherapy (CCRT) is recommended for the adjuvant therapy, some clinical trials of adjuvant chemotherapy for cervical cancer had been conducted. We here examined the clinical efficacy of adjuvant TC (paclitaxel and carboplatin) for patients at risk of recurrence. **Methods** Under approval of Ethical committee in our hospital, 21 cervical cancer patients (FIGO IB=10, IIA=3, IIB=8) who received postoperative adjuvant therapy chemotherapy (TC : paclitaxel [175mg/m<sup>2</sup>] and carboplatin [AUC=6.0]) were investigated (follow-up time : 6-50m, median=19m). We defined lymph node metastasis (LN), parametrium invasion (Pmm), and bulky tumor (>4cm : Bulky) as high-risk and vascular-lymphatic infiltration (VLI) as intermediate-risk of recurrence. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier plot and cox-hazard proportional model. **Results** 17 and 4 patients had high-risk and intermediate-risk factors of recurrence, respectively. 3ys-OS of all patients was 60.5% and 2 ys-PFS was 52.2%, which seemed to be worse than those in general. Cox-hazard model did not detect any independent clinicopathological factor for recurrence. Among nine recurrent patients, six (67%) had recurrence of vaginal stump and all had VLI. **Conclusion** The prognosis of our patients received adjuvant TC seemed to be clearly worse when compared with gen-



eral data of patients received adjuvant CCRT. Since the multivariate analysis did not identify any pathological factor, adjuvant TC might be the most responsible factor resulting in poor prognosis. Our data suggested that adjuvant chemotherapy using TC is not recommended for cervical cancer.

### ISP-38-1

**A case of acute abdominal pain caused by the infarcted parasitic leiomyoma** Yoojung Lee, Jin Woo Shin, Chan Mi Lim, Da hoe Jung *Gachon University of Medicine and Science, Korea*  
**Introduction** Parasitic leiomyomas are rare gynecologic conditions of the incidence ranged from 0.12 to 0.95%. Most case presented as pelvic mass on image such as ultrasonography and CT scan without clinically significant symptoms. The authors report a case of infarcted parasitic leiomyoma after laparoscopic myomectomy, which presented as acute abdominal pain. **Case** A 37-year-old woman underwent laparoscopic myomectomy with power morcellation for removing leiomyoma through trocar site at 12 years ago, came to clinic with acute right lower abdominal pain for 2 days. CT scan revealed multiple intra-abdominal mass. Total of five leiomyomas were removed (up to 6.2cm) with one of which were seeded on right lower part of omentum just the site of patient's tender point and histopathological examination confirmed the infarcted leiomyoma. After removing the infarcted leiomyoma, the abdominal pain was subsided and the patient recovered without complication. **Conclusion** When a woman, who had a history of laparoscopic myomectomy, complaint acute abdominal pain, infarcted parasitic leiomyoma should be considered.

### ISP-38-2

**The value of serum LDH, CRP and D-dimer levels for differentiation among degenerated leiomyoma, variant type leiomyoma and leiomyosarcoma** Kaori Kiuchi<sup>1</sup>, Kiyoshi Hasegawa<sup>1</sup>, Ayano Suzuki<sup>1</sup>, Mariko Watanabe<sup>1</sup>, Nobuaki Kousaka<sup>1</sup>, Takanori Sakamoto<sup>1</sup>, Yoshiko Nishigaya<sup>2</sup>, Yoichi Kobayashi<sup>2</sup>, Ichio Fukasawa<sup>1</sup> *Dokkyo Medical University<sup>1</sup>, Kyorin University<sup>2</sup>*

**Objective** The differential diagnosis of degenerated leiomyoma (dLM) or variant type leiomyoma (vLM : cellular LM or LM with bizarre nuclei) from leiomyosarcoma (LMS) using MRI findings is sometimes difficult. Therefore, in this study, we evaluated the value of serum LDH, CRP and D-dimer levels for differentiation among these diseases. **Methods** Thirteen patients with dLM, six with vLM and five with LMS (three with FIGO stage Ib and two with IIIb) who underwent surgery after 2010 were recruited. The serum LDH, CRP and D-dimer levels were compared among these patients groups. Patients with apparent infectious diseases or thromboembolism were excluded. **Results** The serum LDH level was elevated in 1/13 patients with dLM and in 4/5 with LMS. The serum CRP level was elevated in 1/6 patients with vLM and 5/5 with LMS. The serum D-dimer level was elevated in 1/13 patients with dLM, 1/6 with vLM, and 5/5 with LMS. The serum levels of these three parameters in patients with LMS were significantly higher. Elevated serum levels of all three parameters indicated a diagnosis of LMS, with a sensitivity of 80%, specificity of 100%, positive predictive value (PPV) of 100% and accuracy of 95%. On the other hand, normal serum levels of all three parameters were indicative of not having LMS, with a sensitivity of 79%, specificity of 100%, PPV of 100% and accuracy of 83%. **Conclusion** The serum levels of LDH, CRP and D-dimer may provide a diagnostic method supplementary to MRI findings for differentiation among dLM, vLM and LMS.

### ISP-38-3

**Preoperative prediction of uterine sarcoma using tumor to subcutaneous fat signal intensity ratio by T2 weighted imaging (TFSIR) and apparent diffusion coefficient (ADC) on magnetic resonance imaging (MRI)** Yasuko Oka, Masanori Tamori *Komatsu Municipal Hospital*

**Objective** Preoperative diagnosis of uterine sarcoma is difficult. The author focused on TFSIR and ADC, and previously presented. The purpose of this study is to improve the reliability through further investigations of previous and additional cases. **Methods** MRI was performed in 6 cases (7 tumors) of uterine sarcoma in the last 3 years (sarcoma group), and 31 cases of leiomyoma in 2015 (myoma group). The author calculated TFSIR and ADC, and determined threshold value for each. Finally, a preoperative prediction method using these parameters was considered through the application to the 40 tumors in 2016. This protocol has been approved by the local institutional review board of ethics. **Results** The sarcoma group had significantly higher TFSIR and lower ADC than the leiomyoma group ( $p < 0.01$ ). The minimum cutoff value of TFSIR to diagnose sarcoma is 0.515 (sensitivity 100%, specificity 94%), and the maximum cutoff value of ADC is 1.280 (sensitivity 86%, specificity 87%). All tumors with both positive TFSIR and ADC were sarcoma (High suspicion group). All tumors with negative TFSIR were leiomyoma (low suspicion group). Tumors with positive TFSIR and negative ADC included both (Intermediate group). Among 40 uterine in 2016, 2 belonged to the High suspicion group (all sarcoma), 3 belonged to the Intermediate group (all leiomyoma) and the other 35 tumors belonged to the Low suspicion group (all leiomyoma). **Conclusion** Preoperative prediction of uterine sarcoma is possible using both TFSIR and ADC on MRI.

### ISP-38-4

**Coincidental detection of diffuse large B-cell lymphoma in the inner inguinal lymph node of a woman undergoing pelvic lymph node dissection for uterine endometrial cancer** Kazuaki Ohashi<sup>1</sup>, Takako Shimada<sup>1</sup>, Ayumi Harada<sup>1</sup>, Daisuke Hamaguchi<sup>1</sup>, Michio Kitajima<sup>1</sup>, Atsushi Yoshida<sup>1</sup>, Masanori Kaneuchi<sup>2</sup>, Kiyonori Miura<sup>1</sup>, Hideaki Masuzaki<sup>1</sup> *Nagasaki University Hospital<sup>1</sup>, Otaru General Hospital<sup>2</sup>*

Simultaneous occurrence of non Hodgkins lymphoma (NHL) and solid carcinoma such as colon, lung, breast cancers have been reported. However, synchronous non Hodgkins lymphoma (NHL) and endometrial carcinoma is relatively rare. We report a case of coincidental detection of diffuse large B-cell lymphoma (DLBCL) in the inner inguinal lymph node of a woman undergoing pelvic lymph node dissection for uterine endometrial cancer. The patient was 69-year-old woman and she was aware of increase of the vaginal discharge. She did not have any other symptoms, including genital bleeding, fever, weight loss, or night sweats. She was diagnosed as uterine endometrial carcinoma FIGO clinical stage1A. Laparoscopic hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection was performed. The final pathological examination revealed endometrioid adenocarcinoma grade1 and DLBCL was detected in the inner inguinal lymph node. PET/CT could not detect any other lesions of the malignant lymphoma. We diagnosed her as uterine endometrial carcinoma FIGO surgical stage1A, and the malignant lymphoma as Ann Arbor clinical stage1. Therefore, the postoperative chemotherapy or radiotherapy for the endometrial carcinoma was unnecessary, six cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) for the malignant lymphoma was performed. The patient remains complete remission 8 months after surgery.

### ISP-38-5

**A case of leiomyosarcoma arising from subserosal leiomyoma** Maiko Yamaguchi, Soshi Kusunoki, Rie Seyama, Aya Takayama, Ayako Masuda, Takashi Hirayama, Kazunari Fujino, Yasuhisa Terao, Atsuo Itakura, Satoru Takeda *Juntendo University Hospital*

Uterine leiomyosarcoma (LMS) is a rare tumor. It has not been established if LMSs arise *de novo* or from pre-existing leiomyomas. We report a case of LMS arising from subserosal leiomyoma. A 47-year-old nullipara was diagnosed with a uterine tumor measuring 30 cm in diameter by pelvic MRI. The serum CA-125 level was 369 ng/ml and the WBC count and LDH level were elevated ( $13,000 \times 10^9/l$  and 565 IU/l). PET-CT revealed abnormal uptake ( $SUV_{max}=25.29$ ) into the abdominal tumor. At laparotomy, the huge tumor with solid and cystic components was shown to arise from subserosal leiomyoma, and invaded the great omentum and small intestine. Abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and small intestine resection were performed. Macroscopic findings showed that the LMS was attached to the subserosal leiomyoma without continuity between the tumor and the uterus. Our case supports the hypothesis that LMS can arise from pre-existing leiomyoma.

### ISP-38-6

**A rare case of a primary uterine perivascular epithelioid cell tumor (PEComa) treated with robotic hysterectomy and adjuvant chemotherapy** Mizuki Isayama, Manabu Sakurai, Nobutaka Tasaka, Azusa Akiyama, Ayumi Shikama, Sari Nakao, Hiroyuki Ochi, Takeo Minaguchi, Toyomi Satoh *University of Tsukuba*

Perivascular epithelioid cell tumors (PEComas) are rare neoplasms that express both myogenic and melanocytic markers. Uterine PEComas are usually clinically benign and can often be cured with surgery. However, there have been reported cases of aggressive clinical behavior. Standard treatment for such aggressive PEComas is still unestablished. We report a case of a 30-year-old Caucasian nulligravida with a high risk uterine PEComa. The patient was transferred after presenting to an outside hospital with lower abdominal pain. A diagnosis of PEComa was established from endometrial biopsy results. PET/CT showed no evidence of metastasis, and the tumor was localized within the uterus. Surgical management consisted of a robotic-assisted laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and pelvic sentinel lymph node mapping with bilateral external iliac lymphadenectomy. The specimen was composed of a solid component measuring  $4 \times 3.5 \times 3$  cm and a cystic component measuring  $9 \times 7 \times 5$  cm. Immunohistochemistry revealed HMB45 and SMA positivity. The tumor was classified as high-risk based on the WHO classification system based on its size, presence of necrosis, and high mitotic activity. The patient has now finished two cycles of adjuvant chemotherapy with Adriamycin (A) and Ifosfamide (I) ( $A 60mg/m^2$  day 1,  $I 2g/m^2$  day 1-3, every 21 days). The patient has tolerated the chemotherapy well. The prospective treatment course is to continue with Adriamycin and Ifosfamide. Due to the rarity of uterine PEComas, the effectiveness of adjuvant therapy is still unknown. However, our case reveals that a combination of Anthracycline and Ifosfamide could be considered as effective adjuvant treatment.

### ISP-38-7

**Multimodality therapy for the patients with advanced or recurrent uterine leiomyosarcoma** Mizuho Kuroshima, Yasuhiko Ebina, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

We report five cases (recurrent 3, advanced 2) of advanced or recurrent uterine leiomyosarcoma (LMS) treated with multimodality therapy including novel therapeutic agents. The median age of the patients was 50 years (range, 39 to 65 years). All patients were given chemotherapy; gemcitabine/docetaxel (GD) (n=5), doxorubicin (n=3), ifosfamide (n=2), pazopanib (n=3), trabectedin (n=1), and eribulin (n=1). Three patients underwent surgical resection of recurrent tumor, and three patients were treated with radiation therapy. Maximal efficacy of GD therapy, pazopanib, trabectedin, and eribulin were partial response, stable disease (SD), SD, and PD, respectively. GD therapy maintained stable disease for a long term; 17 courses (n=1) and 24 courses (n=1). SD for 10 months was obtained by pazopanib in one case. However, administration of pazopanib was impossible because of nausea in one case. SD for 5 months was found using trabectedin. After a median follow-up of 63.5 months, three patients had died of disease (29, 30, and 59 months), and two patients live with disease (68 and 80 months). In the three cases that long-term survival was obtained, multiple course of surgery or radiation for the recurrent site were performed. By using multimodality therapy long-term survival could be obtained for the patients with advanced or recurrent LMS.

### ISP-38-8

**Use experience of eribulin for recurrent uterine carcinosarcoma** Masato Nishimura, Ayuka Mineda, Takako Kawakita, Akiko Abe, Minoru Irahara *Tokushima University*

**Objective** Eribulin is a new medicine approved for sarcoma, however the effect is unclear for uterine carcinosarcoma. Second line therapy of carcinosarcoma has not been established for patient with resistance to paclitaxel and carboplatin (TC). We performed this study to clarify the safety and efficacy of eribulin for carcinosarcoma. **Methods**  $1.4mg/m^2$  of eribulin was administered at day 1 and 8 in 5 minutes. The treatment was repeated every 3 weeks. The dose was reduced to  $1.1mg/m^2$  after grade 3/4 neutropenia occurred. **Results** Treatment was administered in 4 patients (12 courses). Grade 3/4 leukopenia was seen in 2 patient (3 courses), neutropenic fever was seen in 1 patient. Duodenal hemorrhage was seen in 1 patient. Response was evaluated in all cases by RECIST. 1 PR, 1 SD, and 2 PD were confirmed. One case of PR was recurrent at 2 para-aortic lymphnodes after one year of surgery. The lymphnode enlarged from 52 to 64mm and 22 to 50mm after 3 courses of TC. Lymphnode was reduced to 42mm and 36mm after CCRT. CA 125 declined from 208 to 96 U/mL after CCRT. We administered eribulin after CCRT. The tumor still shrank to 27mm and 20mm after two courses of eribulin. CA125 elevated to 132U/ml during observation after CCRT, but reduced to 32U/mL after two courses of eribulin. In another case of SD, three recurrent tumors in the abdomen showed same size after 2 courses of eribulin but enlarged during waiting of surgery. **Conclusion** There is possibility that eribulin is effective for carcinosarcoma. Further investigation is needed.

### ISP-38-9

**Uterine sarcoma: 20-year Our hospital Experience of 21 Cases** Takanori Shimizu, Souta Tanaka, Sara Takahashi, Shohei Tanabe, Yoko Yoshida, Izumi Sato, Kaori Suenaga, Akiko Kasai, Goichiro Kasai, Takeshi Aida, Junko Kouno *Hachinohe City Hospital*

**Objective** Uterine sarcoma (US) is a rare tumor, comprising about 4-9% of all uterine malignancies. The aim of this study was to investigate the clinical feature of US in our hospital. **Methods** This study included 21 patients with histologically diagnosed uterine leiomyosarcoma (LMS): 17 patients and endometrial stromal sarcoma (ESS): 5 patients in our hospital

from 1997 to 2017. The medical records were reviewed retrospectively. **Results** The median age was 50 years (range, 40–79). The numbers of FIGO stages 1, 2, 3, 4 were 13, 3, 1, 4, respectively. Thirteen patients (61%) have recurrence of the disease. The most common recurrence site were lung and pelvis (each of 7 cases). Chemotherapy was administered to 8 recurrent patients. Best supportive care was carried out to 2 recurrent patients. Hormone therapy was given to 2 recurrent patients. Chemoradiation was given to 1 recurrent patient. Response rate of chemotherapy was 2 partial responses, 2 stable diseases and 4 progressive diseases. The median overall survival was 30 months (range, 4–223). The 5-year overall survival rate of the 21 patients was 66%. There is no difference with LMS and ESS in 5-year overall survival rate (53% vs 46%,  $p=0.453$ ). **Conclusion** It was indicated that US cases had high recurrent rate, even stage 1 (54%). Therapy of first recurrence was mainly chemotherapy in our hospital and the response rate of chemotherapy was only 25%, poor effect. New therapy such as molecular targeted drugs is expected for the better prognosis.

### ISP-39-1

**Development of a rapid preoperative diagnosis method to assess lymph node metastasis in uterine cancer** Emiko Yoshida<sup>1</sup>, Yasuhisa Terao<sup>1</sup>, Yosuke Ito<sup>1</sup>, Tsuyoshi Ota<sup>2</sup>, Michio Nojima<sup>2</sup>, Daiki Ogishima<sup>2</sup>, Hiroshi Kaneda<sup>1</sup>, Soshi Kusunoki<sup>1</sup>, Kazunari Fujino<sup>1</sup>, Takashi Hirayama<sup>1</sup>, Atsuo Itakura<sup>1</sup>, Satoru Takeda<sup>1</sup> *Juntendo University<sup>1</sup>, Juntendo University Urayasu Hospital<sup>2</sup>, Juntendo University Nerima Hospital<sup>3</sup>, Juntendo University Shizuoka Hospital<sup>4</sup>*

**Objective** Lymphadenectomy in endometrial carcinoma should be performed based on individualized considerations. In a previous study, we identified expression levels of SEMA3D and a novel isoform of TACC2 as promising biomarkers to evaluate lymphatic metastasis based on gene expression patterns in the primary lesion. Since cancer progress with time, diagnosis has to be completed just before performing lymphadenectomy during a single operation. A major difficulty for its clinical application is a requirement in speed of diagnosis. Here, we attempted to accelerate gene quantitative analysis for our biomarkers. **Methods** RT-SmartAmp is a method to detect nucleic acids in one step, which consists of a reverse transcription and an isothermal amplification of DNA. We chose it for RNA quantification in the required period of time. As a first step, we designed a set of primers for SmartAmp across the exon-exon junction of the novel TACC2 isoform. We measured the speed of amplification and target specificity based on cDNA. As a second step, we assessed the reaction based on RNA as the template in one step containing reverse transcription step. **Results** We succeeded to develop a promising candidate of primer set to detect the novel TACC2 isoform by using SmartAmp. This candidate can detect quantitatively within 30 minutes. **Conclusion** Our findings pave the way for support clinical decisions that minimize irrelevant lymphadenectomy. We are going to develop primer sets for the other candidate and control genes, with the aim to establish a system to quantify RNA abundance enabling assessment of lymph node metastasis.

### ISP-39-2

**The real frequency of localized para-aortic lymph node metastasis in endometrial cancer** Asami Toki, Hitoshi Niikura, Satoshi Okamoto, Tomoyuki Nagai, Yusuke Shibuya, Shoko Sakurada, Chiaki Hashimoto, Michiko Kaiho, Hideki Tokunaga, Masafumi Toyoshima, Muneaki Shimada, Nobuo Yaegashi *Tohoku University Hospital*

**Objective** Sentinel lymph node (SLN) mapping for endometrial cancer has become commonly, but the tracer injection site is

still controversial because there is patients occurred localized para-aortic lymph node metastasis through ovarian vessels. The purpose of this study was to clarify the real frequency of localized para-aortic lymph node metastasis without pelvic lymph node metastasis. **Methods** We analyzed pelvic lymph nodes of the patients who had metastasis only in para-aortic basin by ultrastaging method of serial section per 100 $\mu$ m and immunohistochemical staining (AE1/AE3). **Results** Between Apr 2009 to Nov 2016, 217 patients with endometrial cancer received pelvic and para-aortic lymphadenectomy. 32 (14.7%) were defined positive lymph node by conventional pathological method. 20 (9.2%) patients had metastasis in both pelvic and para-aortic basin, 8 (3.7%) had metastasis in only pelvic basin, and 4 (1.8%) had metastasis in only para-aortic basin. After the further analysis of ultrastaging, pelvic lymph node metastases could be identified in 3 of 4 patients. 2 had micrometastasis, and one had isolated tumor cells. **Conclusion** It was suggested that the real frequency of localized para-aortic lymph node was less than reported before. If we examine intrapelvic lymph node by SLN mapping with cervical injection, it would be possible to reduce missing para-aortic metastatic lymph node.

### ISP-39-3

**Is tumor size really an independent predictor of lymph node metastasis in endometrioid endometrial cancer?** Kento Ohnishi<sup>1</sup>, Koji Yamazawa<sup>1</sup>, Yuri Ogata<sup>1</sup>, Hiroki Akaba<sup>1</sup>, Tomoko Gota<sup>1</sup>, Asami Uenoyama<sup>1</sup>, Hajime Oishi<sup>1</sup>, Hirokata Nishi<sup>2</sup>, Miyuki Sadatsuki<sup>1</sup>, Tetsu Yano<sup>1</sup> *Center Hospital of the National Center for Global Health and Medicine<sup>1</sup>, Tokyo Medical University Hospital<sup>2</sup>*

**Objective** To evaluate tumor size as a predictor of lymph node metastasis in endometrioid endometrial cancer patients. **Methods** One hundred eleven patients with endometrioid endometrial cancer who underwent primary surgery including lymphadenectomy from January 2000 to December 2016 were reviewed. Pathological characteristics including tumor size, tumor grade, depth of myometrial invasion, adnexal involvement, cervical involvement, peritoneal cytology, lymphovascular space invasion, and lymph node metastasis were abstracted from the medical records. Univariate and multivariate analyses were performed to evaluate the correlation between the pathological characteristics and lymph node metastasis. Two sets of multiple logistic regression models were analyzed. Tumor size was included in each model as a dichotomous form (less than 2 cm versus 2cm and greater) and a continuous form. SPSS software was used.  $P<0.05$  was considered statistically significant. **Results** Thirteen patients had lymph node metastasis. The distributions of tumor size in patients with or without lymph node metastasis were not significantly different (Mann-Whitney,  $P=0.075$ ). On univariate analyses, lymph node metastasis was not significantly associated with tumor size of greater than 2cm [ $P=0.22$ , odds ratio (OR) 3.73, 95% confidence interval (CI), 0.46–30.2] and continuous tumor size ( $P=0.14$ , OR 1.15, 95% CI 0.95–1.375). On multivariate analysis, only depth of myometrial invasion greater than 50% was a significant predictor of lymph node metastasis ( $P=0.01$ , OR 5.02, 95% CI 1.43–17.6). **Conclusion** Unlike depth of myometrial invasion, tumor size may not be an independent predictor of lymph node metastasis in endometrioid endometrial cancer.

### ISP-39-4

**Administration of cabergoline contributes to preserving fertility in young hyperprolactinemic patients with endometrial cancer treated with medroxyprogesterone acetate** Munekegami Yamaguchi<sup>1</sup>, Erdenebaatar Chimeddulam<sup>1</sup>, Fumitaka Saito<sup>1</sup>, Ritsuo Honda<sup>1</sup>, Hironori Tashiro<sup>2</sup>, Takashi Ohba<sup>1</sup>, Hidetaka

Katabuchi<sup>1</sup> Kumamoto University<sup>1</sup>, School of Health Sciences, Kumamoto University<sup>2</sup>

**Objective** The prevalence of hyperprolactinemia is high in women with reproductive disorders. An association between hyperprolactinemia and endometrial cancer (EC) has been reported. The aim of this study was to confirm the effect of cabergoline on young hyperprolactinemic patients treated with medroxyprogesterone acetate (MPA) for the preservation of fertility which includes the high risk of disease relapse and progression during the observational period. **Methods** A retrospective observational study was conducted to identify patients with atypical endometrial hyperplasia (AEH) or early-stage endometrial cancer (EC) aged 40 years or younger who were treated with oral MPA in our hospital between 1998 and 2016. **Results** Thirty-four patients were identified and divided into two groups of 17 patients each, including a non-administration of cabergoline group (NC) and an administration of cabergoline group (AC). The ratio of pathological diagnoses of EC in the NC group was significantly lower than that in the AC group (29.4% vs. 70.6%,  $P=0.016$ ). The mean serum prolactin levels showed a significant decrease after the administration of cabergoline in the AC group ( $25.2 \pm 24.0$  vs.  $5.2 \pm 4.2$  ng/ml,  $P=0.003$ ), and this decreased level was also significantly lower than that in the NC group ( $5.2 \pm 4.2$  vs.  $12.0 \pm 5.0$  ng/ml,  $P<0.001$ ). Kaplan-Meier analysis conducted over 150 months revealed that the estimated mean period until hysterectomy in the NC group was significantly shorter than that in the AC group (83.5 vs. 140.8 months,  $P=0.007$ ). **Conclusion** The administration of cabergoline may contribute to preserving fertility in young hyperprolactinemic patients with EC who were treated with MPA.

### ISP-39-5

**A retrospective study of endometrial cancer in elderly women aged 80 or older** Souta Tanaka, Sara Takahashi, Shohei Tanabe, Takanori Shimizu, Yoko Yoshida, Izumi Sato, Kaori Suenaga, Akiko Kasai, Goichiro Kasai, Takeshi Aida, Junko Kouno *Hachinohe City Hospital*

**Objective** The aim of this study is to investigate endometrial cancer (EC) in elderly women aged 80 or older. **Methods** We analyzed 32 EC cases aged 80 or older retrospectively in their clinical features, methods of treatment, and prognoses, in our hospital from 2007 to 2016. **Results** Median age of patients was 83 years (range 80–92). The numbers of FIGO stages 1, 2, 3, 4 were 24, 1, 4, 3, respectively. The details of histological types were endometrioid adenocarcinoma (22 cases, G1 : 13, G2 : 4, G3 : 5), clear cell adenocarcinoma (4), serous adenocarcinoma (2), poorly differentiated adenocarcinoma (2), mucinous adenocarcinoma (1), and squamous cell carcinoma (1). All of 5 patients (PS 3–4) had best supportive care (BSC). Eighteen of 27 patients (PS 0–2) underwent surgery (hysterectomy) and their 5-year survival rate was significantly higher than that of the other 9 patients who had radiation therapy or BSC (55.3% vs 16.7%,  $p=0.0185$ ). There was no severe postoperative complication. In 17 cases which operation was performed, the 5-year survival rate of 11 EC (endometrioid) patients was significantly higher than that of 6 EC (serous, clear) (80% vs 0%,  $p=0.0006$ ). **Conclusion** In elderly women aged 80 or older (PS 0–2), our data showed that the feasibility of surgery could be enough to do and the prognosis of type1 EC cases having surgery was good, in contrast, that of type2 was very poor. It is suggested that surgical therapy should be considered first in type1 EC cases and postoperative therapy was required to reconsider in type2.

### ISP-39-6

**Prognostic comparison between laparotomy and laparoscopic surgery for early-stage endometrial cancer** Mayu

Shiom<sup>1</sup>, Eiji Kobayashi<sup>1</sup>, Mamoru Kakuda<sup>2</sup>, Tsuyoshi Takiuchi<sup>1</sup>, Michiko Kodama<sup>1</sup>, Kae Hashimoto<sup>1</sup>, Seiji Mabuchi<sup>1</sup>, Yutaka Ueda<sup>1</sup>, Kenjiro Sawada<sup>1</sup>, Takuji Tomimatsu<sup>1</sup>, Kiyoshi Yoshino<sup>1</sup>, Tadashi Kimura<sup>1</sup> *Osaka University<sup>1</sup>, Sakai City Medical Center<sup>2</sup>*

**Objective** Laparoscopic surgery for early stage endometrial cancer is becoming more common in our country. The primary objective was to confirm non-inferiority of laparoscopy compared with laparotomy for recurrence and survival rate after surgical treatment of endometrial cancer. **Methods** From March 2010 to December 2016, 273 patients who were preoperatively diagnosed as low risk endometrial cancer were surgically treated in our institution. Low risk cancer was defined preoperatively as G1 or G2 endometrioid histology and myometrial invasion <50% based on magnetic resonance imaging (MRI). The surgical procedure was determined by intraoperative frozen section. Medical records were retrospectively reviewed for pathological diagnosis, site of recurrence and survival rate. **Results** A total of 131 (48%) patients were treated by laparoscopy and 142 (52%) by laparotomy. The median follow-up period was 17 months for laparoscopy patients and 51 months for laparotomy patients. There was no significant difference in distribution of BMI, pathological diagnosis and FIGO stage between the two groups. In laparoscopic group, there were 4 recurrences and no death. All 4 recurrent patients were pathological stage I. In laparotomy group, there were 10 recurrences and 4 deaths. Among ten, three were pathological stage III. There was no statistical difference for overall survival and progression free survival between the two groups. **Conclusion** Our findings showed that for endometrial cancer, laparoscopy has provided similar recurrent and survival rates with laparotomy.

### ISP-39-7

**Para-aortic lymphadenectomy at primary surgery is critical for treatment of endometrial cancer** Osamu Kobayashi, Takehiro Nakao, Akiko Kasuga, Yuki Okuma, Remi Hasegawa, Erina Hashimoto, Kaori Shinya, Chuyu Hayashi, Atsushi Komatsu, Shinichi Takada, Fumihisa Chishima, Kei Kawana *Ni-hon University Itabashi Hospital*

**Objective** Para-aortic lymph nodes (PAN) are primary regional lymph node of the endometrial cancer and then should be removed by para-aortic lymphadenectomy (PALA). However, PALA can be omitted in some cases with early stage and well-differentiated adenocarcinoma. We here examined whether omission of PALA is acceptable for curative surgery by using our cases. **Methods** This retrospective study was approved by the Ethic committee of our institute. Subjects of this study were 68 cases with endometrial cancer which underwent primary surgery in our hospital from 2013 to 2016. The operation was abdominal simple/semi-radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy (TAH/AEH+BSO+PLA : omission of PALA) for all cases. Clinico-pathological features (histology, FIGO stage, clinical outcome, recurrent site, etc.) were investigated and analyzed. In our hospital chemotherapy (conventional TC : paclitaxel and carboplatin) was done as an adjuvant therapy for cases with high-risk factors of recurrence. **Results** Among 68 cases, eight cases (8/68 [11%], FIGO stage IA–IV, G1=4, G2/3/others=4) had recurrence and two cases died. Notably, metastases to the PAN occurred in five cases among the recurrent cases (5/8 [63%]). All of four cases with post-operative high-risk factors of recurrence developed PAN metastases. **Conclusion** In our hospital, PALA had not been done for endometrial cancer cases until 2017. High-risk group cases could not be prevented from PAN metastasis even though adjuvant chemotherapy alone had been done. This indicated PALA is effective and should be done for prevention from recurrence for high-risk group.



## ISP-39-8

**A risk factor of treatment failure of conservative management of atypical endometrial hyperplasia and endometrial carcinoma** Masafumi Yasunaga, Keisuke Kodama, Shinichiro Yamaguchi, Hiroshi Yagi, Tatsuhiro Ohgami, Ichiro Onoyama, Eisuke Kaneki, Kaoru Okugawa, Hideaki Yahata, Kenzo Sonoda, Tsunehisa Kaku, Kiyoko Kato *Kyushu University Hospital*

**Objective** Hormonal therapy for atypical endometrial hyperplasia (AEH) and well differentiated endometrial cancer (EC) is one of treatment option for young patients desiring for child-bearing. However, this treatment has not been optimal with high treatment failure rates. This study is to clarify clinicopathologic risk factors of treatment failure of conservative management of AEH and EC. **Methods** The institutional database was searched to identify all AEH and EC patients treated with medroxyprogesterone acetate (MPA) from 1999 to 2015. Clinical information was obtained from electronic medical records. Relationships between clinicopathologic variables and treatment failure were calculated using the Wilcoxon rank sum test or Fisher exact test. All statistical analyses were performed using the JMP software. A 2-sided P value ( $<0.05$ ) was considered significant. **Results** Between 1999 to 2015, 20 patients were identified for analysis. Thirteen patients had EC, 5 had AEH and 2 had atypical polypoid adenomyoma. The median patient age was 30.5 years (range, 17 to 42 years). The median Body Mass Index (BMI) was 22.9 (range, 17.6 to 43.4). Sixteen had a complete response (CR), 2 stable disease and 1 progression of disease. Seven of 16 CR patients relapsed. Hysterectomy has been performed for seven patients who relapsed or had a stable disease. The other 3 patients has been added next cycle of hormonal therapy. There was no significant relationship between BMI and treatment failure ( $p=0.28$  by Wilcoxon test). **Conclusion** Now, we are going to evaluate relationships between endometrial cancer stem cell markers such as ALDH1 or CD99 and treatment failure by immunohistochemical method.

## ISP-39-9

**Diagnostic effectiveness of Sentinel Lymph Node Mapping : Comparison with MRI, PET/CT in early cervical and endometrial cancer** Jeong-Yeol Park, Geon-Woo Lee, Dae-Yeon Kim, Dae-Shik Suh, Jong-Hyeok Kim, Yong-Man Kim, Young-Tak Kim, Joo-Hyun Nam *University of Ulsan College of Medicine, Asan Medical Center, Korea*

**Objective** To substantiate of the usefulness of sentinel lymph node mapping (SLNM) with indocyanine green (ICG) compare to preoperative imaging tools like magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) in early cervical and endometrial cancer. **Materials and Methods** We reviewed 203 patients with early stage cervical and endometrial cancer who underwent laparoscopic or robotic surgery with SLNM between August 1, 2015 and April 30, 2017. All patients underwent preoperative MRI and/or PET/CT and lymphadenectomy was performed during surgery. The diagnostic exactness of MRI, PET/CT, and SLNM was evaluated using McNemar test and logistic regression using generalized estimating equation. **Results** All patients had SLNM of at least one hemipelvis. Lymph nodes metastasis on permanent biopsy were found in 33 patients, and SLNM found metastasis in 31 patients. There was no significant difference in sensitivity (45.5% vs. 45.5%,  $p>0.99$ ), specificity (91.0% vs. 92.8%,  $p>0.99$ ), accuracy (83.5% vs. 85.0%,  $p>0.99$ ), positive predictive value (PPV) (50.0% vs. 55.6%,  $p>0.99$ ), and negative predictive value (NPV) (89.4% vs. 89.6%,  $p>0.99$ ) of MRI and PET/CT. SLNM values were more accurate results shows at sensitivity (93.9%), specificity (99.4%), accuracy (98.5%), PPV (96.9%), NPV (98.8%) and statistical significance was shown at all values ( $p<0.05$ ). In

SLBM in hemipelvis, sensitivity, specificity, accuracy, PPV, and NPV were also more accurate than MRI and PET/CT. **Conclusion** SLNM using ICG is the compatible and best way to evaluate lymph node status before conventional lymphadenectomy in early-stage cervical and endometrial cancer.

## ISP-40-1

**Efficacy and Safety of En bloc Total Parietal Peritonectomy for Primary or Recurrent Ovarian Cancer with Peritoneal Carcinomatosis** Aeran Seol, Hee Seung Kim, Jae-Weon Kim *Seoul National University College of Medicine, Korea*

**Background** To evaluate the efficacy and safety of en bloc total parietal peritonectomy for primary advanced-stage or platinum-sensitive recurrent ovarian cancer with peritoneal carcinomatosis. **Methods** Two gynecologic oncologists enrolled patients prospectively in the same criteria as follows : patients with primary advanced-stage (IIIB to IVB) or platinum-sensitive recurrent ovarian cancer : those expected to receive optimal debulking surgery (residual tumor  $\leq 1$  cm) in preoperative studies : those who received en bloc total parietal peritonectomy for treating peritoneal carcinomatosis. **Results** Among 73 patients, 3 (4.7%), 34 (51.5%), 8 (12.5%) and 20 patients (31.3%) showed IIIB, IIIC, IVA and IVB disease, respectively. The median value of operation time was 465 minutes (range, 100 - 1080 minutes), and 61 patients (83.6%) received transfusion (the median value, 6 ; range, 1-22). Upper abdominal surgery such as splenectomy were performed in all patients, and 58 (79.5%) and 23 patients (31.5%) underwent large and small bowel resection and anastomosis, and 4 patients (5.5%) received prophylactic ileostomy. After the surgery, 54 (84.4%) and 10 patients (15.6%) showed gross-free and minimal residual disease ( $\leq 1$  cm). Disease recurrence was observed in 20 (31.3%) and 6 patients (66.7%) with primary and recurrent ovarian cancer, respectively. Median values of overall survival were 48 months in patients with primary ovarian cancer and 32 months in those with recurrent disease. **Conclusion** En bloc total parietal peritonectomy is feasible with acceptable morbidity in primary or recurrent ovarian cancer, and contributes to cytoreduction for treating peritoneal carcinomatosis.

## ISP-40-2

**Reporting of Double Cancer Survivor : 10 years survival from Synchronous Ovarian and Colorectal Tumour Post-Surgery Post Chemotherapy** Eugene Leong Weng Kong<sup>1</sup>, April Roslaine<sup>2</sup>, Christina Ng<sup>3</sup> *Taylors University School of Medicine, Malaysia<sup>1</sup>, University of Malaya, Malaysia<sup>2</sup>, Sunway Medical Centre, Malaysia<sup>3</sup>*

**Objective** This is just a simple report from a reporter (ELWK) of survival from synchronous ovarian cancer and colorectal cancer in a patient operated by the primary and second author and chemotherapy by the third author whilst in the University of Malaya in 2006. (This was presented as a poster in the OGSM 2016 in Malaysia for local review). Patient is still well as of 2017-every year Chinese New Year she calls me & sends me a cake as she did in 2017. **Methodology** Madam XX has given permission for anonymised report. She was operated in 2006 in the University of Malaya by ELWK, Consultant GynaeOncologist and Consultant Colorectal Surgeon (Dr. April Roslaine, now Professor). She was initially diagnosed pre-operatively as having ovarian cancer but on table a colorectal cancer was discovered as well with histopathological confirmation of both separate tumours. She was subsequently referred for chemotherapy to Dr. Christina Ng (now in Sunway Medical Centre/Hospital Pantai, Bangsar). Every year the patient sends a Chinese New Year cake to ELWK. ELWK last saw her as a patient in 2013. Being a pensioner, she is on follow-up in a government hospital. **Results**

The patient herself (recognizing her voice and diction) called ELWK to send another Chinese New Year cake on the evening of 2. 2. 2016 and in 2017 as has been the patient's wishes every year for the past few years without fail. Her voice is hale and hearty and she reported that her follow-up at her government facility so far reveals no further abnormality with no complaints or any disability despite her age (70 years plus). **Conclusion** It is possible to survive from synchronous ovarian and colorectal cancer in Malaysia with expert surgery and chemotherapy with involvement of the relevant specialities to good effect. This is just a report on survival basis - documenting as such.

### ISP-40-3

**Preoperative neutrophil/lymphocyte ratio and CA125 may be predictive factors for recurrence in stage I ovarian clear cell carcinoma** Yuji Takei, Shizuo Machida, Akiyo Taneichi, Suzuyo Takahashi, Yoshifumi Takahashi, Takahiro Yoshida, Hiroyuki Morisawa, Chikako Yoshida, Ayumi Iwashita, Yasushi Saga, Hiroyuki Fujiwara, Shigeki Matsubara *Jichi Medical University*

**Objective** Ovarian clear cell carcinoma (OCCC) is resistant to chemotherapy and even if stage I, its prognosis differs depending on the substage. If prognostic factors other than FIGO staging were found, it may lead to the development of new therapeutic strategies. Therefore, we examined the recurrence predictive factors for stage I OCCC. **Methods** Patients with stage I OCCC who had undergone staging lymphadenectomy from 1988 to 2014 were selected. We retrospectively evaluated the association between recurrence and the following parameters: age, substage, tumor diameter, implementation of postoperative chemotherapy, preoperative white blood cell (WBC), platelet, neutrophil/lymphocyte ratio (NLR), and CA125. ROC curve analyses were used to determine the cut off values of WBC, Plt, NLR, and CA125. Log-rank test was used to compare the recurrence-free survival of each group. A Cox proportional hazards model was applied for multivariate analysis. **Results** We identified 77 eligible cases. The median tumor size was 13 cm. Fifty-seven patients received postoperative chemotherapy. The cut-off values for WBC, Plt, NLR, and CA125 were  $7,350/\mu\text{l}$ ,  $28.1 \times 10^3/\mu\text{l}$ , 2.79, and 167 U/ml, respectively. Twenty patients had recurrences. The significant recurrence predictive factors were stage IC (vs IA,  $p=0.014$ ), NLR:  $\geq 2.79$  (vs  $< 2.79$ ,  $p=0.012$ ), and CA125:  $\geq 167$  (vs  $< 167$ ,  $p=0.004$ ). The hazard ratios of the above three factors by multivariate analysis were 9.92 [95% CI: 1.28-76.96], 5.71 [95% CI: 1.57-20.77], and 3.65 [95% CI: 1.34-9.94], respectively. **Conclusion** Substage, preoperative NLR, and preoperative CA125 may be associated with recurrence in stage I OCCC. NLR and CA125 may be independent predictive factors for recurrence after adjusting for substage.

### ISP-40-4

**Risk Factors for Venous Thromboembolism in Women with Ovarian Cancer** Tetsuya Kawaguchi, Yasuhiko Ebina, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

**Objective** We clarify the incidence of venous thromboembolism (VTE) before treatment in women with ovarian cancer and identify risk factors for VTE. **Methods** In this prospective study, 110 women underwent venous ultrasonography before cancer treatment and D-dimer levels were measured. We investigated factors predicting deep venous thrombosis by logistic regression. **Results** VTE was detected in 25 women (22.7%) by venous ultrasonography. A total of 21 women (84.4%) with VTE were asymptomatic. D-dimer levels in women with VTE (median, 10.9; range,  $< 0.5$ -98.2  $\mu\text{g/mL}$ ) were significantly higher than those in women without VTE (2.0;  $< 0.5$ -60.8  $\mu\text{g/mL}$ ;  $P < 0.01$ ).

When 10.9  $\mu\text{g/mL}$  was used as a cutoff value for D-dimer levels to predict VTE, specificity, sensitivity, and positive and negative predictive values were 92.9%, 52.0%, 68.4%, and 86.8%, respectively. The multivariate analysis demonstrated that D-dimer level (odds ratio [OR], 19.7; 95% confidence interval [CI], 5.89-76.76) and clear cell histology (OR, 7.1; 95% CI, 2.12-25.67) were independent factors predicting VTE. **Conclusion** Asymptomatic VTE frequently occurred before treatment in patients with ovarian cancer. Because the use of D-dimer as a triage factor was limited, routine venous ultrasound was preferable.

### ISP-40-5

**Incidence and timing of venous thromboembolism in patients with ovarian cancer undergoing primary treatment** Mizuki Uenaka, Yasuhiko Ebina, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

**Objective** To determine the incidence and timing of venous thromboembolism (VTE) in patients with ovarian cancer undergoing primary treatment. **Methods** We conducted a retrospective cohort study for women who were diagnosed as having suspected malignant ovarian tumor and underwent primary treatment between June 2010 and December 2016. The timing and number of VTE were assessed. Deep venous thrombosis (DVT) was based on the results of venous ultrasonography. Women with DVT underwent enhanced CT of the lung to find pulmonary thromboembolism. The timing of VTE were categorized as follows: at diagnosis, during neoadjuvant chemotherapy (NAC), after interval debulking surgery (IDS), after primary debulking surgery (PDS), and during adjuvant chemotherapy. **Results** In 97 women with ovarian cancer and 13 with borderline ovarian tumor, 35 (31.8%) women developed VTE. Twenty-eight women had VTE at diagnosis, and 7 patients developed VTE during NAC or after PDS. The incidence of VTE at diagnosis was higher than that during primary treatment (25.5% vs 6.4%;  $p < 0.001$ ). 4 patients developed VTE after PDS, three patients experienced VTE during NAC. **Conclusion** VTE frequently occurred at diagnosis of ovarian cancer. The incidence of VTE during NAC did not differ from that after PDS.

### ISP-40-6

**Clinical characteristics of patients with ovarian cancer developing VTE** Kohei Yamaguchi<sup>1</sup>, Yoko Matsumoto<sup>1</sup>, Tomoko Kashiyama<sup>1</sup>, Satoko Eguchi<sup>1</sup>, Michihiro Tanikawa<sup>1</sup>, Kenbun Sone<sup>1</sup>, Katsutoshi Oda<sup>2</sup>, Yutaka Osuga<sup>2</sup>, Tomoyuki Fujii<sup>2</sup> *The University of Tokyo Hospital<sup>1</sup>, The University of Tokyo<sup>2</sup>*

**Objective** Ovarian cancer has a higher incidence of venous thromboembolism (VTE) than other cancers. The aim of our study was to identify the predisposing factors for VTE in ovarian cancer. **Methods** VTE events were identified from hospital records for patients with ovarian cancer who were diagnosed and treated between 2012 and 2017 under informed consent and approval of our ethical committee. Pathological results, clinical stage, the timing of occurrence of VTE and anticoagulant were analyzed. **Results** Of 235 ovarian cancer patients, overall incidence of VTE was 36 cases (15.3%). Pulmonary embolism was detected in 21 cases. Diagnosis of VTE was made during pre-treatment period in 22 cases, after surgery in 4 cases and during chemotherapy in 8 cases. Risk factors of the occurrence of VTE were advanced stage (Stage III-IV) ( $p < 0.05$ ), and clear cell subtype was not an obvious risk factor ( $p = 0.22$ ) by univariate analysis. We treated VTE with unfractionated heparin for about 10 days followed by oral anticoagulant such as edoxaban ( $n=16$ ), warfarin potassium ( $n=16$ ), rivaroxaban ( $n=2$ ) as maintenance therapy. No progression of VTE was observed during follow up, but we experienced incidence of bleeding that required suspended administration in 2 cases of edoxaban. **Conclusion** The



incidence of VTE was high in ovarian cancer with advanced stage. Over 60% cases, VTE was found during pre-treatment. Advanced clinical stage should be incorporated to protocols of VTE prophylaxis in patients with ovarian cancer. After diagnosis, prompt management for VTE with anticoagulant would be needed.

### ISP-40-7

**Efficacy and safety of bevacizumab for advance and recurrent Müllerian carcinoma** Hiroaki Matsubara, Takeshi Fukuda, Masahiro Shimomura, Yuta Inoue, Mari Kasai, Yasunori Hashiguchi, Tomoyuki Ichimura, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

**Objective** The aim of this study was to evaluate the efficacy and safety of bevacizumab in patients with Müllerian carcinoma. **Methods** We reviewed 46 patients with Müllerian carcinoma treated at our hospital from April 2014 to March 2017 and evaluated efficacy based on RECIST and safety based on CTCAE. **Results** 27 patients were treated primarily with advanced disease and 19 patients were treated with recurrent disease. The patients with primary treatment consisted of 18 serous carcinomas (66.7%), 4 clear cell carcinomas (14.8%), 2 endometrioid carcinomas (7.4%), 1 mucinous carcinoma (3.7%) and 2 other types (7.4%) in histological types. The combined chemotherapy regimen for primary treatment was all TC (paclitaxel, carboplatin). The response to primary treatment were 19 CRs (70.4%), 6 PRs (22.2%), 1 SD (3.7%) and 1 PD (3.7%). The patients with recurrent treatment consisted of 9 serous carcinomas (47.4%), 4 clear cell carcinomas (21.0%), 1 endometrioid carcinoma (5.3%), 2 mucinous carcinomas (10.5%) and 3 other types (15.8%) in histological types. The combined chemotherapy regimens for recurrent treatment were 13 TCs, 2 DCs (docetaxel, carboplatin), 2 pegylated liposomal doxorubicins, 1 gemcitabine and 1 irinotecan+cisplatin. The response to recurrent treatment were 11 CRs (57.9%), 4 PRs (21.1%), 3 SDs (15.8%) and 1 PD (5.3%). The adverse effects specific to bevacizumab were five grade 2 hypertension (10.9%), four grade 1 proteinuria (8.7%), one grade 2 proteinuria (7.2%), four grade 3 proteinuria (8.7%) and three grade 4 ileal perforation (6.5%). **Conclusion** Bevacizumab is an effective drug when administered with careful observation.

### ISP-40-8

**Retrospective analysis of stage II~IV epithelial ovarian cancer patients treated with systematic pelvic and para-aortic lymphadenectomy followed by chemotherapy** Koutarou Sueoka, Natsuko Shimizu, Kengo Nakashima, Takuya Kajimura, Toshiaki Taketani, Norihiro Sugino *Yamaguchi University*

**Objective** To clarify the benefit of systematic lymphadenectomy (SLNE) in advanced epithelial ovarian cancer. **Methods** From January, 2007 to December, 2015, 37 cases who were diagnosed stage II~IV epithelial ovarian or peritoneal cancer and treated including pelvic and para-aortic lymphadenectomy followed by chemotherapy in our hospital were enrolled. We routinely perform SLNE for patients achieved complete and optimal surgery at PDS or IDS. **Results** The patients were diagnosed as stage II in 6 cases, III in 25 cases, IV in 6 cases, and histological subtype was serous carcinoma in 27 cases. SLNE was performed at PDS in 18 cases, IDS in 19 cases and in 20 cases lymph node (LN) were involved microscopically. 27 cases had resulted in complete surgery, 10 cases in optimal surgery. In this population, 5Y-PFS was 48.1% and 5Y-OS was 79.1%, respectively. Moreover, in patients with microscopic LN metastasis, 5Y-PFS was 46.0% and 5Y-OS was 76.3%, respectively, which were not significantly different from patients without nodal metastasis and same result was observed in only complete

surgery group. We observed 18 patients had recurrence and the sites were distributed to LN in 8 cases, dissemination in 12 cases, distant organ in 2 cases. Especially in 20 patients with LN metastasis, 7 patients had recurrence and 5 of 7 had involved LN at recurrence but 13 with LN metastasis had not recurrence anywhere. **Conclusion** Systematic lymphadenectomy might reduce the frequency of the lymph node recurrence in stage II~IV epithelial ovarian cancer but could not contribute to improve the prognosis.

### ISP-40-9

**Drug-induced aortitis in a patient with ovarian cancer treated with bevacizumab combination therapy** Soshi Kusunoki, Kengo Hiranuma, Takashi Hirayama, Kazunari Fujino, Tsuyoshi Ota, Yasuhisa Terao, Atsuo Itakura, Satoru Takeda *Juntendo University*

Drug-induced vasculitis is an extremely rare complication of chemotherapy. Few reports have investigated drug-induced large vessel vasculitis. We report a case of a 47-year-old woman with ovarian cancer who developed aortitis during bevacizumab combination chemotherapy. Contrast-enhanced CT showed concentric thickening of the descending aorta. The cause of aortitis was considered to be treatment with granulocyte-colony stimulating factor or bevacizumab. Aortitis should be considered in patients receiving bevacizumab combination therapy who develop persistent fever and upper-abdominal pain. Contrast-enhanced CT is useful for detecting drug-induced aortitis.

### ISP-40-10

**Identification of Potential Biomarkers of recurrent advanced ovarian cancer during bevacizumab maintenance therapy as part of first-line treatment** Ryosuke Saito, Nozomu Yanaiharu, So Hirose, Takafumi Kuroda, Kazuaki Takahashi, Motoaki Saito, Hirokuni Takano, Seiji Isonishi, Aikou Okamoto, Suguru Odajima, Junya Tabata *The Jikei University School of Medicine*

**Objective** Although the use of bevacizumab (BEV) in first-line treatment for ovarian cancer has been found to extend progression-free survival, its effect in improving overall survival is limited. The search for validated biomarkers to predict disease recurrence is important for the selection of appropriate patients. We investigated blood biomarkers and clinicopathological attributes to identify predictors of recurrence during BEV maintenance therapy. **Methods** The study included 48 stage III or IV ovarian cancer patients who underwent debulking surgery with combination chemotherapy of paclitaxel, carboplatin, and BEV between 2013 and 2016. We compared histotype, postoperative residual tumor, lymph node metastasis status, and several blood parameters (CRP, WBC, hemoglobin, platelet, neutrophil-to-lymphocyte ratio, and CA125) between 12 patients who recurred during BEV maintenance therapy and 36 who did not. **Results** The median age was 52.5 years in the recurrence group and 53 years in the recurrence-free group. There was a significant correlation between presence or absence of residual tumor and disease recurrence ( $p=0.009$ ). There was no significant correlation with either histotype or presence or absence of lymph node metastasis. Blood CRP and hemoglobin levels before administration of first-line chemotherapy differed significantly between the two groups (CRP :  $p=0.048$  ; hemoglobin :  $p=0.001$ ). **Conclusion** Pre-chemotherapy CRP levels could be a potential predictor of recurrence during BEV maintenance. Further investigation of novel biomarkers associated with disease recurrence is required.

### ISP-41-1

**Prognostic value of preoperative lymphocyte-monocyte ratio**

**in elderly patients with advanced epithelial ovarian cancer** Hyun Joo Lee, Byung Su Kwon, Seo Yoon Hwang, Sul Lee, Hye Kyung Noh, Dong Soo Suh, Ki Hyung Kim *Pusan National University Hospital, Korea*

**Objective** To investigate the prognostic significance of preoperative lymphocyte-monocyte ratio (LMR) in elderly patients with advanced epithelial ovarian cancer (EOC) receiving primary cytoreductive surgery and adjuvant platinum-based chemotherapy. **Methods** A total of 42 elderly patients ( $\geq 65$  years) diagnosed with EOC who are receiving primary cytoreductive surgery and adjuvant platinum-based chemotherapy from 2009 to 2012 was included. LMR was calculated from complete blood cell count sampled before operation. Receiver operating characteristic (ROC) curves were used to calculate optimal cut-off values for LMR. Prognostic significance with respect to overall survival (OS) and progression-free survival (PFS) were determined using log-rank test and Cox regression analysis. **Results** The optimized LMR cut-off value determined by ROC curve analysis was 3.63 for PFS and OS. The high LMR group (LMR  $\geq 3.63$ ) was found to be significantly more associated with optimal debulking (P=0.045) and platinum response (P=0.018) than the low LMR group. In addition, Kaplan-Meier analysis revealed the LMR-high group was significantly more associated with high PFS and OS rates (P=0.023, P=0.033, respectively), and univariate analysis revealed that a high LMR, histology type, and optimal debulking and platinum responses were significantly associated with prolonged PFS and OS. However, subsequent COX multivariate analysis showed only optimal debulking and platinum response were independent prognostic factors of PFS or OS. **Conclusions** This study suggests that LMR might be associated with treatment and survival outcomes in elderly patients with EOC receiving standard oncology treatment.

### ISP-41-2

**Differences in correlation of Progression-Free Survival and Overall Survival by clinical variables in epithelial ovarian cancer** Hyea Park, Youjean Chang, E Sun Paik, Jihye Kim, Tae-Joong Kim, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae, Chel Hun Choi *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

**Objective** To investigate significance of progression-free survival (PFS) as optimal surrogate endpoint for overall survival (OS), and the differences in correlation of PFS and OS by different clinical variables in epithelial ovarian cancer (EOC) patients. **Methods** The clinical records of 1,134 EOC patients treated at Samsung Medical Center between 2002 and 2015 were retrospectively reviewed. Correlation analyses with all pair-wise comparison were performed to assess the association of PFS and OS for each clinical variable. After multivariate analysis for PFS and OS, scatter plot with hazard ratio (HR) (with 95% CI) of PFS and OS were drawn for clinical variables. **Results** For entire cohort, there is a significant linear correlation between PFS and OS (p-value  $< 0.0001$ ), and the degree of correlation is high (Spearman correlation coefficient = 0.8243). In Z-test using Fisher's transformation, patients with early stage (I, II) (0.9059, p  $< 0.001$ ), lower grade (0.9019, p  $< 0.001$ ), and non-serous histology (0.8853, p  $< 0.001$ ) showed higher correlation coefficient. In patients with no residual disease (0.8661, p  $< 0.001$ ), no pelvic lymph node metastasis (0.8275, p  $< 0.001$ ), no paraaortic lymph node metastasis (0.8267, p  $< 0.001$ ), higher correlation coefficient was shown. In scatter plot for HR of PFS and OS, presence of residual disease, high grade, neo-adjuvant chemotherapy, lymph node metastasis were not located within estimated regression area implicating low correlation coefficient. **Conclusion** The treatment effect on OS is largely predictable according to that on PFS in EOC, especially for patients with early stage, low

grade, non-serous, no residual disease, without lymph node metastasis.

### ISP-41-3

**Pathological findings and prognosis of ovarian epithelial-borderline malignant tumors** Yoshiko Oyama, Hideki Tokunaga, Satomi Kameda, Shoko Sakurada, Yusuke Shibuya, Chiaki Hashimoto, Tomoyuki Nagai, Michiko Kaiho, Masafumi Toyoshima, Muneaki Shimada, Hitoshi Niikura, Nobuo Yaegashi *Tohoku University*

**Objective** The WHO histological classification of ovarian tumors was revised in 2014. The definition of micro invasion was changed from within 10 mm<sup>2</sup> to 5mm in diameter. The recommended treatments for ovarian tumors are different whether or not there is stromal invasion so that pathological diagnosis plays an important role. In Japan, mucinous and serous tumors are majority of borderline malignancies. **Methods** There were 85 cases of mucinous and 40 cases of serous tumors between 2005 and 2014 in our institute. In the mucinous tumors, (a) 6 cases had expansile invasion within 10mm<sup>2</sup>, (b) 7 cases showed expansile invasion exceeding 10mm<sup>2</sup> and (c) 5 cases had infiltrative invasion. **Results** Case in (a) group were not changed its malignancy according to new criteria that determine "invasive". Among the cases of (b) and (c), one case and three cases did not match the new criteria for invasive carcinoma, respectively. Three cases of serous tumors with tumors with invasion of the previous criteria "over 10mm<sup>2</sup>" showed obvious invasion exceeding 5 mm in diameter. There was no recurrence in the four cases of mucinous carcinoma those might be borderline malignancies. Three cases of them received chemotherapy after surgery. **Conclusion** Cases around the boundary between the borderline malignancy and carcinoma have good prognosis, adaptation of chemotherapy should be carefully examined.

### ISP-41-4

**Primary Fallopian Tube Cancer : Clinicopathological Features of Tumor occupying Lesions** Shoko Sakurada<sup>1</sup>, Yoh Watanabe<sup>2</sup>, Hideki Tokunaga<sup>1</sup>, Hidekazu Yamada<sup>3</sup>, Kazuhiro Takehara<sup>4</sup>, Nobuo Yaegashi<sup>1</sup> *Tohoku University<sup>1</sup>, Tohoku Medical and Pharmaceutical University<sup>2</sup>, Miyagi Cancer Center<sup>3</sup>, Shikoku Cancer Center<sup>4</sup>*

**Objective** Recent studies reported the fimbriae of the fallopian tube as a significant origin of ovarian high-grade serous adenocarcinoma. However, primary epithelial ovarian cancer occurs at a frequency almost 50 times higher than that of PFTC. Furthermore, no previous study of PFTC has reported clinicopathological differences among the types of tumor-occupying lesions in the fallopian tube. Therefore, this study aimed to clarify the clinicopathological differences of tumor-occupying lesions in patients with PFTC. **Methods** A multicenter clinical survey was conducted at three institutions. Using macroscopic and microscopic findings, PFTCs were classified according to the occurrence of fallopian tube lesions as follows : only ampulla-occupying type (Type A), only fimbriae-occupying type (Type F), both ampulla- and fimbriae-occupying but ampulla-dominant type (Type AD) or fimbriae-dominant type (Type FD), and undeterminable type (Type UD). The clinicopathologic characteristics and P53 immunohistochemical features of each type were compared. **Results** Forty patients with PFTC were enrolled in this study. The median age was 58 years. Thirty four (85.0%) patients had serous carcinoma. FIGO stage III (50.0%) was most frequently observed. The median survival duration was 6.5 years. P53 overexpression was confirmed in 22 (55.0%) tumors. Nine, 9, 9, 8, and 5, cases of A, F, AD, FD, and UD were reported, respectively. However, no significant differences in clinicopathologic factors, including P53 overexpression and

long-term prognosis, were observed among the types of tumor-occupying lesions. **Conclusion** The present study found no significant correlation of tumor occupying lesions in the fallopian tube with PFTC carcinogenesis.

### ISP-41-5

**Treatment-free interval (TFI) is useful not only for choice of second-line agents but for prognostic factor in ovarian high-grade serous carcinoma cases stage III/IV** Remi Hasegawa, Chuyu Hayashi, Yuki Okuma, Erina Hashimoto, Osamu Kobayashi, Kaori Shinya, Akiko Kasuga, Takehiro Nakao, Atsushi Komatsu, Shinichi Takada, Fumihisa Chishima, Kei Kawana *Nihon University*

**Objective** Since most of high-grade serous carcinoma (HGS) progress to advanced stage III/IV, HGS often acquire platinum-resistance during first-line chemotherapy. Stratification by treatment-free interval (TFI) is useful for choice of second-line agents and platinum-partially sensitive cases (TFI: 6m < TFI < 12m) are considered to receive first-line agents again. We here examine whether TFI-guided second-line agents was best choice for recurrent HGS cases. **Methods** Under approval by Ethical committee in our hospital, twenty-two HGS cases with FIGO stage III/IV treated in our hospital were investigated retrospectively (follow-up time 13-62m, median=41m). Surgically-debulked cases had undergone conventional paclitaxel (175mg/m<sup>2</sup>) and carboplatin (AUC=6.0) (plus bevacizumab [n=4]). Recurrent cases with TFI>6m received TC again. The progression-free survival (PFS), overall survival (OS) were analyzed by Kaplan-Meier plot and cox-proportional hazard model. **Results** 3ys-OS and PFS of all ovarian HGS cases with stage III/IV was 79% and 23%, respectively. Median PFS of our cases was 12 m. Among 16 recurrent cases, median OS of platinum-partially sensitive and resistant cases was 44m vs. 40m, respectively. Cox-hazard model revealed that TFI was independent prognostic factor with statistical significance (p=0.05). Lymphadenectomy (LA) was not a prognostic factor for stage III/IV HGS. **Conclusion** TFI was not only a useful marker to choose second-line agents but an independent prognostic marker for recurrent HGS cases. Our data confirmed that platinum-partially sensitive cases receive TC again at the recurrent treatment. More effective second-line agents must be needed for treatment of HGS cases at least with TFI of shorter than 6m.

### ISP-41-6

**Oligoclonality following chemotherapy in high grade serous ovarian cancer** Hisamitsu Takaya, Hidekatsu Nakai, Takako Tobiume, Ayako Suzuki, Kosuke Murakami, Shiro Takamatsu, Masao Shimaoka, Yoshie Yo, Masato Aoki, Risa Fujishima, Hanako Sato, Noriomi Matsumura *Kindai University*

**Objective** High grade serous ovarian cancer (HGSOC) was genetically characterized TP53 mutation resulted in intratumor heterogeneity due to dysregulation of apoptosis and DNA repair process. Intratumor heterogeneity give rise to tumor progression and recurrence and chemo-resistance, but few studies have been reported about quantification of intratumor heterogeneity throughout cancer treatment in HGSOC. The aim of this study is to reveal relation between clonal diversity of HGSOC and clinical course. **Methods** A whole genome single nucleotide polymorphism array was applied to generate the genome-wide segmentation data which included log2 ratio (L2R) and B-allele frequency (BAF). Two-dimensional plots of L2R and BAF were classified with percentage of aberrant cells at the part of loss of heterozygosity and we could estimate the clonal composition by the number of plots line. We analyzed the clonal composition of tumor in 34 tumor samples from 20 HGSOC cases at the time of primary surgery (biopsy or maximum cytoreductive surgery),

after neoadjuvant chemotherapy (NAC; in 4 cases), and recurrence (in 10 cases). **Results** Higher number of clonal composition (>2) had a tendency of poor progression free survivals (p value=0.0821). The number of clonal composition of the 4 NAC cases was as follows: (pre NAC, post NAC, at recurrence) = (3, 1, 3), (3, 1, 2), (2, 1, 2), and (2, 1, N/A; no recurrence), indicating oligoclonality following chemotherapy. **Conclusion** HGSOC would consist of chemo-sensitive and chemo-resistant clones and intratumor heterogeneity of HGSOC would relate with recurrence.

### ISP-41-7

**Difference in prognosis and prognostic factors of patients with epithelial ovarian cancer according to age** Masahiro Shimomura, Takeshi Fukuda, Yuta Inoue, Hiroaki Matsubara, Mari Kasai, Yasunori Hashiguchi, Tomoyuki Ichimura, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

**Objective** The aim of this study was to compare the prognosis of patients with epithelial ovarian cancer between old patients (≥65 years old) and young patients (<65 years old), moreover to investigate the difference of prognostic factors between these patients. **Methods** 114 patients with epithelial ovarian cancer who were treated in our hospital between January 2008 and December 2011 were enrolled in this study. We divided these patients in two groups, the one included old patients (≥65 years old) and the other included young patients (<65 years old). We compared the characteristics and prognosis retrospectively and multivariate analysis was performed to investigate the prognostic factors of these groups. **Results** There were no statistically significant differences in performance status, clinical stage, lymph nodes status, serum albumin level, hemoglobin level, CA 125 level, the completion rate of the standard treatment and the size of postoperative residual disease between two groups. However, there was a statistically significant differences only in distribution of histological types (P=0.006). As for the prognosis, there were no statistically significant differences in overall survival and disease free survival between two groups. The multivariate analysis revealed that clinical stage and the completion rate of the standard treatment were independent prognostic factors of young patients (P<0.001) and performance status was independent prognostic factors of elderly patients (P=0.019). **Conclusion** There was difference in prognostic factors between two groups although they had equivalent prognosis. We might need different strategy according to patients age to improve the prognosis of the patients with ovarian cancer further.

### ISP-41-8

**Hyperfibrinogenemia shortens progression-free survival in women with ovarian cancer** Yuka Murata, Yasuhiko Ebina, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

**Objective** To determine clinical factors which are associated with progression-free survival (PFS) in women with ovarian cancer. **Methods** A retrospective cohort study enrolled 81 women who were diagnosed as having ovarian cancer between June 2010 and December 2015. The median age was 59 (range 21-91) years. This study evaluated whether laboratory findings and clinicopathological factors were associated with PFS. The laboratory findings included elevated levels of D-dimer (>1.0 µg/ml), hyperfibrinogenemia (>400 mg/dl) and thrombocytosis (>40×10<sup>4</sup>/µl). The clinicopathological factors included the age, presence of venous thromboembolism, FIGO stage, histology, tumor diameter, presence of ascites and CA-125 levels. Kaplan-Meier method and Cox proportional hazards regression model were used. **Results** In univariate analyses, advanced stage (p<0.001), presence of ascites (p<0.05), hyperfibrinogene-

mia ( $p < 0.05$ ) and thrombocytosis ( $p < 0.001$ ) were associated with shortened PFS. Cox regression model demonstrated advanced stage (stage III or IV) (hazard ratio 27.8, 95% confidence interval 3.6–201.1,  $p < 0.05$ ) and hyperfibrinogenemia (2.6, 1.0–6.3,  $p < 0.05$ ) were independent prognostic factors for shortened PFS. **Conclusion** Hyperfibrinogenemia shortens progression-free survival in women with ovarian cancer independently of advanced stage. These results have important implications for clinicians.

### ISP-41-9

**Diagnostic utility of peritoneal effusion cell-block and immunocytochemistry for advanced-stage ovarian/peritoneal cancer prior to neoadjuvant chemotherapy** Yasuhiko Ebina, Kaho Suzuki, Senn Wakahashi, Yoshiya Miyahara, Hideto Yamada *Kobe University*

**Objective** To assess if peritoneal effusion cell-block (CB) and immunocytochemistry could be useful in recognition of ovarian/peritoneal cancer cells prior to neoadjuvant chemotherapy (NAC). **Methods** We conducted a prospective study for women who were diagnosed as having suspected stage III–IV ovarian/peritoneal cancer (ovarian cancer  $n=26$ , peritoneal cancer  $n=5$ ) between September 2010 and May 2017. A total of 31 peritoneal effusion cytology and concurrently prepared CB obtained from paracentesis were reviewed. The median age was 66 (range 38–88) years. The correlation between the cytology/CB result and final histological diagnosis was assessed. **Results** Of the 31 peritoneal effusion specimen, 21 malignancies were detected by cytology; however, CB increased the number of detected malignancies to 25 for an increased diagnostic yield of 19%. Twenty-three (92%) showing morphologic features consistent with ovarian/peritoneal cancer were PAX8+/WT-1+. The remaining 2 adenocarcinoma cases with CK20+/CDX2+/PAX8-/WT-1- represented metastasis from stomach and pancreas. Six patients who had benign results of CB underwent exploratory laparotomy and were diagnosed as primary ovarian/peritoneal cancer. Twenty-six patients received NAC and 17 patients underwent interval debulking surgery (IDS) afterward. Residual tumor measuring  $< 0.5$  cm was achieved in 94% of the patients. The incidence of serous carcinoma (76%) in the patients having malignant CB result was significantly higher than that in the patients with benign CB result (17%,  $p=0.018$ ). **Conclusion** Peritoneal effusion CB and immunocytochemistry is useful for the patients before NAC to confirm primary ovarian/peritoneal cancer. In case of benign CB results, non-serous histological types should be considered.

### ISP-42-1

**Effect of red ginseng on genotoxicity and health-related quality of life after adjuvant chemotherapy in patients with epithelial ovarian cancer: a randomized, double blind, placebo-controlled trial** Soo Jin Park, Hee Seung Kim, Jae-Weon Kim *Seoul National University College of Medicine, Korea*

**Objective** We evaluated the effect of red ginseng on toxicity, health-related quality of life (HRQL) and survival after adjuvant chemotherapy in patients with epithelial ovarian cancer (EOC). **Methods** A total of 30 patients with EOC were randomly assigned to placebo ( $n=15$ ) and red ginseng groups ( $n=15$ ) after cytoreductive surgery and adjuvant chemotherapy. All patients took placebo or red ginseng (3,000 mg/day) for three months. Then, we compared toxicity using laboratory markers, adverse events and genotoxicity between the two groups at week 0 (before consumption) and week 12 (after consumption). For genotoxicity, we evaluated binucleated cells (BN) index and micronuclei (MN) yield. Moreover, HRQL was investigated using questionnaire of the EORTC QLQ-C30, BFI, BPI, HADS and MOS-

SS. **Results** Red ginseng reduced MN yield in comparison with placebo despite no difference of BN index. Although red ginseng increased serum levels of alanine aminotransferase and aspartate aminotransferase significantly, they were within the normal value. Moreover, there were no differences in adverse events between placebo and red ginseng groups. In terms of HRQL, red ginseng was associated with improved emotional functioning and decreased symptoms of fatigue, nausea and vomiting, and dyspnea, reduced anxiety and interference affecting life and improved daytime somnolence. However, there was no effect of red ginseng on prognosis of EOC. **Conclusion** Red ginseng may be safe and effective to reduce genotoxicity and improve HRQL despite no benefit of survival in patients with EOC who received chemotherapy.

### ISP-42-2

**Practice patterns of debulking surgery for advanced-stage ovarian cancer: analysis from national and society-sponsored surveys** Soyeon Kweon, Hee Seung Kim, Jae-Weon Kim *Seoul National University College of Medicine, Korea*

**Background** To investigate practice patterns of debulking surgery, and identify surgical trends for advanced-stage ovarian cancer (AOC). **Methods** After searching for 878 studies on debulking surgery for AOC till 2016, we extracted 19 questions with similar query and answer formats in eight survey studies. Among them, five (26.3%), one (5.3%), and 13 (68.4%) questions were classified into general, training, and procedure information. **Results** In general information, there was a higher preference for optimal debulking surgery defined as no visible tumor (44%) compared with residual tumors  $< 1$  cm (38%) or  $< 2$  cm (2%), and omental disease involving the spleen or pancreas became more important as an intraoperative finding precluding optimal debulking surgery (35%) since 2010. The preference for neoadjuvant chemotherapy was the highest at use for 1–10% (36%) of AOC patients, which was preferred in Europe over the United States. In training information, there was a lack of additional training outside of gynecological fellowships (30%). In procedure information, conventional gynecological surgery was mainly performed by gynecological oncologists, whereas more than 50% of upper abdominal or urological surgeries were conducted by other surgeons or their cooperation. European clinicians showed a higher response rate of diaphragmatic stripping (88% vs. 60%) or resection (69% vs. 24%) than those from the United States. **Conclusion** No visible tumor as the criterion for optimal debulking surgery has become important in AOC, which requires aggressive surgery based on additional training programs. A high preference for neoadjuvant chemotherapy is associated with high preference of aggressive surgery.

### ISP-42-3

**The clinical significance of tertiary lymphoid structures (TLS) and tumor infiltrating B cells in ovarian cancer** Masayo Ukita, Junzo Hamanishi, Ryusuke Murakami, Kaoru Abiko, Tsukasa Baba, Masaki Mandai *Kyoto University*

**Objective** Tertiary lymphoid structure (TLS) are transient ectopic lymphoid organizations which develop under chronic inflammation. CXCL13 was shown to play a major role in TLS neogenesis. Recently TLS were detected in various type of cancers, however there are few reports about TLS in ovarian cancer. We investigated clinical significance of TLS in ovarian cancer. **Methods** 32 patients who were diagnosed with ovarian cancer (HGSC) and treated surgically in our hospital were selected from microarray data (KOV-75; GSE39204/55512). We evaluated TLS and tumor infiltrating lymphocyte (TIL) subsets (CD8+ T cell, CD20+ B cell, CD38+ plasma cell) and correlation between expression of CXCL13 and TIL subsets by using immu-



nohistochemical staining. We analyzed the correlation between gene expression of CXCL13 and survival time of the patients (pts) by using KOV-75 and the cancer genome atlas (TCGA) data set. **Results** Immunohistochemical staining revealed that TLS were detected in 72% (23 pts) of ovarian cancer patients, and the numbers of tumor infiltrating CD8+T cells, CD20+B cells and CD38+ plasma cells were significantly higher in cases with TLS ( $p < 0.05$ ). The numbers of tumor infiltrating CD20+B cells and CD38+plasma cells were significantly higher in CXCL13 high tumor than in CXCL13 low tumor ( $p < 0.05$ ). And also in microarray analyses of both KOV-75 and TCGA, high CXCL13 gene expression was significantly correlated with both favorable progression free survival and overall survival ( $p < 0.05$ , each). **Conclusion** CXCL13 contributes to better prognosis in HGSCs by inducing tumor infiltrating B cells and plasma cells. Induction of CXCL13 might be a new therapeutic target for HGSC.

### ISP-42-4

**Management of a ruptured perivascular epithelioid cell tumor during and after pregnancy : a case report** Kenta Nitahara<sup>1</sup>, Megumi Sasaki<sup>1</sup>, Hiroaki Hiraga<sup>1</sup>, Saori Ichikawa<sup>1</sup>, Keita Tsuji<sup>1</sup>, Yuji Yoshida<sup>1</sup>, Shinji Fukunaga<sup>2</sup> *Japanese Red Cross Ishinomaki Hospital<sup>1</sup>, Shin-Yurigaoka General Hospital<sup>2</sup>* Perivascular epithelioid cell tumors (PEComas) are a rare group of tumors with the distinctive feature of epithelioid cell proliferation. Their clinical behaviors are unclear ; however, they show an anatomical predilection for the gynecological tract. We report a case of a ruptured PEComa at 34 weeks of pregnancy that was found incidental to intra-abdominal bleeding. A 30-year-old woman, gravida 2, abortus 1, presented with sudden-onset left lower quadrant pain at 34 weeks of pregnancy. Computed tomography and sonography revealed abundant hemorrhagic ascites. An emergent exploratory laparotomy showed that the source of the bleeding was rupture of a hematoma-like tumor on the left round ligament of the uterus. The hemorrhage was controlled by excising the tumor. A pathological diagnosis of PEComa was confirmed following the observation of epithelioid perivascular cell proliferation, and positive immunostaining for both melanocytic (Melan A, HMB45) and smooth muscle markers (SMA, desmin, caldesmon). The pregnancy continued and ended with an uncomplicated full-term vaginal delivery. Because PEComas have a borderline malignant nature and a possible recurrent mass was detected by postoperative magnetic resonance imaging, we performed an additional surgical resection of the left round ligament. Though no palpable mass was found, pathological findings showed vascular invasion and a possible residual lesion. We are continuing postoperative outpatient follow-up without adjuvant chemotherapy. Because of the scarcity of such cases, universally established management methods for PEComas are lacking, particularly during pregnancy. We consider that primary surgical resection and additional chemotherapy in case of recurrence are a good choice of treatment.

### ISP-42-5

**A case of a postmenopausal woman with a spontaneously ruptured seromucinous borderline tumor of the ovary : A review of the literature** Mamiko Ohta, Noriyoshi Oki, Naoko Koriyama, Moyu Narita, Yukiko Mizuno, Ritsuko Yasuda, Mieko Inagaki, Homare Murakoshi, Juzo Okada, Satoru Motoyama, Shigeki Yoshida *Chibune General Hospital* Ovarian seromucinous borderline tumor (SMBT) has been newly categorized according to the WHO classification of tumors of the female reproductive organs revised in 2014. This type of tumor is rare and comprises 7.8% of all of ovarian bor-

derline tumors. Here, we present the first documented case of a spontaneously ruptured SMBT of the ovary in a postmenopausal woman. **Case A** 56-year-old nulliparous woman presented to the emergency department with an acute abdomen. MRI showed a 10 cm-left ovarian cyst with thick walls that exhibited hypointensity on T1WI and hyperintensity on T2WI, with retention of ascites and no solid component, which suggests a ruptured endometrial cyst. Through laparoscopy, a ruptured left ovarian cyst and retention of brown ascites were observed. We therefore performed a left salpingo-oophorectomy, and because postoperative pathological examination revealed SMBT of the left ovary, the patient additionally underwent total abdominal hysterectomy, right salpingo-oophorectomy, omentectomy, appendectomy, and biopsies of brown nodules on the peritoneum. Pathological examination confirmed SMBT of the left ovary with no metastases, and the brown nodules on the peritoneum in the pelvis were found to be noninvasive epithelial implants. The patient was diagnosed with stage IIB disease, did not receive additional chemotherapy, and has been recurrence free for 11 months since surgery. **Conclusion** Because of the rarity of endometrial cyst ruptures in postmenopausal women, an awareness of the possibility of ovarian borderline or malignant tumors, including SMBT, is necessary when a ruptured endometrial cyst is suspected in postmenopausal women.

### ISP-42-6

**Advanced ovarian cancer developing in a cyst of the canal of Nuck** Kazue Togashi, Noriaki Ohya, Hirokazu Sato *Japanese Red Cross Akita Hospital*

Ovarian cancer metastasizing to rare regions is sometimes challenging to diagnose. A cyst of the canal of Nuck is a rare cause of inguinal swelling in adult women. A 45-year-old woman presented with swelling in her right groin. The mass lesion measured 4×3 cm. Ultrasonography, magnetic resonance imaging suggested that it is a cyst of the canal of Nuck, and also suggested a left ovarian incidental tumor measured 7×4 cm. Pathological diagnosis during surgery revealed it to be an unusual metastatic cyst in the canal of Nuck. TAH+BSO+OMT, excision of the right inguinal mass lesion, and closure of the deep inguinal ring were performed. In women presenting with swelling of the groin, a cyst of the canal of Nuck might be a suggestion of ovarian cancer.

### ISP-42-7

**A case of neuroendocrine carcinoma developing from the broad ligament of the uterus** Yui Itonaga, Masakazu Nishida, Harunobu Matsumoto, Kaie Nasu, Hisashi Narahara *Oita University Hospital*

Neuroendocrine carcinoma (NEC), also called small cell carcinoma or large cell carcinoma, is a rare and aggressive tumor that develops mainly in the lung and intestine. More rarely, NEC develops in gynecologic organs, with poor prognoses. We experienced a case of NEC in the broad ligament of the uterus. The patient was a 74-year-old woman with symptoms of abdominal distension and constipation. Ultrasound sonography detected an abdominal tumor larger than 10 cm. She was then admitted to our hospital. She underwent surgery under the diagnosis of ovarian cancer, but the bilateral ovaries and uterus were normal in appearance, and a tumor was developing instead from the broad ligament of the uterus. The patient then received a hysterectomy, salpingo-oophorectomies, and lymphadenectomy, and the peritoneal membrane was stripped around the pelvic space. Despite our suggestion, she never accepted the adjuvant treatment. She discontinued her periodic follow-up with us and was followed in another hospital. Generally, the prognosis of NEC is poor, and there is no established treatment for a tumor



in a gynecologic lesion. However, we anticipate that the accumulation of experience treating such cases will eventually lead to a standard treatment for NEC.

### ISP-43-1

**Incidence and clinical outcomes of ovarian clear cell carcinoma in surgically resected endometrioma** Jinju Lee, Jigeun Yoo, Keun-Ho Lee *Seoul St. Mary's Hospital, The Catholic University of Korea, Korea*

**Background** We reviewed clinical features and survival outcomes of ovarian clear cell carcinoma patients who were initially diagnosed and surgically treated as benign ovarian endometrioma. **Methods** This study retrospectively reviewed medical records of patients who were surgically diagnosed with ovarian endometrial cyst from July 2008 to June 2014 in Seoul St. Mary's hospital. We also reviewed records of clear cell carcinoma patients who underwent surgery at the same period of time. We compared clinical characteristics, stage of cancer at the time of diagnosis, and survival data of each group. **Results** Eight out of 529 patients (1.51%) who were treated surgically for benign endometrioma were diagnosed with clear cell carcinoma on pathologic examination. Six patients were diagnosed with malignancy on frozen section during the operation, followed by staging surgery including total hysterectomy, bilateral lymphadenectomy and omentectomy. Two patients were diagnosed on final pathologic report after unilateral or bilateral salpingo-oophorectomy, and did not take restaging surgery. All 8 patients had stage I disease, and showed no recurrence. The median follow up period was for 58.5 months. We also identified 24 patients who were primarily diagnosed with ovarian clear cell carcinoma and underwent surgical treatment during the same period of time. The median follow up period was for 46 months. Among them, 11 (45.8%) patients had surgically or pathologically proven endometriosis simultaneously, and they showed comparable recurrence rate and overall survival with the suspected endometrioma group. Thirteen patients, who were not associated with endometriosis showed more advanced stage at the time of diagnosis, higher rates of recurrence and death, while mean tumor size was smaller (14.45 cm vs. 11.09 cm,  $p=0.05$ ). **Conclusion** We measured 1.51% of patients who were surgically treated for endometrial cyst were finally diagnosed with clear cell carcinoma on the pathological review. They were diagnosed with relatively lower stages of cancer and showed better survival outcomes. We were also able to confirm that endometriosis in those with clear cell cancer is associated with better survival outcomes.

### ISP-43-2

**Primary retroperitoneal Müllerian adenocarcinoma (PRMA) : A Case Report and Review of the Literatures** Chia-Yi Lee, Wen-Chun Chang *National Taiwan University Hospital, Taiwan*

Müllerian adenocarcinoma rarely originates from retroperitoneal space. Different differentiated cell types had been reported. Laparotomic tumor excision with avoidance of intra-operative rupture is an ideal surgical treatment. However, the recommended adjuvant treatment remains elusive due to limited case number and treatment experience.

### ISP-43-3

**Alpha-fetoprotein-producing ovarian malignant tumor in a postmenopausal woman** Shozo Yoshida, Akira Onogi *Osaka Gyomeikan Hospital*

Most of the AFP-producing ovarian tumors are germ cell tumors and occur in young women. We report a case of AFP-producing ovarian malignant tumor in postmenopausal woman. A

53 year-old nulliparous woman who had been postmenopausal for 3 years visited to our hospital with the chief complains of abdominal fullness and appetite loss. Magnetic resonance imaging of the abdomen and pelvis demonstrated a huge multilocular cystic mass with enhanced irregular solid component, measuring at least 30cm in diameter. Serum level of AFP was markedly elevated to 77,657.2 ng/ml, CA125 was 122.8 U/ml and CA19-9 was 305.9 U/ml. These results suggested the mass seemed to be a malignant ovarian germ cell tumor. The patient underwent surgical resection including a total hysterectomy, bilateral salpingo-oophorectomy and omentectomy. The mass was right ovary and weighed about 10kg. Postoperative histological examination revealed the tumor consisted of both germ cell and epithelial tumor components. Germ cell tumor component was yolk sac tumor and epithelial one was endometrioid adenocarcinoma with the background of endometriotic cyst. Immunohistochemical staining showed that yolk sac component was positive for AFP and SALL4 and endometrioid adenocarcinoma component was positive for CK7 and p53. After the surgery, the patient underwent six courses of adjuvant chemotherapy with docetaxel and carboplatin. Serum AFP level gradually decreased to below normal level 74 days after surgery. She is currently doing well without any sign of recurrence, 15 months postoperatively.

### ISP-43-4

**A case of Serous Tubal Intraepithelial Carcinoma detected by abnormal cervical cytology** Masahiro Sumitomo, Takahito Ashihara, Naoki Horikawa, Hirofumi Nonogaki *Shiga Medical Center for Adults*

**Introduction** Serous Tubal Intraepithelial Carcinoma (STIC) is very rare findings in women without genetic risk factor for ovarian and breast cancer. In this presentation, we describe a case of STIC without genetic risk factor diagnosed by abnormal cervical cytology. **Case** Forty-eight years old Japanese woman, Gravid 3 Para2, was referred to our hospital for further examination of abnormal cervical cytology. She had no familial history of ovarian and breast cancer. A cytological finding was adenocarcinoma, but no abnormal findings were detected in corn biopsy and endometrial curettage specimen. One year later, cervical cytology was detected adenocarcinoma once again, therefore she wished to be performed hysterectomy, and salpingectomy as well for reducing ovarian cancer risk. Histological findings in removed fallopian tube revealed serous intraepithelial carcinoma in distal fimbriated end. P53 staining was positive in immunohistological study. Adenocarcinoma cells derived from cervical cytology were remarkably similar to tubal intraepithelial carcinoma cells. **Discussion** We sometimes experience tubal cancer case diagnosed by abnormal cervical cytology, but in this case just epithelial lesion in distal end of fallopian tube was diagnosed by abnormal cervical cytology. This clinical course is thought to be extremely rare. Furthermore, this STIC lesion is considered to remain intraepithelial (not invaded into stroma) for more than one-year period because her adenocarcinoma cells were detected 1 year before hysterectomy. **Result** We experienced a rare case of STIC diagnosed by cervical cytology. From this case, it is suggested STIC remains intraepithelial for a long time.

### ISP-43-5

**Malignant ovarian tumors diagnosed after laparoscopic surgery at a general gynecological unit** Yoko Hasumi, Takahiro Hino, Yu Takahashi, Masakazu Sato, Nao Itaka, Chiharu Ueshima, Maki Nakata, Minako Koizumi *Mitsui Memorial Hospital*

**Objective** To assess characteristics of malignant ovarian tumors

diagnosed after laparoscopic surgery at a gynecology unit. **Methods** A retrospective study of malignant ovarian tumor patients who underwent laparoscopic surgery at a single institution from January 2015 to August 2017 was performed. **Results** We identified 6 patients. One patient had ovarian cancer and five patients had low potential malignancies. The median age was 55 (31–74) years old, The median size of the tumor was 4.5 (3–10) cm. One patient underwent cytectomy and five patients underwent salpingo-oophorectomy, of which four patients underwent follow-up hysterectomy and omentectomy. All cases had stage I disease. Compared to the 13 malignant ovarian tumor patients who underwent laparotomy during the same period, the laparoscopic surgery group had tendency of smaller tumors with smaller solid parts in the tumor, and poor contrast enhancement of blood supply in the tumor upon preoperative ultrasound and MRI evaluations. **Conclusion** Although the incidence is low, there are malignant ovarian tumor cases which are difficult to predict preoperatively. Especially in elderly patients, it is important to be aware of this possibility and to provide sufficient information for patients upon treatment.

### ISP-43-6

**Endometrioid adenocarcinoma arising from deep infiltrating endometriosis involving the bladder : A case report and review of the literature** Yosuke Tarumi, Taisuke Mori, Fumitake Ito, Takuya Sugahara, Hiroyuki Okimura, Eiko Maeda, Hisashi Kataoka, Osamu Takaoka, Yukiko Tanaka, Akemi Koshiba, Izumi Kusuki, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Introduction** Endometriosis is a common disease, but deep infiltrating endometriosis (DIE), especially DIE involving the bladder, is rare. Malignant transformation of endometriosis is well-established pathology, but only 8 cases of malignant transformation of DIE involving the bladder have been reported. We report a very rare case of endometrioid adenocarcinoma arising from DIE involving the bladder. **Case** Our patient was a 45-year-old woman who presented with frequent urination and micturition pain during her menstrual period. Transvaginal ultrasonography and MRI revealed a lesion in the posterior wall of the bladder. Preoperative cystoscopy findings revealed focal lesions of endometriosis, and a blueberry spot on the mucous membrane of the bladder. We preoperatively diagnosed DIE involving the bladder and performed laparoscopic total hysterectomy and partial bladder resection. Histopathological examination revealed the co-existence of endometriosis and endometrioid adenocarcinoma involving the bladder wall, and the continuum between the benign focus and malignant glands in sections of deep infiltrating endometriosis involving the bladder. Postoperative CT findings showed no other malignant lesions. We regarded this case as peritoneal carcinoma because the lesions were adjacent to the peritoneal serosa, and administered 6 cycles of adjuvant chemotherapy. There was no evidence of recurrence or metastasis after 30 months of follow-up. **Conclusion** The treatment for malignant transformation involving the bladder is poorly defined. Further case studies are needed to confirm the optimal treatment and the likely prognosis of this malignancy.

### ISP-44-1

**Video endoscopic inguinal lymphadenectomy via the hypogastric subcutaneous approach (VEIL-H) : A preliminary series report** Yifeng Wang, Gaowen Chen, Zengying Cui, Youhong Zheng, Xiaoxuan Li, Ying Wang, Ying Zhu *Southern Medical University, China*

**Objective** To summarize our experiences and preliminary results of video endoscopic inguinal lymphadenectomy via a hypogastric subcutaneous approach (VEIL-H) in the management

of vulvar cancer. **Methods** From 2009 to 2015, 21 women with vulvar cancer underwent VEIL-H, this inguinal procedure were performed with four working ports placed in the hypogastric area. **Results** All patients underwent the bilateral VEIL-H, and six of which underwent additional laparoscopic pelvic procedure following VEIL-H via the initially working ports. The mean (range) operative time of VEIL-H was 89.5 minutes (70–127 minutes), with the retrieval of 16.5 (12–22) superficial nodes and 8.9 (6–13) deep nodes. The estimated median blood loss was 21.7 ml (5–120ml) and the drain volume was 103.6 ml (60–220 ml) on average. The median hospital stay was 8.3 days (3–14 days). The great saphenous vein (GSV) was spared in 39 limbs. No major intraoperative complications occurred except the hypercarbia and rupture of GSV. The postoperative complications included hypesthesia of groin, infection of skin edges surrounding the working port, lymphocele, mild-moderate lymphedema and local erythema. With a median follow-up of 69 months (41–97 months), isolated skin bridge metastasis within the right groin was identified via biopsy in one patient with ipsilateral lesion (4cm) postoperatively. Surgical resection had been attempted. **Conclusion** This preliminary series indicates that VEIL-H could be an alternative to the open approach for the treatment of genitourinary malignancies. However, a larger series with more cases and longer follow-up are necessary to evaluate the full therapeutic efficacy of this novel technique.

### ISP-44-2

**Repurposing itraconazole as an anticancer agent : rapid clinical response of metastatic vaginal melanoma** Roze Nakata, Kayo Inoue, Yu Kato, Shinichiro Saeki, Hidetake Kamei, Tomoko Ueda, Hiroshi Tsubamoto, Hiroaki Shibahara *The Hospital of Hyogo College of Medicine*

**Background** Itraconazole, a common anti-fungal agent, has anticancer activity. We have reported preclinical and clinical studies in various types of cancer. We show the rapid clinical response in a patient with metastatic vaginal melanoma. **Case** 64-year-old woman presented vaginal bleeding and left inguinal pain with lymphnode swelling. Vaginal examination showed the fragile hemorrhagic vaginal tumor of ping-pong ball size with intact cervix. Metastatic vaginal cancer was diagnosed, and informed consent of a window of opportunity trial of itraconazole (UMIN00018388) was obtained. She was administered 400ml itraconazole per day. Pathological diagnosis was malignant melanoma, having 20% expression of PD-L1 without VRAF mutation. PET/CT scan showed metastases to pelvic and left inguinal lymphnodes and her right foot. Brain MRI revealed 2 metastases. After 10-day intake of itraconazole, her left inguinal lymphnodes shrunk and, her pain or tender was diminished. Administration of itraconazole continued until she completed stereotactic radiosurgery of brain metastases, then she received nivolumab. After 28-day administration of itraconazole, 18-FDG uptake in any lesion decreased. mRNA isolated from obtained tissue by biopsy before and 10-day after itraconazole administration was subjected to cDNA microarray analysis. Transcript of 4 genes coding statherin, EEF1A2, transthyretin, and N-cadherin was down-regulated to the level of <1/100. **Conclusion** Two clinical trials of plitidepsin targeting EEF1A2 had modest activity in patients with melanoma. Expression of transthyretin and N-cadherin were reported to be associated with progression of melanoma. Itraconazole could be an alternative drug with safe and low cost for malignant melanoma.

### ISP-44-3

**Anaplastic lymphoma kinase-negative uterine inflammatory myofibroblastic tumor containing the *ETV6-NTRK3* fusion gene : the first case report** Akimasa Takahashi, Mao Uemura,

Jun Kitazawa, Yoshihiko Hayashi *Nagahama City Hospital*

An inflammatory myofibroblastic tumor (IMT) is currently regarded as a neoplasm of low malignant potential, and it is the most commonly found tumor in the lung or orbit. However, the uterus is a distinctly rare site of occurrence. About 50% of patients have anaplastic lymphoma kinase (ALK) gene rearrangement, and recent studies have described novel fusions involving the *ROS1*, *PDGFR-β*, and *ETV6* genes in a subset of ALK-negative patients. We describe the case of a uterine IMT in a 44-year-old woman presenting with anemia. Her ultrasonogram and magnetic resonance imaging scan showed a myxoid degenerative myoma-like mass measuring 70 mm in maximum diameter on the left side wall of the uterine body. Hysterectomy was performed as definitive treatment. Microscopic examination revealed spindle cell proliferation with numerous lymphocytes and plasma cells. Immunohistochemically, the spindle cells were negative for *ALK-1*, desmin, and smooth muscle actin. The pathologic diagnosis was IMT arising from the uterus. Her tumor showed *ETV6-NTRK3* translocation, as demonstrated by fluorescence in situ hybridization, not *ALK*, *ROS1*, or *PDGFR-β* translocation. She underwent computed tomography (CT) of her lung and abdomen at 31 months postoperatively, and the CT scans showed no disease recurrence. This is the first report of the presence of the *ETV6-NTRK3* fusion oncogene in an ALK-negative IMT of a patient's uterus. Its association with the *ETV6-NTRK3* fusion gene provides some clues to better understand this neoplasm and to eventually develop specific therapies.

#### ISP-44-4

**Trousseau's syndrome associated with gynecologic malignancies. Clinicopathologic features of 11 cases** Kazuya Onuma, Takanori Fukuda, Remi Watanabe, Yutaka Kohata, Tomoyuki Ichida, Yuri Aihara, Ayumi Kumagai, Yuina Kubo, Yoshie Uzawa, Kenji Hishikawa, Takeshi Kusaka, Hiromi Inoue *Shonan Kamakura General Hospital*

**Objective** Trousseau's syndrome (TS) is known to be typically associated with pancreatic, gastric, or pulmonary carcinoma, but rarely documented in association with gynecologic malignancies. **Methods** Our oncology database was searched for cases of gynecologic malignant neoplasms with the document of TS, infarction, or embolism for a 5.5-year period. For the cases meeting the diagnosis of TS, medical records were retrieved to obtain the data including age, BMI, clinical manifestation, D-Dimer (DD), stage, outcome and the size and histologic type of tumor. **Results** Eleven cases with available data were subjected to this study. The patient age ranged from 35 to 75 (median 63), and BMI from 16.3 to 29.5 (mean 21.3). The events of TS were pulmonary embolism (5), cerebral infarction (5), and multiple organ infarction (1). TS was the initial presentation, leading to discovery of malignant neoplasms in 6 cases. All but one patient with endometrial carcinoma had ovarian carcinoma, and mostly in advanced stage. The mean size of ovarian tumor was 11 cm. Clear cell carcinoma (CCCA) was the most common histologic type, comprising 6 of 10 cases, and followed by mucinous tumor in 2 cases. The mean of DD was 21.0 μg/ml. With prompt diagnosis and management, TS did not affect the prognosis in most patients. **Conclusion** TS was mainly associated with ovarian carcinomas and CCCA was the most common histologic type. Thromboembolic events of TS were frequently the initial presentation prior to the diagnosis of malignancy. We should be aware of occurrence of TS in patients with ovarian carcinoma.

#### ISP-44-5

**Vulvar apocrine adenocarcinoma responded to weekly paclitaxel and biweekly bevacizumab. A case report** Shinichiro

Saeki, Tomoko Ueda, Roze Nakata, Michie Matsuoka, Riya Sakane, Kayo Inoue, Hiroshi Tsubamoto, Hiroaki Shibahara *The Hospital of Hyogo College of Medicine*

Apocrine adenocarcinoma (AA) of the skin sweat gland is a rare disease. Among previous reports of about 50 AA cases, vulvar AA counted for only 9 cases. **Case A** 63-year-old woman was referred to our institution with a complaint of her left vulvar mass and the lymphedema of the left leg with slight pain. Biopsy of her enlarged inguinal lymphnode showed adenocarcinoma. PET/CT scan revealed 18-FDG uptake in the left vulvar and in the pelvic, para-aortic, and the left supraclavicular lymph nodes. Local resection of vulvar tumor was conducted, and metastatic AA was diagnosed with positive androgen receptor and GCDFP-15. The first regimen of 175mg/m<sup>2</sup> of paclitaxel (PTX) and AUC5 of carboplatin was conducted according to the previous report of head AA. After the first cycle, her leg swelling was improved with 3kg weight loss. However, her leg began to swell again after 2 cycles. After 3 cycles, the lymphedema extended to her lower abdomen with redness, warmth, and pain. Her serum creatinine and CEA elevated. She had the left hydronephrosis and ureter stent was placed. The second regimen with PTX and bevacizumab (Bev) was conducted according to TNBC. Combination of weekly administration of PTX (80 mg/m<sup>2</sup>) and biweekly administration of bevacizumab (10 mg/kg) was reported to have synergistic effect in platinum resistant ovarian cancer. After she received the second regimen (wPTX/Bev), her symptom was improved and PET/CT scan revealed loss of 18-FDG uptake in any lymphnodes. **Conclusion** wPTX/Bev could be a promising candidate for the treatment of AA.

#### ISP-44-6

**Three different clinical courses and the conservative management of uterine arteriovenous malformation (AVM) diagnosed by color Doppler ultrasonography** Madoka Tsuzuki, Tomohiko Ishida, Hiroaki Naitou, Ritsuko Ishii, Mariko Tomosaka, Emi Saga, Kazuya Abe, Sumiko Hasegawa, Hirohumi Ohashi, Shinichiro Takubo *Itabashi Chuo Medical Center*

Uterine arteriovenous malformation (AVM) used to be a rare and life threatening disease, with a massive genital hemorrhage of unknown origin. Nowadays, the ultrasonography (US) guides us to diagnose AVM more easily and in earlier stage of the disease, bringing more opportunities of conservative management. Three cases of acquired AVM with successful conservative treatment are shown, in which the accurate diagnosis was established by two-dimensional (2D) and three-dimensional (3D) color Doppler US, and in which various clinical courses were observed. **Case 1** Primipara 33 years old, a month after the preceding artificial abortion. **Case 2** Primipara 26 years old, and **Case 3** Primipara 39 years old, both 2 weeks and 1 week after the spontaneous miscarriage emission and both post IVF-ET. The 2D color Doppler showed clearly that both arterial and venous vessels are combined in a complex. The 3D color Doppler made it more visible, proved that it rather has the nidus than the fistula. All were considered to go under the uterine conservative management. In Case 1, gonadotropin-releasing hormone agonist (GnRHa) was given and abnormal vessels all regressed to an undetectable level after few months. In Case 2, uterine artery embolization (UAE) was introduced, and prompt regression was observed. In Case 3, UAE was also performed, then continuous GnRHa was given due to poor response to UAE. Quick diagnosis of AVM in early stage of the disease using ultrasonography provides more opportunities of uterine conservative management, which definitely fulfills the wish of patients.

## ISP-44-7

**A case of lymphangiomyomatosis with suspected primary peritoneal cancer and struggling to control ascites** Ken Matsukuma, Koichiro Kawano, Sayo Kubo, Jongmyung Park, Hiroki Nasu, Atsumu Terada, Shin Nishio, Naotake Tsuda, Kan Komai, Kimio Ushijima *Kurume University Hospital*

Lymphangiomyomatosis (LAM) is a rare disease with a incidence of 1.9 to 4.5 cases per million, and it occurs exclusively in women of reproductive ages. LAM cells showing smooth muscle cell-like morphology proliferate in the lungs, axial lymphatics including the mediastinum, retroperitoneum. Approximately 15% of patients have been diagnosed based on the presence of chylothorax, chylous ascites, and lymphangioliomyomas of the retroperitoneum and pelvis. A 44-year-old woman was referred with a suspicious of primary peritoneal cancer due to the findings of pleural effusion, ascites, pelvic lymph node swelling, and peritoneal irregularity. Exploratory laparoscopy revealed chylous ascites and pelvic lymphadenopathy without peritoneal dissemination. Right splingo-oophorectomy, left salpingectomy, omentectomy, and pelvic lymphadenectomy was performed. Pathological diagnosis showed no adnexal tumor but paraganglioma in pelvic lymph nodes. Postoperatively, we could not control the chylous ascites by fasting, diuretics, somatostatin analogue, and cell-free and concentrated ascites reinfusion therapy. Therefore, laparotomy was performed. Because we failed to identify lymphatic efflux sites using indocyanin green, the lymph duct above the excised lymph node was ligated. Histological findings of lymph node showed that cells with homogeneous circular nuclei in the eosinophilic cytoplasm formed vesicular nests. Immunohistochemistry was positive for alpha smooth muscle actin, HMB45, and Melan A. Computed tomography revealed the vesicular lesion in her both lungs. These findings were diagnosed as LAM and we started to administrate sirolimus. Her symptoms dramatically improved after the initiation of sirolimus. Although there was no change in pulmonary lesions, ascites markedly decreased without a sign of relapse for 6 months.

## ISP-44-8

**A case of amelanotic malignant melanoma arising from vagina** Takashi Hirayama, Soshi Kusunoki, Kazunari Fujino, Yasuhisa Terao, Atsuo Itakura *Juntendo University Hospital*

Malignant melanoma (MM) arising from vagina is an extremely rare and highly malignant disease. It constitutes less than 0.3% of all melanomas and less than 3% of all malignant vaginal tumors. In the MM, it contains 15–20% of amelanotic MM showing only a few or no melanin component in the tumors on the pathological findings. Therefore it is often difficult to diagnose and to determine the surgical margin preoperatively. We describe a 66-year-old female patient with an MM arising from vagina, which was almost composed of an amelanotic lesion. She visited a local hospital due to abnormal genital bleeding. Since endocervical cytology showed AGC and endocervical biopsy showed MM, she was referred to our hospital suspected MM from uterine cervix. We found the black spots suspected MM at the vagina, around the external urethral orifice, uterine cervix and vulva preoperatively. There is no metastasis on the PET-CT. Therefore, we performed the anterior pelvic exenteration, pelvic lymphadenectomy and transverse rectus myocutaneous flap to resect completely including urinary organs suspected unexpected spread of tumors. As a result of pathological findings, the MM originated from vagina spread widely at vulva, urethral orifice and uterine cervix, and almost the MM lesions were amelanotic. Since the tumor thickness was 50 µm and the surgical margin and lymph nodes metastasis were negative, we confirmed that complete resection was achieved. In case of MM

arising from genital tract, we should consider the possibility of amelanotic lesion and determine the surgical procedure carefully to perform complete resection.

## ISP-44-9

**Isolated fallopian tube torsion diagnosed and treated with laparoscopic surgery** Yuji Takahashi, Fumitake Ito, Osamu Takaoka, Hiroshi Tatsumi, Izumi Kusuki, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Among diseases causing acute lower abdominal pain in women, isolated fallopian tube torsion is very rare with an annual prevalence of 1 in 1.5 million. Because it has fewer findings on imaging compared to adnexal torsion, the correct diagnosis can rarely be made before an operation. We present a case of isolated fallopian tube torsion that was suspected preoperatively by its clinical course and findings on computed tomography. A 24-year-old woman repeatedly experienced acute colicky pain in the right lower back. Transvaginal ultrasonography and magnetic resonance imaging showed a right pelvic cystic lesion with intact ovaries; these findings led us to schedule a laparoscopic examination. However, the patient presented to the emergency room with acute severe right back pain. The preoperative diagnosis considering the computed tomography findings and clinical course was consistent with fallopian tube torsion. An earlier diagnosis may have help to preserve the fallopian tube and future fertility.

## ISP-44-10

**Primary peritoneal malignant mesothelioma with massive ascites : a case report** Yayoi Higuchi, Takashi Ushiwaka, Yusuke Ujihara, Ruriko Yamada, Kayo Taniguchi, Nagamasa Maeda *Kochi Medical School*

**Background** Primary peritoneal malignant mesothelioma (PPMM) is a very rare tumor. This disease accounts for about 10–15% in all types of mesothelioma. It is difficult to differential diagnosis from peritoneal cancer. We demonstrate in this paper a case of PPMM that is very rare and also difficult to differential diagnose from peritoneal cancer. **Case** Eighty-four years old woman complained lower abdominal pain and abdominal distension. Massive ascites was pointed out and consulted to our clinic. According to CT examination, massive ascites and peritoneal thickening were observed. PET-CT revealed high FDG accumulation in the omentum and peritoneum. Though the abdominal puncture was performed twice, but cyto-diagnosis for ascites was negative. Thus, exploratory laparotomy was performed for its diagnosis. Intra-operative findings revealed about 4,000ml of thin-yellow ascites and diffuse white nodular lesions spreading in omentum and peritoneum. According to the pathological and immunohistological findings, the tumor was diagnosed for epithelial type PPMM, especially decidual type that is a subtype. General condition was getting worth after laparotomy because of massive ascites. Medical staff and her family decided not to perform chemotherapy because of rapid decline of the general condition. The patient was deceased on the 27th day after admission. **Conclusion** Because PPMM is originated from the peritoneum, differential diagnosis with peritoneal cancer may be extremely difficult. When cyto-diagnosis for ascites cannot be identified regardless of massive ascites and widespread peritoneal lesions, PPMM should be considered.

## ISP-45-1

**Epidemiology of prolonged pregnancy in Mongolia : Incidence and risk factors** Saruulsaikhan Erdenebat, Amgalanbaatar Dorjkhuu, Enebish Sundui, Enkhsetseg Jamsranjav *Mongolian National University of Medical Sciences, Mongolia*

**Aim** Prolonged pregnancy is associated with an increased fre-



quency of perinatal mortality, maternal complications, labor dysfunction and postpartum hemorrhage. The purpose of our study was to investigate the incidence and some risk factors for prolonged pregnancy in Ulaanbaatar, Mongolia. **Methods** We retrospectively analyzed 13,444 cases with prolonged pregnancy in the period of 2014–2016. The information was obtained from the patients' histories in four maternity hospitals in Ulaanbaatar, Mongolia. **Results** In the period of 2014–2016, there were 123,218 deliveries in Ulaanbaatar. Of these 13,444 (10.9%) were prolonged pregnancies. Among the prolonged gestation, 67% were multiparous women and 33% in primiparous women. The risk of prolonged pregnancy is higher in the age group under 20 and over 36 years old mothers. There was a significant difference between gender of a fetus ( $P < 0.000001$ ). The overall risk of pregnancy loss (stillbirth and infant mortality) significantly increased as compared with term births (0.6% vs. 0.2%  $P < 0.000001$ ). Also, Neonatal mortality rates fell significantly increased with advancing gestation to reach at 41 weeks of gestation. **Conclusion** Our data showed that prolonged pregnancy is associated with an excess of stillbirth, a gender of the fetus and maternal age.

### ISP-45-2

**JICA projects to disseminate cardiocotography in Mongolia** Kazutomo Ohashi<sup>1</sup>, Masayuki Endo<sup>2</sup> *Osaka University, Division of Health Sciences<sup>1</sup>, Osaka University<sup>2</sup>*

**Objective** We conducted two JICA projects to disseminate CTG in Mongolia, and present our views on international cooperation among Japanese obstetricians. **Methods** We introduce two JICA projects in Mongolia : 1) Midwifery training course (2013–2016) and 2) Feasibility survey for introducing cardiocotography (2016). In Project 1, 20 pairs of midwives and obstetricians participated in training in Japan. Project 2 was a JICA partnership with private sector activities in developing countries and we examined the effect of introducing a CTG central monitoring system in one tertiary hospital from May to September 2016 with three visits to Mongolia. On the second visit in August, we organized a CTG seminar for medical staff and medical engineers (ME). Clinical data were divided into two stages : stage 1 (before the second visit) and stage 2 (after the second visit). **Results** The ex-participants in Project 1 supported the operation of Project 2. The numbers of deliveries were 483 and 307 in stages 1 and 2, respectively. The numbers (%) of vacuum extractions, neonatal resuscitations and neonatal deaths were 9 (1.86%) vs. 15 (4.89%), 14 (2.90%) vs. 3 (0.98%), and 6 (1.25%) vs. 3 (0.96%), respectively. Additionally, the use of a central monitoring system led to reduce working hours and improvement of the working environment. **Conclusion** Project 2 was planned according to requests of participants in Project 1. When developing overseas support projects, it is important to sufficiently grasp the needs of medical professionals working at the site. Multidisciplinary cooperation was essential for the project's success.

### ISP-45-3

**An effective introduction and practice of "DRCBRAVADO" as an educational tool of Cardiocotogram for medical students in bed-side learning** Mariko Watanabe, Susumu Miyashita, Shoko Ochiai, Ayano Suzuki, Chiyori Sakamoto, Emi Motegi, Kazumi Tada, Ichio Fukasawa *Dokkyo Medical University*

**Objective** ALSO (Advanced Life Support in Obstetrics), multidisciplinary simulation training course, employs "DRCBRAVADO", initial letters for systematic review of cardiocotogram as an educational tool. We investigated the effect on the introduction and practice of DRCBRAVADO for bed-side learning (BSL) of medical students. **Methods** An inclusive lecture and

drill (L&D) using DRCBRAVADO were given to each BSL group, consisting of 5–8 persons of the fifth-year medical students. We analyzed self assessment score sheets recorded before and after L&D. The sheet included multiple items scored 0–5 points separately. **Results** Twenty-five groups, total of 170 students were enrolled. Prior learning score were quite low but their need for an efficient method to learn cardiocotogram was very high ( $2.9 \pm 0.066$  (mean  $\pm$  SE),  $4.9 \pm 0.020$ ). Scores were increased significantly ( $p < 0.01$ ) after the L&D in overall confidence to assess cardiocotogram, understanding of the learning points and interpretability of them ( $1.4 \pm 0.047$  vs  $4.0 \pm 0.049$ ,  $1.7 \pm 0.052$  vs  $4.3 \pm 0.046$ ,  $1.3 \pm 0.042$  vs  $3.8 \pm 0.051$ ). There revealed a positive correlation between "understanding" and "interpretability" ( $R=0.60$ ,  $P < 0.001$ ) but little relation between "interpretability" and "feel useful" or "feel applicable" ( $R=0.36$ ,  $0.37$ , NS). **Conclusion** Introduction and practice of DRCBRAVADO as an educational tool seemed to be useful to enhance the motivation for learning but not to be sure about long-term effect on assessment skills because they had limited opportunity for clinical application.

### ISP-45-4

**Imprisoned and Pregnant : Evaluating the Use of Correctional Restraints** Mallory Fox, Kelly Best *University of Florida College of Medicine, USA*

**Background** The use of physical restraints in pregnant incarcerated patients is commonplace in many health care institutions. The American College of Obstetricians and Gynecologists (ACOG) among other organizations have adopted position statements opposing the use of physical restraints. My project aimed to assess the baseline knowledge of the correctional guard staff implementing restraints, and to educate guard staff in efforts of aligning practices in accordance with ACOG. **Methods** An educational seminar was presented to a voluntary group of correctional guards involved in the care of UF Health obstetric patients. The lecture covered associated health risks and current practice recommendations. An anonymous pre and post IRB approved survey was administered. The rate of correct answers by question was described across time periods using counts and percentages, and analyzed using Fisher's exact tests and Wilcoxon's Signed Rank Test using SAS<sup>®</sup> Version 9.4 for Windows. **Results** Fifteen correctional guard staff participated and completed the pre and post survey. There was no significant relationship between time period (pre/post) and correct responses ( $p=0.2148-1.0$ ). Additionally, there was no significant change in overall score between time periods ( $p=0.1052$ ). **Conclusion** The current study showed that several guard staff are not familiar the current guidelines set forth by ACOG and the Florida State Statute. While there was not a statistically significant difference in pre and post survey answers, the need for education remains evident. Efforts should be made to limit the use of physical restraints to improve quality of care and patient safety.

### ISP-45-5

**Determinants of Utilization of Antenatal Care Services among Women in Kungyangone Township, Myanmar** San San Myint *University of Medicine 1, Myanmar*

This study was to detect the determinants of utilization of antenatal care services in Kungyangone Township, Myanmar. This cross-sectional analytic study was done using both quantitative and qualitative methods from January 2014 to January 2015. 284 women (83 from urban and 201 from rural area) rearing under one year old child were interviewed with a structured questionnaire. For qualitative approach, six focus group discussions and nine in-depth interviews were conducted. Qualitative and qualitative data were analyzed using SPSS version 16 and manually.



There were 64.1% of mothers took proper antenatal care. In urban areas, 56.6% took proper antenatal care whereas 67.2% took proper antenatal care in rural areas. In multivariable model, educational level of husband, neonatal complication in previous pregnancies, mode of transportation, waiting time at antenatal clinic were significantly associated with antenatal care utilization. The respondents mentioned that availability of transportation to antenatal clinic, the condition of being apparently healthy pregnant women, migration to different places and opening hours of the antenatal clinic are main factors influencing the proper antenatal care. The majority of women in the qualitative study supported antenatal care. A few mentioned the benefits of antenatal care such as birth plan, preparedness for emergency situation and timely referral of high risk cases. A few respondents had awareness of early antenatal visit, antenatal care timing and minimal antenatal care frequency. To conclude, these results would be valuable to raise awareness of proper antenatal care in the community to ensure good maternal and fetal outcome thereby reducing maternal and perinatal morbidity and mortality.

### ISP-45-6

#### Transvaginal And Colour Doppler Ultrasound In Pregnant Women With Previous Caesarean Scar With Placental Praevia

Mar Ma Wynn *University of Medicine 1, Myanmar*

This study was a hospital-based prospective descriptive study, done in Central Women's Hospital, Yangon from October 2013 to September 2014, to determine placenta accreta in pregnant women with previous caesarean scar with placenta praevia by Transvaginal colour Doppler ultrasound and to assess the accuracy of detection of placenta accreta by Doppler ultrasound. Fifty patients with caesarean section scar with placenta praevia were recruited for transvaginal colour Doppler ultrasound. Among them, 39 (78%) patients had one previous caesarean section, 10 (20%) patients had two previous caesarean section and one patient had three previous scars. Presence of placenta accreta were detected by transvaginal colour Doppler ultrasound and were confirmed at caesarean section. Morbid adhesion of placenta praevia were diagnosed by ultrasound in 8 patients. Among them, 4 patients really had morbid adhesion and the rest had no occurrence of morbid adhesion at caesarean section. Positive predictive value of TVCDS in detection of placenta praevia is 50% and negative predictive value was 100%. Correctly diagnosed morbid adhesion (accuracy of percentage agreement) was 92%. Four cases of placenta accreta had to undergo hysterectomy for life-saving. One maternal death was occurred due to uncontrolled PPH with morbid adhesion with Rh negative blood group. Women in this study are high risk for placenta accreta. Antenatal imaging techniques should be considered where part of the placenta lies under previous scar. If there is imaging evidence of morbid adhesion, delivery should be planned in setting with adequate resources.

### ISP-45-7

#### Fear of childbirth and associated factors among pregnant women in Siriraj Hospital

Matus Phunymmalee, Dittakarn Boriboonhirunsarn *Siriraj Hospital, Thailand*

**Objective** To determine prevalence of childbirth fear among un-complicated pregnant women in Siriraj Hospital and possible associated factors. **Methods** A total of 315 uncomplicated, singleton pregnant women were enrolled during early third trimester. All participants were interviewed regarding baseline demographic, social, economic, family, and obstetric characteristics. Fear of childbirth (FOC) was evaluated by Thai version of Wijma Delivery Expectancy/Experience Questionnaire Version A (WDEQ-A). Prevalence of low, moderate, high and severe fear

of childbirth were estimated according to WDEQ-A scores ( $< 37$ , 38-65, 66-84, and  $\geq 85$  respectively). WDEQ-A scores and level of FOC were compared between various characteristics to determine possible associated factors. **Results** Mean age was 29.1 years, mean GA was 34.6 weeks, 50.2% were nulliparous, 22.6% had prior abortion, 22.6% were housewives, 33.8% graduated bachelor degree or higher, 56.7% were in extended family, 28.9% had inadequate family income. Of them, 63.6% were planned pregnancy. Majority (96.1%) had ever been told about delivery experience and 76.7% had ever witnessed delivery. Mean WDEQ-A scores was 51.9+14.4. Prevalence of low, moderate, high, and severe FOC were 18.4%, 64.9%, 16.1%, and 0.7%, respectively. Mean FOC score was significant higher in women with unplanned compared to planned pregnancy (542 vs. 506,  $p=0.033$ ). Significant higher prevalence of high/severe FOC was observed in women who had inadequate family income (23.9% vs. 13.8%,  $p=0.033$ ), without family support (31.3% vs. 15%,  $p=0.02$ ), never been told about delivery experience (41.7% vs. 15.7%,  $p=0.034$ ) and never witness delivery (26.8% vs. 13.7%,  $p=0.01$ ). **Conclusion** Prevalence of high and severe FOC were 16.1% and 0.7%, respectively. High/severe FOC was related to low financial and family support and less understandings on delivery process.

### ISP-45-8

#### Evidence of exposure to chemicals and heavy metals during pregnancy in Japanese women

Ryo Maekawa<sup>1</sup>, Yumiko Mihara<sup>1</sup>, Yuichiro Shirafuta<sup>1</sup>, Masahiro Shinagawa<sup>1</sup>, Lifa Lee<sup>1</sup>, Isao Tamura<sup>1</sup>, Hiromi Asada<sup>1</sup>, Toshiaki Taketani<sup>1</sup>, Hiroshi Tamura<sup>1</sup>, Tsunehisa Makino<sup>2</sup>, Norihiro Sugino<sup>1</sup> *Yamaguchi University<sup>1</sup>, Yurin-Koseikai Fujiyama Hospital<sup>2</sup>*

**Objective** Prenatal exposure to environmental chemicals such as phthalates, PFCs, pesticides, bisphenol A, nicotine, PBDEs, and heavy metals is a growing concern because such exposures have been shown to be associated with various diseases. The levels of chemicals and heavy metals in maternal blood, cord blood, maternal urine and amniotic fluid in Japanese pregnant women were investigated. **Methods** One hundred and forty-five women, including 14 fetal growth restriction cases, were included in this study. The levels of phthalates (DEHP and MEHP), PFCs (PFOS, PFHxS, PFOA and PFNA), pesticides (DMP, DMTP, DEP, DETP, 3-PBA and S-421), bisphenol A, nicotine (NIC, NNIC, COT, NCOT and HCOT), PBDEs and heavy metals were measured. The relationship between fetal growth and the levels of chemicals and heavy metals were also investigated. **Results** Phthalates, PFCs, pesticides, PBDEs and heavy metals were detected in high frequency, whereas nicotine and bisphenol A were almost negative. The levels of phthalates, PFCs and several heavy metals in the maternal blood, cord blood and amniotic fluid indicated that these contaminants were transferred to the fetus. High PFNA levels in the maternal blood and cord blood were significantly and negatively associated with fetal growth. **Conclusion** The present study showed the levels of chemicals and heavy metals in the maternal blood, cord blood and amniotic fluid in pregnant women in Japan. Pregnant women in Japan and their fetuses are exposed to a variety of chemicals and heavy metals.

### ISP-45-9

#### Impact of maternal inadequate gestational weight gain on neonatal birth weight in Japanese women

Satoru Ikenoue, Kei Miyakoshi, Yu Sato, Yohei Akiba, Toshimitsu Otani, Marie Fukutake, Yoshifumi Kasuga, Daigo Ochiai, Tadashi Matsumoto, Mamoru Tanaka, Daisuke Aoki *Keio University*

**Objective** Japanese pregnant women are characterized as low rate of overweight and high rate of inadequate gestational

weight gain (GWG), compared to those in other developed countries. To date, the impact of GWG in Japanese women on neonatal outcomes has not been fully understood. The aim of this study was to investigate the association between GWG and neonatal birth weight (BW) in Japanese women. **Methods** We retrospectively analyzed uncomplicated Japanese singleton pregnancies who delivered at term gestation from 2011 to 2016 in our hospital. The association between GWG and BW was analyzed by multiple linear regression. Potential confounding factors included maternal age, parity, pregravid BMI and neonatal sex. The association between inadequate GWG, determined by the Institute of Medicine recommendations, and small-for-gestational age (SGA : birth weight <10th percentile) was also examined by logistic regression. **Results** A total of 2,246 mother-neonate dyads were analyzed. Maternal GWG was  $9.81 \pm 3.85$  kg (mean  $\pm$  SD), and 1,519 (67%) had inadequate GWG. After adjustment for confounding factors, GWG significantly correlated with BW ( $\beta=0.189$ ,  $p<0.001$ ), and inadequate GWG increased the risk of SGA (adjusted odds ratio (aOR) =2.31 [95%CI : 1.50–3.53]). This association was significant in underweight (aOR=2.97 [1.13–7.75]) and normal weight mothers (aOR=2.16 [1.32–3.53]), not in overweight mothers. **Conclusion** Our study demonstrated that maternal GWG was associated with BW in Japanese women with singleton pregnancies. Inadequate GWG was related to increased risk of SGA in underweight and normal weight mothers.

### ISP-45-10

**Fluctuation of Oral Microbiome during pregnancy in Maternity Log Study** Riu Yamashita<sup>1</sup>, Daisuke Ochi<sup>2</sup>, Takafumi Yamauchi<sup>2</sup>, Yoshiki Tsunemoto<sup>2</sup>, Yuki Harada<sup>3</sup>, Maiko Wagata<sup>5</sup>, Osamu Tanabe<sup>5</sup>, Nobuo Yaegashi<sup>1</sup>, Masao Nagasaki<sup>1</sup>, Junichi Sugawara<sup>5</sup> *Tohoku University Tohoku Medical Megabank Organization<sup>1</sup>, NTT DOCOMO, INC./Tohoku University<sup>2</sup>, Tohoku University<sup>3</sup>, Department of Biobank, Tohoku University Hospital<sup>4</sup>, Department of Community Medical Supports, Tohoku University Tohoku Medical Megabank Organization<sup>5</sup>*

**Objective** Oral microbiome changes during pregnancy, and the changes are possibly associated not only with oral health but also with pregnancy-related diseases such as preterm birth. However, there is still only limited knowledge on the changes. Here we focused on the fluctuation of oral microbiome in “Maternity Log Study”, a prospective cohort study recruiting pregnant women, for the investigation of the relationships between pregnancy-related diseases, environmental factors, and multi-layer omics data. **Methods** We have collected dental plaque (by tooth brushing) and saliva at two time points during pregnancy from 302 participants. After DNA purification, we performed amplicon sequencing of the V4 region of the 16S rRNA gene. We have obtained 138 data sets of both first and second samplings with more than 5,000 sequence reads. Microbiome annotation was performed by our original pipeline to associate the reads with bacteria species. **Results** We compared oral microbiomes between first and second samplings. Although the number of identified bacteria did not significantly change between the two samplings ( $p=0.45$ ), the relative abundances of some bacteria showed significant change. While *Corynebacterium durum* and *Cardiobacterium horminis* decreased, *Campilobacter gracillis* increased during pregnancy ( $p<0.05$ ). Interestingly, both *Porphyromonas gingivalis* ( $p=0.05$ ) and *Tannerella forsythia* ( $p=0.07$ ), members of “Red Complex” often observed in the periodontal disease, increased. These data are consistent with the clinical observations that the risk of periodontal disease increases during pregnancy. **Conclusion** The relative abundance of several bacteria including those related to the periodontal disease changes during pregnancy. Our microbiome data should contribute to further investigation of oral health during pregnancy.

### ISP-46-1

**Expression of progesterone induced blocking factor (PIBF) in women with severe fetal growth restriction** Tomohiro Oba, Akihiro Kawashima, Keiko Miyagami, Keiko Koide, Ryu Matsuoka, Kazuhisa Shimodaira, Akihiko Sekizawa *Showa University*

**Objective** Progesterone induced blocking factor (PIBF) was reportedly associated with trophoblast invasion, and a failure of trophoblast invasion could lead to fetal growth restriction. However, the molecular mechanisms have not been elucidated. The objective of this study is to explore PIBF expression in the placenta and the blood of patients with fetal growth restriction (FGR). **Methods** A case-control study of pregnant women were conducted and approved by the ethical committee. Cases were severe FGR patients whose birth weight were <3% tile ( $n=6$ ). Birth weight >10% tile was defined as control ( $n=10$ ). The maternal blood samples were collected at 22–34 weeks of gestation to quantify serum PIBF and progesterone levels using ELISA. The postpartum placenta samples were also collected for immunohistochemical staining to detect PIBF expression in the placenta. **Results** Birth weight (g) (cases vs controls) were  $1,074 \pm 484$  ( $-3.0 \pm 0.4SD$ ) vs  $3,021 \pm 317$  ( $0.3 \pm 0.7SD$ ) ( $p<0.05$ ), gestational weeks of blood sampling were  $29 \pm 3.5$  vs  $31.5 \pm 3.4$ . The level of serum PIBF in Cases is higher than that of Controls ( $225 \pm 100$  ng/ml vs  $73 \pm 33$  ng/ml  $p<0.05$ ). On the other hand, the level of progesterone expressed similarly in both groups. In immunohistochemical study, PIBF increased in syncytiotrophoblast parts of the placenta of FGR cases. **Conclusion** In severe FGR, PIBF expressed higher in their placenta and also in their circulation without the change of progesterone. PIBF expression might be an intrauterine environmental factor associated with a part of placentation in fetal growth restriction.

### ISP-46-2

**Systolic and diastolic time interval ratios of the ductus venosus flow velocity waveform in fetal growth restriction** Natsuko Yokoi<sup>1</sup>, Masami Hayashi<sup>1</sup>, Aki Takase<sup>1</sup>, Yasushi Kurihara<sup>2</sup>, Kayoko Nakagawa<sup>2</sup>, Hiroko Katayama<sup>1</sup>, Akihiro Hamuro<sup>1</sup>, Takuya Misugi<sup>1</sup>, Akemi Nakano<sup>1</sup>, Daisuke Tachibana<sup>1</sup>, Masayasu Koyama<sup>1</sup> *Osaka City University<sup>1</sup>, Kashiwara Municipal Hospital<sup>2</sup>, Izumiotsu Municipal Hospital<sup>3</sup>*

**Objective** The objective of this study is to investigate the sequential changes of time intervals of the ductus venosus (DV) flow velocity waveform (FVW) in fetuses with growth restriction (FGR). **Methods** This is a retrospective longitudinal observational study on 26 FGR cases, and the study population was divided into two groups : Group 1 with abnormal umbilical artery (UA) Doppler, which is defined as elevated UA pulsatility index (PI) more than 95 percentile of the normal reference range, and Group 2 with normal UA Doppler. Time intervals of systolic (S) and diastolic (D) components of DV-FVW were measured and the ratios (S/D) were calculated and converted to z scores for statistical analysis. The measurements performed within 7 days before delivery and those performed one week before the last examination were compared. **Results** Thirteen cases in Group 1 and 11 cases in Group 2 were included in this study. The median gestational age of delivery and birth weights were 28w2d (range, 27w1d–32w3d) and 626g (range, 350–1,026) in Group 1 and 38w2d (range, 36w3d–40w3d) and 1,972g (range, 1,503–2,360) in Group 2. Comparing the difference between the last measured values and those of one week before the last examination, in Group 1, S/D decreased significantly ( $p=0.028$ , median  $-1.85$  SD to  $-2.12SD$ ), while in Group 2, the S/D showed no significant change ( $p=0.722$ , median  $-0.15SD$  to  $-0.34SD$ ). **Conclusion** S/D of DV-FVW decreased in FGR with abnormal UA Doppler in the last week of pregnancy. Our findings suggest that S/D of

DV-FVW might predict deterioration of fetal status.

### ISP-46-3

**Biomarkers for predicting delivery before 34 weeks of gestation in fetal growth restriction** Akihiro Kawashima, Tomohiro Oba, Akihiko Sekizawa *Showa University*

**Objective** The molecular mechanisms involved in placental implantation are associated with the proliferative and invasive capacity of trophoblast cells. Current pieces of evidence suggest a conjunction between the placental implantation and tumor progression. This study aims to develop a model of prediction of SGA who deliver before 34 weeks of gestation based on serum protein related with tumor progression. **Methods** Severe FGR is defined by estimated weight below the third percentile. We collected blood samples from women with severe FGR (n=24) and normal growth fetus (n=31) before 34 weeks of gestation after obtaining the written consent. The serum proteins were assayed using Bio-Plex Pro Human Cancer Biomarker Panel including 23 proteins. Logistic regression analysis was used to develop a prediction model. **Results** In the women with severe FGR, 15 cases were delivered before 34 weeks of gestation, and the median of the delivery week was 32 weeks of gestation (range : 26–33 weeks). In severe FGR group, the serum levels of sCD40L, Endoglin, Leptin, IGFBP1, sVEGFR1 were increased, and PLGF was decreased. At the estimated detection rate of 100%, the specificity by a combination of the six proteins was 77.8% for severe FGA requiring delivery before 34 weeks of gestation in severe FGR group and 44.4% for total cases of this study. **Conclusion** In pregnancies with severe FGR, the women requiring before 34 weeks of gestation could be identified. This study yields the groundwork for future investigations to analyze the molecular biomarkers for management of FGR.

### ISP-46-4

**Superb microvascular imaging of the fetus, placenta, and umbilical cord** Kenta Yamamoto, Mohamed Aboellail, Masato Mashima, Nobuhiro Mori, Kenji Kanenishi, Toshiyuki Hata *Kagawa University*

**Objective** Superb microvascular imaging (SMI) is a new Doppler technology that uses a unique algorithm to minimize motion artifacts by eliminating tissue motion (clutter), and can depict low-velocity blood flow in small vessels due to significantly reducing motion artifacts. We present our experience of using SMI to assess fetal organ vasculature, placental vascularity, and umbilical cord. **Methods** Fetal organ vasculature, placental vascularity, and umbilical cord were assessed using the SMI with a high-resolution probe in 7 normal and three fetal growth restriction (FGR) pregnancies at 11–33 weeks of gestation. **Results** Fetal intra-cranial, pulmonary, splenic, renal, and intercostal vessels were clearly depicted. In the first-trimester placenta, the primary and secondary stem villous vessels, and spiral artery jet flow were noted. In the second- and third-trimester placentas, the primary, secondary, and tertiary stem villous vessels, and whole spiral artery jet flow were clearly depicted using SMI, compared with conventional two-dimensional color/power Doppler sonography. In the thick heterogeneous placenta with severe FGR, SMI demonstrated very sparse villous trees in the placenta, and each stem villous vessels became straight. Especially, primary stem villous vessels were thick and long (Baobab-tree-like appearance). Velamentous cord insertion was clearly identified using SMI at 11 weeks and 3 days of gestation. **Conclusion** SMI provides a more comprehensive, detailed view of fetal organ vasculatures, placental vascularity, and umbilical cord, and might facilitate precise diagnosis of normal and abnormal pregnancies.

### ISP-46-5

**Fetal echocardiographic evaluation of dilated cardiomyopathy during mouse pregnancy** Takao Owa<sup>1</sup>, Takekazu Miyoshi<sup>2</sup>, Yoko Kawanishi<sup>3</sup>, Aiko Okada<sup>2</sup>, Etsuko Kajimoto<sup>3</sup>, Hiroko Tanaka<sup>3</sup>, Aiko Kakigano<sup>3</sup>, Kazuya Mimura<sup>3</sup>, Masayuki Endo<sup>3</sup>, Takuji Tomimatsu<sup>1</sup>, Tadashi Kimura<sup>3</sup> *National Cerebral and Cardiovascular Center, Department of Regenerative Medicine<sup>1</sup>, National Cerebral and Cardiovascular Center Department of Perinatology and Gynecology<sup>2</sup>, Osaka University<sup>3</sup>*

**Objective** The knock-in mouse having a deletion mutation  $\delta K$  210 in the cardiac troponin T gene develop enlarged hearts with left ventricular (LV) systolic dysfunction and premature sudden cardiac death. However, the fetal cardiac function of this dilated cardiomyopathy (DCM) model mouse remains unknown. Our objective is to evaluate the fetal cardiac function of this model by successive echocardiography, compared with histology and gene expression analysis. **Methods** We studied mouse fetuses (embryonic day 16.5 and 18.5) by using a high-frequency ultrasound and evaluate cardiac function and hemodynamics. Cardiothoracic area ration, LV area, and % fractional shortening were examined. At embryonic day 18.5, fetal hearts were sampled. **Results** Echocardiography demonstrated the increase of left ventricular end-diastolic dimension and progressive reduction of left ventricular ejection fraction from embryonic day 16.5 to 18.5 in mutant fetuses. In histology, the ventricle of mutant fetuses showed enlargement and thinning. The gene expression of atrial natriuretic peptide were increased in mutant heart, however those of  $\alpha$ -myosin heavy chain (MHC) and  $\beta$ -MHC were not altered significantly. **Conclusion** Fetal cardiac dysfunction of this DCM model mouse is aggravated in prenatal period.

### ISP-46-6

**Relationship between maturation of the autonomic nervous system in fetal growth restricted mice and onset of cerebral hemorrhage at ischemia-reperfusion load** Takahiro Minato<sup>1</sup>, Takuya Ito<sup>2</sup>, Sayaka Ooshio<sup>1</sup>, Yoshitaka Kimura<sup>1</sup>, Nobuo Yaegashi<sup>1</sup> *Tohoku University Hospital<sup>1</sup>, Jichi Medical University<sup>2</sup>*

**Objective** Fetal growth restriction (FGR) is a risk factor exacerbating a poor neurological prognosis at birth. A disease exacerbating a poor neurological prognosis is cerebral hemorrhage including intraventricular hemorrhage. It is believed to be caused by an inability to autoregulate cerebral blood flow and blood pressure due to autonomic nerve immaturity. **Methods** Here autonomic nerve immaturity in mouse FGR fetuses was evaluated and the relationship with cerebral hemorrhage incidence when applying hypoxic load to resemble the brain condition at the time of delivery was examined. Furthermore, FGR incidence on cerebral nerve development and differentiation was examined at the gene expression level. FGR model fetuses were prepared by ligating uterine arteries to reduce placental blood flow. To compare autonomic nerve development in FGR mice with that in control mice, fetal short-term variability (STV) was measured from electrocardiograms. **Results** In the FGR group, a significant decrease in the STV was observed and immature autonomic nerves were confirmed. Among genes related to nerve development and differentiation, Ntrk and Neuregulin 1, which are necessary for neural differentiation and plasticity, were expressed at reduced levels in FGR fetuses. And the cerebral hemorrhage rate significantly increased in the FGR group. **Conclusion** FGR delays autonomic nerve development, which becomes a risk factor for cerebral hemorrhage onset at birth. This study demonstrated that cerebral hemorrhage risk may be evaluated before delivery for FGR management by evaluating autonomic nerve immaturity. Further, this study suggests that choosing an appropriate delivery timing and delivery method

contributes to neurological prognosis improvement.

## ISP-46-7

**Low socioeconomic status is a risk factor for small for gestational age birth in Japan** Ken Yamaguchi, Kaoru Kawasaki, Sachi Yamamura, Eri Ogura, Yu Matsuzaka, Masahito Takakura, Mari Ujita, Yumi Takao, Kenji Takakura, Ikuo Konishi *Kyoto Medical Center*

**Objective** Small for gestational age (SGA) birth increases the neonatal risk for chronic diseases including heart disease and diabetes in the future. Socioeconomic status (SES) has been related to SGA birth in developing countries. The aim of this study is to evaluate the effect of socioeconomic inequalities among Japanese pregnant women and lifestyle-related factors before pregnancy on the prognosis of pregnancy and birth outcomes. **Methods** From January 2007 to December 2011, Japanese singleton pregnant women (n=2,686) were enrolled into this study. We used the pregnant-childbirth hospitalization support policy system as an indicator of low SES, and investigated whether SES status affects adverse delivery and birth outcomes including preterm birth, emergency cesarean section, still birth, and SGA. **Results** The proportion of low SES pregnant women was 12.1%. There were significantly more SGA infants in the low SES group, and the crude odds ratio was 1.64 (95% CI=1.14-2.36, p=0.008). The odds ratio for SGA in low SES adjusted by maternal age, pre-pregnancy body mass index, pre-pregnancy smoking behavior, and gestational body weight gain was 1.57 (95% CI=1.03 - 2.39, p=0.035). However, low SES did not influence preterm birth, emergency cesarean section, and stillbirth. **Conclusion** Low SES among Japanese pregnant women is associated with SGA birth. These findings suggest that improvement of socioeconomic disparities are important for the prevention of chronic diseases in the future.

## ISP-46-8

**Clinical significance of umbilical venous NT-proBNP and troponin T in the cases with at-risk for fetal circulatory compromise before 36 weeks' gestation** Takaaki Shinagawa, Toshiyuki Yoshizato, Takashi Horinouchi, Yutaka Kozuma, Kimio Ushijima *Kurume University Hospital*

**Objective** To evaluate the clinical significance of umbilical venous N-terminal pro brain natriuretic peptide (NT-proBNP) and troponin T, biomarkers for cardiac failure, in the cases with at-risk for fetal/neonatal circulatory compromise before 36 weeks' gestation. **Methods** Subjects with NT-proBNP and troponin T were 327 and 55 cases of preterm delivery at 26-35 weeks' gestation in our hospital between 2009-2017 and 2016-2017, respectively. Umbilical venous NT-proBNP and troponin T levels were measured at birth. At-risk groups were 137 cases with NT-proBNP and 26 cases with troponin T having maternal and fetal complications including severe form of pregnancy-induced hypertension, oligohydramnios, fetal growth restriction and umbilical arterial pH<7.2. Control groups were 190 cases with NT-proBNP and 29 cases with troponin T not having the above-mentioned complications. The gestational age was divided into early (26-30 weeks) and late (31-35 weeks) groups. NT-proBNP and troponin T levels were compared between at-risk and control groups in the early and late gestational ages. The statistical analysis was made using Mann-Whitney test and the significance was set at P<0.05. **Results** In the early gestational age, NT-proBNP levels of at-risk group (median : 6,085.3, range : 571.7-160,271.0 pg/mL) were higher than control group (2,066.1, 28.9-32,001.0 pg/mL) but no difference was found in the troponin T level. In the late gestational age, neither NT-proBNP nor troponin T levels showed any differences between the groups. **Conclusion** Umbilical venous NT-proBNP but not troponin T may

be a possible marker in utero and ex utero to evaluate fetal/neonatal circulatory compromise before 31 weeks' gestation.

## ISP-47-1

**17-alpha-hydroxyprogesterone caproate combined maintenance tocolysis could prolong gestational period in case of preterm labor with mild intra-amniotic inflammation** Satoshi Yoneda, Noriko Yoneda, Mika Ito, Yosuke Ono, Arihiro Shiozaki, Shigeru Saito *University of Toyama*

**Objective** Although progesterone therapy is effective for those with asymptomatic short cervical cases and for those with a history of preterm birth, it is unclear whether 17-alpha-hydroxyprogesterone caproate (17-OHPC) combined maintenance tocolysis is effective in cases of preterm labor (PTL) cases with intact membranes. **Methods** One hundred and six PTL patients who administered appropriate antibiotic therapy using PCR detection system were selected, and they were divided into group T (tocolysis only : n=54) and group P (tocolysis and 17-OHPC : n=52), respectively. The severity of amniotic inflammation at admission was classified into sub-group A (no inflammation), B (mild) and C (severe) by amniotic IL-8 level. The obstetrical and neonatal prognosis was examined statistically. **Results** 1) Prolonged gestational days (group T vs. group P) was 66 (43-119) vs. 64 (40-91) in sub-group A (n=22), 50 (8-104) vs. 75 (13-126) in sub-group B (n=66) and 26 (8-67) vs. 22 (8-88) in sub-group C, respectively, and there was significant difference in sub-group B (p=0.016). 2) The rate of neonatal total morbidity and NICU admission were similar. 3) The amount administered Rit (mg/day) in sub-group B was 95 (0-150) in group P, which was significantly lower than that [115 (55-150)] in group T (p<0.01). **Conclusion** We firstly showed that 17-OHPC combined maintenance tocolysis can prolong gestation period in PTL cases with mild intra-amniotic inflammation. 17-OHPC did not prolong gestation period in no intra-amniotic inflammation cases and severe inflammation cases.

## ISP-47-2

**Neurological outcome in preterm infants with maternal Tocolytic management** Emi Kino<sup>1</sup>, Masanao Ohashi<sup>2</sup>, Hiroshi Sameshima<sup>3</sup>, Ichiro Yasuhi<sup>3</sup>, Sachie Suga<sup>3</sup>, Masato Kamimoto<sup>4</sup>, Toru Funakoshi<sup>5</sup> *University of Miyazaki Hospital<sup>1</sup>, Miyazaki Medical Association Hospital<sup>2</sup>, Nagasaki Medical Center<sup>3</sup>, Kagoshima City Hospital<sup>4</sup>, Hyogo Prefectural Kobe Children's Hospital<sup>5</sup>*

**Objective** To investigate the effects of tocolytic agents on infants' neurodevelopment of preterm infants. **Methods** This is a retrospective cohort study of birth between 28 and 36 weeks of gestation at 4 perinatal tertiary centers in Japan. 1,083 cases of 2-year survivors were categorized into four groups : no-tocolytics, magnesium sulfate (Mg),  $\beta$ -stimulant ( $\beta$ ) and the combination of Mg and  $\beta$  (Combined) group. The diagnosis of cerebral palsy (CP) or mental retardation (MR) at 2-year old was confirmed by pediatric neurologists in each of the 4 institutions. **Results** Mg group consists of 218 cases with 2 (1.8%) of CP and 1 (0.9%) of MR. No tocolytics group of 418 with 10 (2.4%) of CP and 16 (3.8%) of MR. A multivariate analysis of the data, including tocolytics, gestational age, sex, fetal growth restriction, antenatal steroids, low pH (<7.1), pathological chorioamnionitis and facilities, showed that the Mg administration during pregnancy had significantly lower rate of mortality and brain damage (CP or MR) with odds ratio (OR) 0.43 and 95% confidence interval (CI) 0.24- 0.74. A stratified subgroup analysis of infants born between 28 and 33 weeks of gestation showed that the incidence of normal development infants in Mg group is significantly highest among four groups with multiple comparison. **Conclusion** This study found that administration of magnesium sulfate for the



management of preterm labor had the ability to improve the infant mortality rate and brain damage between 28 and 36 weeks of gestation at birth. Antepartum exposure to magnesium sulfate is one of the preferred options for infant neuroprotection.

### ISP-47-3

**Changes of leukocyte migration during pregnancy** Ai Takamizu, Jun Takeda, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Juntendo University*

**Objective** Preterm birth is a worldwide problem. Its prediction has been needed for appropriate intervention; however there are no tests that can positively predict when pregnant women will deliver. We focus on the leukocyte infiltration to the uterus or the placenta which is important in parturient mechanism. We hypothesized that more leukocytes migrated as gestation progressed. Using the principle of leukocyte invasion of the uterus at each delivery, we determined whether the Leukocyte Migration Assay (LMA) could predict the timing of delivery by using Modified Boyden chemotaxis chambers. **Methods** Leukocytes (100,000) were obtained from pregnant women sequentially at 1st, 2nd, 3rd trimester, labor and postpartum day 3, and placed into the upper chamber. Chemotactic factor isolated from term labor fetal membranes were placed in the lower chamber. Migrated leukocytes number and its subtypes were assessed by flow cytometry using antibodies. **Results** Migrated leukocytes count of the 2nd trimester was significantly higher than those of the 1st ( $p=0.03$ ). Unexpectedly, leukocytes in the 2nd trimester significantly more migrated than those of the 3rd trimester ( $P=0.002$ ). No differences were found between the 3rd trimester and the time of labor in this study. More than 80% of the migrated leukocytes were granulocytes, and what is more, 95% of those are CD11b positive. The ratio of leukocyte population was remained same throughout the gestation. **Conclusion** The leukocytes specifically changed their property during pregnancy. CD11b positive leukocytes migrated toward the chemoattractants not gradually through the gestation but higher in the 2nd trimester and labor.

### ISP-47-4

**Longitudinal Lifestyle Monitoring for Prediction of Preterm Birth in Maternity Log Study** Daisuke Ochi<sup>1</sup>, Takafumi Yamauchi<sup>1</sup>, Yoshiki Tsunemoto<sup>2</sup>, Maiko Wagata<sup>3</sup>, Riu Yamashita<sup>4</sup>, Yuki Harada<sup>3</sup>, Osamu Tanabe<sup>3</sup>, Nobuo Yaegashi<sup>5</sup>, Masao Nagasaki<sup>3</sup>, Junichi Sugawara<sup>3</sup> *NTT DOCOMO, INC./Tohoku University Tohoku Medical Megabank Organization<sup>1</sup>, NTT DOCOMO, INC.<sup>2</sup>, Department of Integrative Genomics, Tohoku University Tohoku Medical Megabank Organization<sup>3</sup>, Department of Biobank, Tohoku University Tohoku Medical Megabank Organization<sup>4</sup>, Tohoku University Hospital<sup>5</sup>, Department of Community Medical Supports, Tohoku University Tohoku Medical Megabank Organization<sup>6</sup>*

**Objective** Pregnancy related disorders, including preterm birth (PTB), are caused by a complex interaction of genetic and environmental factors such as lifestyle and living environment. We have designed a prospective cohort study named "Maternity Log Study" to investigate unrevealed mechanisms of those disorders from both genetic and environmental aspects. **Methods** 302 participants were recruited by written informed consent. We collected daily lifelogs of physiological data (body weight, blood pressure, pulse rate, physical activity, body temperature, and hours of sleep) and symptoms (morning sickness, abdominal pain, uterine contraction, and bowel movement) as well as blood and urine samples at several points throughout pregnancy. We analyzed the association between the course of lifelogs and PTB. **Results** Several lifelog features showed differences between a spontaneous PTB (SPTB) group ( $n=14$ ) and a control group

( $n=130$ ). Especially, daily caloric expenditure of the SPTB group measured by a wearable activity monitor was significantly lower than controls after 20 weeks of gestation ( $1,577 \pm 180$  vs  $1,915 \pm 291$  kcal,  $p < 0.0003$ ). Interestingly, morning body temperatures of the control group decreased gradually according to the gestational age ( $36.55 \pm 36.35^\circ\text{C}$  from 16 to 30 weeks of gestation), while those of the SPTB group did not as much ( $36.62 \pm 36.53^\circ\text{C}$  during the same period as the control). A SPTB prediction model using lifelogs before 26 weeks of gestation demonstrated sensitivity higher than 0.95 and specificity higher than 0.90. **Conclusion** Combinations of daily lifelogs could be predictive markers for SPTB. Further combinations with genome, transcriptome, and metabolome data may improve our prediction model and reveal underlying mechanisms of SPTB.

### ISP-47-5

**The effect of antepartum MgSO<sub>4</sub> therapy on pathological chorioamnionitis and infants outcome** Masanao Ohashi<sup>1</sup>, Hiroshi Sameshima<sup>2</sup>, Emi Kino<sup>2</sup>, Ichiro Yasuhi<sup>3</sup>, Sachie Suga<sup>4</sup>, Masato Kamitomo<sup>4</sup>, Toru Funakoshi<sup>5</sup> *Miyazaki Medical Association Hospital<sup>1</sup>, University of Miyazaki Hospital<sup>2</sup>, Nagasaki Medical Center<sup>3</sup>, Kagoshima City Hospital<sup>4</sup>, Hyogo Prefectural Kobe Children Hospital<sup>5</sup>*

**Objective** Infants neurological outcome is associated with both preterm birth and pathological chorioamnionitis (pCAM). The risk of poor neurological outcome in the setting of preterm birth can be decreased by antenatal maternal administration of magnesium sulfate (Mg). We examined the effects of Mg on neonatal outcomes in the setting of preterm birth complicated by pCAM. **Methods** We conducted an analysis of data from multicenter retrospective cohort study. Using singleton non-anomalous pregnancies born between 28 and 36 weeks of gestation, we compared the effect of pCAM by the administration of Mg or not. Primary outcome was poor neonatal outcome which consists of neonatal death, cerebral palsy by the age of 2 years and neurodevelopmental delay including mental retardation. **Results** Of the 1,143 infants included in this study, 1083 infants were included in this analysis. 160 (14.8%) were diagnosed with pCAM. Neonates exposed to Mg in the absence of pCAM had a significant reduction in poor outcome at 2 years of age compared to neonates non-exposed to Mg in the presence of pCAM (adjusted OR 0.40, 95% CI : 0.18-0.90). In the setting of pCAM, there was a tendency of reduction in poor outcome at age 2 years with magnesium therapy, but not significantly different. **Conclusion** Mg does not demonstrate a significant protective effect in the setting of pCAM, but showed the ability of improvement in neonatal outcome. We need to collect more data to clarify the effectiveness of Mg on neonatal outcome with pCAM.

### ISP-47-6

**Accuracy of maternal clinical signs for prediction of histological chorioamnionitis in preterm labor** Yohei Maki, Hiroshi Sameshima *University of Miyazaki*

**Objective** To evaluate the accuracy of clinical signs for histological chorioamnionitis. **Methods** This was a retrospective cohort study. We reviewed the medical records of pregnant women with preterm delivery between 22 and 33 weeks of gestation and obtained clinical data and histopathological placental findings at our hospital and their neonatal outcome including neonatal death, death within 1 year, neuroimaging abnormalities, and composite outcome, defined as 1 or more of them between January 2007 and May 2017. Results were compared between CAM group and non-CAM group. **Results** Infants in the CAM group had significantly earlier gestational age ( $26.93 \pm 1$  weeks vs  $25.4 \pm 2.9$  weeks,  $p < .01$ ), lower birth weight ( $1,053 \pm 423$  g vs  $860 \pm 388$  g,  $p < .01$ ), higher incidence of neuroimaging ab-



normalities (18% vs 35.4%,  $p < .05$ ) and poorer composite outcome (21.2% vs 42.9%,  $p < .01$ ). Pregnant women in the CAM group had significantly higher body temperature ( $36.9 \pm 0.42^\circ\text{C}$  vs  $37.1 \pm 0.58^\circ\text{C}$ ,  $p < .01$ ), higher incidence of fever ( $\geq 38^\circ\text{C}$ ) (0% vs 11.1%,  $p < .05$ ), higher white blood cell (WBC) counts ( $10,295 \pm 2,549/\mu\text{L}$  vs  $13,493 \pm 3,996/\mu\text{L}$ ,  $p < .001$ ), higher incidence of leukocytosis ( $\text{WBC} \geq 15,000/\mu\text{L}$ ) (2.3% vs 35.1%,  $p < .001$ ), and higher C-reactive protein level ( $0.97 \pm 1.07\text{mg/dL}$  vs  $3.22 \pm 2.66\text{mg/dL}$ ,  $p < .001$ ). The cut-off value of CRP  $1.24\text{mg/dL}$  had the highest accuracy of 70.8% while fever and  $\text{WBC} \geq 15,000/\mu\text{L}$  had accuracy of 40.5% and 55.1%, respectively. The accuracy of any one sign of fever, leukocytosis and/or  $\text{CRP} \geq 1.24\text{mg/dL}$  was 75.2%. **Conclusion** Any one sign of fever, leukocytosis and/or high CRP level can be useful for prediction of histological chorioamnionitis.

### ISP-48-1

**Case report of spontaneous septostomy of the dividing membrane accompanied with cord entanglement in a monozygotic diamniotic twin : Importance of identification of dividing membrane** Tomoki Kotera, Takashi Shibata, Hisato Tokuda, Noriaki Iiduka, Satoshi Nakago *Takatsuki General Hospital*

We experienced a case of the spontaneous septostomy of the dividing membranes (SSDM) in monozygotic diamniotic twin (MD twin). One fetus with the loss of end-diastolic velocity of umbilical artery caused by the cord entanglement was saved by a cesarean section. This case was 37-year-old, G1P0. At ten weeks of pregnancy, she had a diagnosis of MD twin by the ultrasonography because the dividing membrane was recognized in a yolk sac. At 15 weeks of pregnancy, the consecutive dividing membrane from the anterior wall to posterior wall was became invisible. However, the part of the membrane was found in the amniotic cavity and we did not think of possibility of the SSDM. At 27 weeks of pregnancy, the prolong deceleration and the loss of end-diastolic velocity of umbilical artery was suddenly found in one fetus. Cesarean section was promptly performed. At the operation, dividing membrane in the amniotic cavity was not found. However, the residual membrane was identified also found between placental attachments of the two umbilical cords, suggested SSDM. This case was accompanied with nine times cord entanglements and two cord knots. Apgar scores at the five minutes of both newborn infants were eight. The pH of umbilical artery was 7.329 and 7.400, respectively. When the consecutive dividing membrane in the amniotic cavity became invisible during pregnancy course of MD twin, we should think of recognize the possibility that of SSDM occurs. This may rescue fetal loss caused by umbilical cord entanglement.

### ISP-48-2

**The outcome of fetoscopic laser photocoagulation using the Solomon technique versus selective coagulation for twin-twin transfusion syndrome** Seiji Kanazawa, Noriyuki Nakamura, Rika Sugibayashi, Katsusuke Ozawa, Seiji Wada, Haruhiko Sago *National Center for Child Health and Development*

**Objective** We compared the outcomes in monozygotic twins who underwent fetoscopic laser photocoagulation (FLP) for twin-twin transfusion syndrome (TTTS) using selective coagulation of placental anastomoses (standard technique) and equatorial dichorionization of the anastomoses (Solomon technique). **Methods** The outcomes were retrospectively analyzed in TTTS cases who underwent FLP in our institution from 2010–2016 and were followed to delivery. We adopted the Solomon technique for selective coagulation in August 2014 and compared outcomes before and after that point. **Results** Among 286 cases, 198

underwent the standard technique (group 1), and 88 underwent the Solomon technique (group 2). Gestational age (GA) at FLP, operation time, laser coagulation time, and laser coagulation total energy were not markedly different between the groups. Four cases of recurrent TTTS (2.0%) and 3 cases of twin anemia-polycythemia sequence (TAPS) (1.5%) occurred postoperatively in group 1; there were no such cases in group 2. There were no significant differences between the groups in the double survival rate (74.7% vs. 79.5%;  $P=0.381$ ) or at least one survival rate (95.5% vs. 97.7%;  $P=0.358$ ). Placental abruption was significantly more frequent in group 2 than in group 1 (2.5% vs. 11.3%, OR 4.9,  $P=0.005$ ), as was premature rupture of membrane (PROM) (OR 3.1,  $P < 0.001$ ), but GA at delivery ( $32.8 \pm 4.4$  vs.  $32.8 \pm 4.0$  weeks;  $P=0.899$ ) was not significantly different between the groups. **Conclusion** The Solomon technique decreased recurrent TTTS and TAPS following FLP but increased the occurrence of placental abruption and PROM. There were no significant differences in the GA at delivery or twin survival rates.

### ISP-48-3

**Meckel-Gruber syndrome involving both fetuses in a DD twin pregnancy, a case report** Shoko Ochiai, Susumu Miyashita, Chiyori Sakamoto, Emi Motegi, Tatsuya Kuno, Kazumi Tada, Hiroshi Watanabe, Ichio Fukasawa *Dokkyo Medical University Hospital*

**Case A** 29-year-old woman, 2-gravida, 0-para, was referred because of brain ventriculomegaly in both of twin fetuses on 13 weeks. DD chorionicity had been confirmed at eight weeks. She had been healthy and no remarkable familial history. Serial ultrasound scans revealed deformed cranium, encephalocele and dysplastic enlarged kidney in both fetuses, which were compatible with Meckel-Gruber syndrome (MGS) involving both of them. The couple decided termination of pregnancy after serial genetic counseling. The fetuses were stillborn on 21 weeks and we confirmed occipital encephalocele, bilateral dysplastic kidney and polydactyly in both. After the investigation of causative genes revealed a compound heterozygosity of deletions in exon 34 and 35 of *CC2D2A* in both of the fetuses, which were inherited from the parents. The fetuses were proven to be monozygotic by another investigation using multiple genetic markers. She got singleton pregnant spontaneously one year later. Excessive large low echoic area in the fetal brain was noted in nine weeks. After the serial scan deformed cranium and occipital encephalocele were confirmed on 11 weeks. Termination was decided again and encephalocele was confirmed in the aborted fetus, in which the mutations of *CC2D2A* were under the investigation. **Discussion** We had a case of MGS in monozygotic dichorionic twin fetuses. Investigation for causative genes and the zygosity was significant for the genetic counseling in this case. We could recognize abnormal findings in fetal brain at first trimester scan, which provided an essential information to support the parents for making a decision.

### ISP-48-4

**What should we know about Turner syndrome before pregnant?-2 cases with different outcomes-** Tomohiro Arai<sup>1</sup>, Kouki Samejima<sup>1</sup>, Sumiko Era<sup>1</sup>, Yoshihisa Ono<sup>1</sup>, Yasushi Takai<sup>2</sup>, Masahiro Saitoh<sup>1</sup>, Kazunori Baba<sup>1</sup>, Hiroyuki Seki<sup>1</sup>, Sachie Seto<sup>1</sup>, Ryugo Okagaki<sup>3</sup>, Yoshimasa Kamei<sup>3</sup>, Osamu Ishihara<sup>3</sup> *Center for Maternal, Fetal and Neonatal Medicine, Saitama Medical Center, Saitama Medical University<sup>1</sup>, Saitama Medical Center, Saitama Medical University<sup>2</sup>, Saitama Medical University Hospital<sup>3</sup>*

**Background** Although primary ovarian insufficiency is a classic feature of Turner syndrome (TS), more TS women have used assisted reproductive technology (ART) with donated oocytes (OD) to become pregnant recently. Whereas, as well as

Marfan syndrome and vascular Ehlers–Danlos syndrome, TS demonstrate a high rate of aortic dissection (DA) which is increased by 100-fold compared with the general female population. Aortic size index (ASI, diameter of the ascending aorta normalized to body surface area) may serve to predict risk for DA, but is not well-known in obstetrics and reproductive area. We report two cases of TS women which followed different courses. **Case 1** A 36-year-old TS woman became pregnant after ART with OD in Taiwan. At 14 weeks, she presented with chest pain. Transthoracic echocardiography (TTE) suggested dilated aorta (ASI 2.37 cm/m<sup>2</sup>). Although enhanced CT showed no significant findings, she decided to have an artificial abortion. **Case 2** A 37-year-old TS woman became pregnant after ART with OD in United States. Although she presented with back pain from 8 weeks, repetitive TTEs did not suggest aortic dilation (ASI 1.61–1.83 cm/m<sup>2</sup>). She is now in 35 weeks with an uneventful course. **Conclusion** Although TS women need to be aware of significant risk of aortic dissection, favorable obstetric outcomes are achievable with careful cardiovascular assessment and multidisciplinary antenatal monitoring. ASI may be a marker which should be evaluated before ART with OD for TS women.

### ISP-48-5

**Case Report : The outcomes of fetal bradycardia** Ryoko Ono, Masahiro Nakao, Takuya Kawamura, Ryo Suzuki, Ikuno Kawabata, Atsushi Yoshida, Shinji Katsuragi *Sakakibara Heart Institute*

**Background** Fetal bradycardia can be detected during the fetal heart monitoring or routine prenatal ultrasound examination. Sustained bradycardia is often associated with structural heart disease. These cases have reported a worse outcome compared to fetuses with isolated bradycardia. They require a risk assessment and careful management during pregnancy. **Case Presentation** We present three retrospective case reports in which fetal bradycardia with structural heart disease was diagnosed by echocardiography. Two of the three cases showed sinus bradycardia with a fetal heart rate (FHR) of 90–100 beats per minute (bpm). The remaining one showed 2 : 1 atrioventricular block with a ventricular rate is 60 bpm. The common findings of them are complex cardiac malformations and interruption of the inferior vena cava with azygos continuation. All cases had a diagnosis of left isomerism at the CT scan after birth. During pregnancy, we performed a frequent evaluation of the fetuses by ultrasonography and determined the time of delivery. None of them showed severe fetal hydrops. All cases resulted in full-term delivery. The elective cesarean section was performed in the case of the atrioventricular block due to poor tracing of the FHR monitoring. In the other two cases, FHR tracing allowed to assess fetal well-being during labor resulting in normal vaginal delivery. **Conclusion** In cases of fetal bradycardia with structural heart disease, there are often some ultrasound findings of left isomerism. The magnitude of bradycardia affects the fetal prognosis and time and mode of delivery.

### ISP-48-6

**Prenatal diagnosis of hypospadias in a tertiary care center : a retrospective analysis of 10 years** Takashi Kaji, Atsuko Hichijo, Naoto Yonetani, Minoru Irahara *Tokushima University Hospital*

**Objective** Hypospadias is a common congenital anomaly with a prevalence rate of approximately 1 per 500 live male births, wherein the urethral meatus is located on the ventral side of the penis. In the present study, we determined the efficacy of ultrasonography in establishing a prenatal diagnosis of hypospadias in our tertiary care center. **Methods** We retrospectively studied 29 consecutive patients born at our center who were diagnosed

with hypospadias after birth between January 2008 and August 2017. **Results** Of the 29 cases, 14 (48%), 9 (31%), and 7 (24%) were complicated with fetal growth restriction (FGR), anomalies other than hypospadias, and hypertensive disorders of pregnancy (HDP), respectively. In all fetuses except one, the external genitalia were assessed using an axial view of the perineum using two-dimensional ultrasonography to determine the sex of the fetuses. Only 10 of the 29 (35%) cases were prenatally detected using the image of the ventrally curved penis between the scrotums. Three (10%) cases were diagnosed prenatally by visualizing the urethral meatus on the ventral side on the sagittal view of the penis during fetal micturition. **Conclusion** Prenatal detection of hypospadias remains uncommon ; furthermore, prenatal diagnosis is rare in our tertiary care center. The commonly used axial view of the fetal perineum appears inadequate for detecting hypospadias. However, a sagittal view of the penis may improve the efficacy of prenatal detection of hypospadias, particularly in high-risk pregnancies involving FGR, anomalies, and HDP.

### ISP-48-7

**Novel technique to assess fetal fractional shortening by two-dimensional tracking** Sumito Nagasaki, Masahiko Nakata, Mayumi Takano, Kento Usui, Junya Sakuma, Mineto Morita *Toho University Omori Medical Center*

**Objective** To assess the usefulness of novel 2D tracking technique to measure fetal cardiac fractional shortening automatically (Auto FS) in normal singleton pregnancies. **Methods** Two-dimensional tracking system to pursue wall motion of fetal heart, Auto FS, was constructed. In this study, temporal changes of Auto FS throughout gestation was studied in normal singleton pregnancies. At first, cardiac motion of the four chamber view was recorded in B-mode and then the Auto FS was calculated. The Region of interest (ROI) was set at a two-third of the wall from apex, in-to-in of the ventricular wall or septum, and tracking was performed. The values measured between the ventricular septum and at left side are defined as L-Auto FS. That at right side is R-Auto FS. We also obtained the value between each ventricular septum, which was defined as Combined-Auto FS. **Results** This study was carried out from May to September 2017. The data was obtained from 95 of singleton fetuses. L-Auto FS decreased significantly with gestational weeks, and R-Auto FS showed the same tendency (Spearman correlation analysis :  $p=0.30$  and  $p=0.55$  respectively). Combined-Auto FS showed the same decline as gestational age ( $p=0.62$ ). **Conclusion** Two-dimensional and automatically calculation of fractional shortening was succeeded. This novel technique can assess fetal heart contractility by being combined with both longitudinal and short-axial dimensions. All L- R- and Combined Auto FS showed a trend towards a negative correlation with gestational weeks. Further examination would be needed for clinical usage.

### ISP-48-8

**A case with BASM (biliary atresia splenic malformation) syndrome diagnosed with agenesis of inferior vena cava without visceral heterotaxy in utero** Kunio So, Takaaki Shinagawa, Masato Yokomine, Toshiyuki Yoshizato, Kimio Ushijima *Kurume University Hospital*

**Introduction** Agenesis of inferior vena cava (IVC) is often associated with visceral heterotaxy syndrome. We present a case with prenatal diagnosis of agenesis of IVC without visceral heterotaxy and BASM (biliary atresia splenic malformation) syndrome was confirmed for additional postnatal findings of biliary atresia and splenic abnormality. **Case** A 30-year-old pregnant woman was referred to our department because of agenesis of

IVC on a routine screening at 32 weeks' gestation. The ultrasonographic examination revealed situs solitus with normal intracardiac structure. IVC was not detected. A dilated vein running along with the descending aorta was connected with the superior vena cava, indicating a dilated azygos vein. Spleen was observed on the left adjacent to stomach. Agnesis of IVC with azygos connection but no visceral heterotaxy was diagnosed. At 37+2 weeks' gestation, a 2910g male neonate was delivered with 1/5-min Apgar scores of 9/10 points, respectively, and was discharged on day 7 after birth. On day 42, he was consulted with a pediatrician because of umbilical hernia and referred to our hospital for further examinations of jaundice and whitish stool. The laparotomy on day 60 showed that the gallbladder and extrahepatic biliary tracts were hypoplastic and biliary atresia type III-C1-v was diagnosed. The abnormal contour of spleen was found on MRI. **Conclusion** BASM syndrome should be considered in cases with agnesis of IVC without visceral heterotaxy and the extensive examinations for the presence/abnormalities of gallbladder, biliary tract and spleen should be made before and after birth.

### ISP-48-9

**Prenatal genetic diagnosis for neonatal alloimmune thrombocytopenia for women with the history of neonatal alloimmune thrombocytopenia** Akari Shirakuni<sup>1</sup>, Masashi Deguchi<sup>1</sup>, Maho Miyaji<sup>1</sup>, Yutoku Shi<sup>1</sup>, Akiko Uchida<sup>1</sup>, Sanae Ichihashi<sup>1</sup>, Masashi Nishimoto<sup>1</sup>, Tokuro Shirakawa<sup>1</sup>, Kenji Tanimura<sup>1</sup>, Mayumi Morizane<sup>1</sup>, Ichiro Morioka<sup>2</sup>, Hideto Yamada<sup>1</sup> *Kobe University Hospital<sup>1</sup>, Department of Pediatrics, Kobe University Hospital<sup>2</sup>*

**Objective** Neonatal-alloimmune-thrombocytopenia (NAIT) is blood-related disease caused by maternal antibodies against alloantigens on fetal platelets. NAIT can be a cause of perinatal intracranial-hemorrhage (ICH) and death or severe sequelae. We experienced two cases of prenatal genetic diagnosis and perinatal management of women with history of NAIT. **Case1** A Russian woman with human platelet antigens (HPA)-1a antibody married again and get pregnant with another Japanese. Her first child suffered ICH and thrombocytopenia due to HPA-1a antibody. Genetic test of HPA-1 of parents was HPA-1b/b (patient) and HPA-1a/a (spouse). Fetal genotype was presumed as HPA-1a/b and suspected risk for NAIT. C-section was chosen to minimize the ICH risk. Newborn suffered thrombocytopenia but not ICH. **Case2** A Japanese woman with HLA-A2 antibody conceive the second or third pregnancy. Her first child suffered thrombocytopenia and diagnosed as NAIT by HLA-A2 antibody. Serological test shows positive HLA-A2 antibody, then amniocenteses were performed to determine HLA-type of fetuses. The third fetus carried HLA-A2 but not second. Vaginal delivery was chosen for second, and C-section for third. Both newborn did not suffer thrombocytopenia. **Conclusion** Perinatal genetic diagnosis of the NAIT risk for women with history of NAIT by HPA antibody might be effective to decrease ICH by caesarian delivery, prepare antigen negative donor platelets for the neonates and avoid unnecessary cord blood sampling or caesarian delivery. On the other hand, HLA antibody is still controversial to cause NAIT, prenatal genetic diagnosis is not recommended for NAIT due to HLA antibody.

### ISP-48-10

**Chromosomal abnormalities : ultrasonographic soft signs in first and second trimester—an evidence-based review** Coralia Stefanescu, Eduart Balasa *Euromaterna Hospital, Romania*  
Down syndrome (trisomy 21) is the most common karyotypic abnormality in live-borns. Other sonographically detectable aneuploidies include trisomy 13, trisomy 18, monosomy X, and triploidy. The scan detects 2 types of markers. Markers for major fe-

tal structural abnormalities comprise the first type, the others often include mild or moderate non-specific, sometimes transient, modifications ("soft markers", "soft signs"). Unfortunately, studies evaluating the significance of these soft signs vary widely and show contradictory results. In this paper, the authors review the most used soft markers and discuss ultrasound techniques and measurement criteria for their detection. We also evaluated the clinical significance to aneuploidy risk assessment and evidence-based strategies for the management of affected pregnancies and correct counselling of the parents.

### ISP-49-1

**Intracranial pathologies during pregnancy** Yuri Niwa, Tomomi Kotani, Teruyuki Mizutani, Asuka Tachi, Masataka Nomoto, Yukako Itani, Mayo Miura, Yoshinori Moriyama, Takafumi Ushida, Kenji Imai, Tomoko Nakano, Fumitaka Kikkawa *Nagoya University*

Intracranial pathologies during pregnancy are uncommon, but special considerations are required for the management. To reveal their clinical course and perinatal outcome, we retrospectively investigated cases of intracranial pathologies during pregnancy treated at one tertiary hospital between January 1, 2007 and December 31, 2016. Among 4,426 deliveries in this period, 27 patients with intracranial tumors including 5 post-operative cases, 23 patients with cerebrovascular diseases including 9 post-operative cases and 3 patients with previous history of cerebral hemorrhage or cerebral infarction were detected. Seventeen cases (63.0%) in tumor cases were pituitary tumor, and seven cases (30.4%) in cerebrovascular cases were Moyamoya disease. Preterm birth rate in the tumor group was higher than that in the cerebrovascular group (22.2 vs. 8.7%,  $p=0.26$ ). More patients in tumor cases discontinued pregnancy for deterioration of intracranial pathologies. Four patients (17.4%) in cerebrovascular group developed bleeding or infarction during pregnancy, but had normal courses. Ten cases (28.5%) among patients without intervention at preconception required intervention during pregnancy, but none (0.0%) required among patients with intervention at preconception (28.6 vs. 0.0%,  $p=0.002$ ). In conclusion, perinatal prognosis of pregnant women with intracranial pathologies might be improved by intervention at preconception, although further study is needed.

### ISP-49-2

**Five cases of intracranial diseases in pregnant women** Chie Koide, Satoshi Urabe, Takako Sadakane, Norifumi Tanaka, Eiji Hirata, Yoshiki Kudo *Hiroshima University Hospital*

**Introduction** The awareness of saving the lives of pregnant women has been increasing. When pregnant women develop cranial neurological diseases such as stroke, rapid diagnosis and treatment at high-level facilities with appropriate provisions for neurosurgery are required. We reviewed 5 cases of intracranial disease occurring in pregnant women. **Methods** Between January 2010 and August 2017, 5 of the 2,785 pregnant women admitted to our hospital developed fatal intracranial diseases. We reviewed the diagnosis, treatment, and influence of pregnancy on these diseases. **Results** The 5 cases of intracranial diseases in pregnant women included one case each of subarachnoid hemorrhage, basal nucleus bleeding, multiple bleeding lesions due to acute lymphocytic leukemia, anaplastic astrocytoma, and glioblastoma. As symptoms, headache was observed in 3 cases, paralysis in 3 cases, convulsions in 1 case, and declining consciousness level in 2 cases. In all the cases, diagnosis was performed using computed tomography or magnetic resonance imaging. In 4 cases, cesarean section was performed under general anesthesia at from 24 to 40 weeks of gestation because the women required treatment for the underlying cranial disease. In

the case with subarachnoid hemorrhage, pregnancy was maintained. Only 1 patient completely recovered, 2 underwent rehabilitation, 1 was receiving treatment for the primary cranial disease, and 1 died because of the primary cranial disease. **Discussion** An intracranial disease during pregnancy can be life-threatening. Therefore, rapid diagnosis, and adequate and timely treatment of these diseases is essential. Cooperation between the several medical departments involved is needed for effective treatment in such cases.

### ISP-49-3

**Impact of maternal schizophrenia on protein expression of fetal immune system** Yoshinori Moriyama, Tomomi Kotani, Masataka Nomoto, Mayo Miura, Yukako Iitani, Asuka Tachi, Yumiko Ito, Takafumi Ushida, Kenji Imai, Tomoko Nakano, Fumitaka Kikkawa *Nagoya University*

**Objective** There is accumulating evidence showing involvement of intrauterine environment (IUE) in fetal life in the onset of various diseases. It is known that children born to mothers with schizophrenia (SCZ) have an elevated risk of SCZ, but the influence of IUE has not been investigated well. Here, we performed proteomic analysis of cord blood to evaluate the influence of maternal SCZ on the next generation via IUE. **Methods** Six pregnant women with SCZ and as many pregnant controls were included. Cord blood was sampled at delivery, and centrifuged for serum isolation. Proteome of the serum was measured by LC-MS/MS, and then analyzed by gene ontology (GO) and pathway enrichment analysis. Maternal blood samples during the third trimester for 5 case-control pairs were put into the same analysis. **Results** In cord blood, 348 proteins were detected, 81 of which showed more than 2-fold differential expression in one or more case-control pairs. In GO enrichment analysis, "complement activation," "classical pathway" had the largest significance ( $P=1.1 \times 10^{-41}$ ). Pathway enrichment analysis revealed "Complement And Coagulation Cascades" The most significant ( $P=5.9 \times 10^{-27}$ ). As for maternal blood, 83 proteins with over 2-fold change was identified, and the same GO term and pathway were listed as the most significant. **Conclusion** In the children of mothers with SCZ, complement pathway had already activated during their fetal period, similarly to their mothers, suggesting they could be "programmed" for some diseases by maternal SCZ. Reduction of this effect via improved IUE could contribute to prevention of diseases later in their life.

### ISP-49-4

**Maternal myasthenia gravis : Management of labor and delivery** Kotoi Tsurane, Yoshie Oka, Mayuko Saito, Sakiko Oshiro, Atsushi Fusegi, Shinji Baba, Izumi Honda, Tsutomu Ida, Kazunori Koike, Yoshimi Taniguchi, Akira Kohyama *Tokyo Metropolitan Tama Medical Center*

**Objective** In Myasthenia gravis (MG)-affected pregnancy, it is crucial to ease the second stage of labor, because maternal voluntary muscle weakness can be exacerbated during expulsive efforts or postpartum period. Although obstetric analgesia is a good option for circumventing the effects of maternal fatigue on delivery, the appropriate management is not well understood. The aim of this study is to assess the impacts and outcomes of labor and delivery, and to establish a protocol in management of maternal MG. **Methods** In this prospective study, we developed an algorithm to manage the delivery depending on the severity of the disease : For mild to moderate (asymptomatic) disease conditions, spontaneous vaginal delivery is chosen and vacuum delivery is performed when needed. For those who have moderate (symptomatic) to severe disease condition, obstetric analgesia plus immediate vacuum delivery once achieving a position enabling suction is conducted. **Results** Total of six patients were en-

rolled to the study. Two had mild disease condition and underwent normal vaginal delivery. Four were symptomatic and obstetric analgesia plus operative vaginal delivery was chosen. All patient's parturition took place smoothly and no adverse event occurred during the labor. No neonatal complication was noted. **Conclusion** In conclusion, MG-affected pregnancy can safely undergo spontaneous or operative vaginal delivery depending on the severity. Obstetric analgesia is a good option for circumventing the effects of maternal fatigue on delivery.

### ISP-49-5

**Case Report : Nonimmune Fetal Hydrops Following Maternal Suicide Attempt** Kristen Elmezzi<sup>1</sup>, Scott Petersen<sup>1</sup>, Barton Staat<sup>1,2</sup>, Kimberly Hickey<sup>1</sup> *Walter Reed National Military Medical Center, USA<sup>1</sup>, Uniformed Services University of the Health Sciences, USA<sup>2</sup>*

**Background** Hydrops is the abnormal accumulation of fluid in fetal cavities and soft tissues in two or more locations. Etiologies include infectious processes, fetal anomalies and hematologic abnormalities. Diagnostic criteria include abnormal fluid collections such as abdominal ascites, pleural or pericardial effusions and skin edema measuring >5 mm. Additional sonographic findings may include placental thickening and polyhydramnios. **Case** A 24 years old gravida 3 para 1,011 attempted suicide by ingestion of Acetaminophen/Aspirin/Caffeine/Benadryl tablets at 21 weeks gestation. Her prenatal course was complicated by limited obstetrical care. While hospitalized, her acetaminophen levels, salicylate levels and hepatic enzymes were mildly elevated. She received N-acetylcysteine and bicarbonate with normalization of all levels. Fetal anatomic survey was obtained at the time of admission without apparent abnormality. After discharge from the hospital, the patient reported absence of fetal movement during her obstetrics visit. Hydrops was seen on a limited ultrasound at this office evaluation visit and the patient was subsequently transferred to a tertiary care facility for further evaluation. Unfortunately, after weekly monitoring, the patient was diagnosed with a fetal demise at 29+2 weeks and underwent an uncomplicated induction of labor. **Conclusion** Nonimmune fetal hydrops results from various etiologies. This case is unique due to the timing of the diagnosis and the possible relation to ingestion of the medication. Evaluation for infection, fetal anomalies and genetic syndromes were negative. PUBS performed at 25+6 weeks revealed normal fetal liver enzymes and a low albumin. Catastrophic liver damage remains a possible etiology.

### ISP-49-6

**Postnatal depression associated with pregnancy induced by assisted reproductive technology** Haruhiko Udagawa, Hiroaki Aoki, Miki Muto, Keiko Yabuzaki, Akihiro Hasegawa, Tomona Matsuoka, Michihiro Yamamura, Yuki Ito, Kazuhiro Kajiwara, Satoshi Sohda, Osamu Samura, Aikou Okamoto *The Jikei University School of Medicine*

**Objective** Although the number of pregnancies resulting from assisted reproductive technology is increasing annually, the risks associated with these treatments are not fully understood. In this study, we investigated whether infertility treatment constitutes a risk factor for postnatal depression. **Methods** 827 women who gave birth at our hospital between January and December 2015 were evaluated for postpartum depressive tendencies 1 month after delivery using the Edinburgh Postnatal Depression Scale (EPDS). We excluded women with a known psychiatric disorder and those whose babies had been admitted to the neonatal intensive care unit. Patients were stratified into EPDS high-scoring ( $\geq 9$  points) and low-scoring groups ( $\leq 8$  points) and retrospectively analyzed for the use of infertility



treatment, age, previous miscarriage, and previous deliveries. **Results** Responses to the EPDS questionnaire were received from 573 women. There were 77 women (13.4%) in the high-scoring group and 496 women (86.6%) in the low-scoring group. A significantly higher proportion of infertility treatment utilization was found in the high-scoring group (32/77 (41.6%) vs 148/496 (29.8%) ;  $p=0.0393$ ). Multiparity was associated with lower risk for postnatal depression (23/77 (29.9%) vs 229/496 (46.2%) ;  $p=0.0073$ ). No significant difference was found among women who became pregnant after the age of 35 ( $p=0.7579$ ) or whom had a previous miscarriage ( $p=0.5146$ ). **Conclusion** Women who had utilized infertility treatment to induce pregnancy accounted for a significantly higher proportion of participants with a high EPDS score, suggesting that use of infertility treatment may be a risk factor for postnatal depression.

### ISP-49-7

**Clinical study of pregnant women with psychotic disorders** Sara Takahashi, Souta Tanaka, Shohei Tanabe, Takanori Shimizu, Yoko Yoshida, Izumi Sato, Kaori Suenaga, Akiko Kasai, Goichiro Kasai, Takeshi Aida, Junko Kouno *Hachinohe City Hospital*

**Objective** In recent years the number of pregnant women with psychotic disorders is increasing. To consider how to manage pregnant women with psychotic disorders, we investigated the clinical outcomes of pregnant women with depression, manic depression and schizophrenia. **Methods** Out of 4,759 deliveries at our hospital from April 2014 to September 2017, there were 52 cases (1.1%) of depression, 12 cases (0.25%) of manic depression and 11 cases (0.23%) of schizophrenia. Pregnant women with depression, manic depression and schizophrenia were divided into groups who needed medication therapy during pregnancy ( $n=36$ ) and groups who did not need medication therapy ( $n=39$ ). We analyzed retrospectively whether they needed support of social workers or not. **Results** 5 cases (6.7%) were preterm birth. 16 cases (21.3%) underwent cesarean section not due to their mental disorders. 8 cases (10.6%) were threatened premature birth. Ratios of preterm birth, cesarean sections and threatened premature birth did not have a significant difference between the ratios of women without psychotic disorders in our hospital. 25 cases of 36 (69.4%) pregnant women who needed medication therapy during pregnancy required support of social workers. On the other hand, 15 cases of 39 (38.4%) pregnant women who did not need medication therapy required. **Conclusion** This study suggests that women with psychotic disorders who need medication during pregnancy are likely to have need of support of social workers. Consistent management by both obstetrician and psychiatrist might be required for women with psychotic disorders, and social workers would be essential to support mothers after pregnancy.

### ISP-49-8

**The Effect of the Edinburgh Postnatal Depression Scale at Postpartum Checkup** Asuka Tachi, Tomomi Kotani, Teruyuki Mizutani, Yuri Niwa, Yukako Iitani, Masataka Nomoto, Yumiko Ito, Masanori Moriyama, Takafumi Ushida, Kenji Imai, Tomoko Nakano, Fumitaka Kikkawa *Nagoya University*

**Objective** We have provided a postpartum checkup under the protocol including the Edinburgh Postnatal Depression Scale (EPDS). We tested whether EPDS is useful for finding a risk of postpartum depression (PPD) and need for postpartum support. **Methods** We collected the data from 44 women delivered in May–August 2017. Based on the EPDS scores, they were divided into 2 groups, Group A ( $n=33$ , EPDS score  $<9$ ) and Group B ( $n=11$ , EPDS score  $>8$  defines depressive symptoms). We analyzed the risk factors of PPD and need for postpartum support.

**Results** Group B showed higher mean score ( $3.05 \pm 2.74$  vs  $13.4 \pm 5.31$ ). Despite no significant differences between 2 groups in most risk factors ; age at delivery, cesarean section rate and presence or absence of past mental illness, there were significantly more first-births ( $P=0.013$ ) and infertility treatment ( $P < 0.01$ ). Public health nurse, midwife, obstetrician, psychologist, and/or psychiatrist were selected as postpartum support depending on patient situation. All cases in Group B received some support. Four needed psychiatrist and public health nurse support. Three of them had a history of mental illness showed no deterioration, but supports continued ; two-person support seems appropriate. Another patient developed PPD state. It was not contradictory from the onset frequency of PPD. In Group A, 4 needed support, and only one ended support at first time. EPDS cannot sufficiently extract patients who require support. **Conclusion** While the screening effect of EPDS for PPD was confirmed, it was not sufficient as mental examination tool. This study suggests that overall examination of perinatal mental health is needed.

### ISP-50-1

**Obstetric and neonatal complications in pregnancies achieved by oocyte donation in our institution** Naoko Takahashi, Tatsuya Miyake, Hitomi Nakamura, Aiko Kakigano, Tsuyoshi Takiuchi, Shinya Matsuzaki, Kazuya Mimura, Keiichi Kumasawa, Takuji Tomimatsu, Masayuki Endo, Tadashi Kimura *Osaka University*

**Objective** To assess the risk of adverse obstetrics and perinatal outcomes in pregnancies achieved by oocyte donation (OD). **Methods** Obstetrics and neonatal outcomes were retrospectively compared between 3 groups, the oocyte donation pregnancies group ( $n=18$ ), extremely advanced maternal aged pregnancies (over 45 years old) achieved by in vitro fertilization with autologous oocytes (IVF) group ( $n=9$ ), and spontaneous conception ( $n=16$ ). All deliveries were performed in our hospital from January 2008 to August 2017. **Results** The oocyte recipients were aged 42 – 55 years (mean  $\pm$  SE ;  $49.2 \pm 0.86$  years). Multiple gestations were 2 cases (11.1%), and both of them were twins. Antenatal complications included hypertensive disorders of pregnancy ( $n=7$ ), gestational diabetes ( $n=4$ ), preterm delivery ( $n=5$ ), postpartum hemorrhage ( $n=12$ , included 3 postpartum hysterectomy), and low birth weight ( $<2,500$ g) ( $n=5$ ). Thirteen (72.2%) deliveries were performed by Caesarean section. The gestational age at delivery for singletons was  $36.8 \pm 0.96$  weeks (range 29–41 weeks), with birth weight  $2,644.4 \pm 195.5$  g. Neonatal complications occurred in 4 babies included light for date ( $n=2$ ), tetralogy of Fallot ( $n=1$ ), respiratory distress syndrome ( $n=1$ ). Compared with IVF and spontaneous conception groups, the risk of hypertensive disorders of pregnancy and preterm delivery is higher. Moreover, compared with spontaneous conception group, oocyte donation and IVF groups are at higher risk of having Caesarean section and postpartum hemorrhage. **Conclusion** Pregnancies by oocyte donation have increased risk of a range of obstetrics and neonatal complications.

### ISP-50-2

**Analysis on the perinatal outcome of pregnant patients complicated with inflammatory bowel disease** Kunihiro Yoshida<sup>1</sup>, Masayuki Yamaguchi<sup>1</sup>, Tomoyuki Sekizuka<sup>1</sup>, Ryo Tamura<sup>1</sup>, Mina Itsukaichi<sup>1</sup>, Taro Nonaka<sup>1</sup>, Kazufumi Haino<sup>1</sup>, Koichi Takakuwa<sup>2</sup>, Takayuki Enomoto<sup>1</sup> *Niigata University Medical and Dental Hospital<sup>1</sup>, Center for Perinatal, Maternal and Neonatal Medicine, Niigata University Medical and Dental Hospital<sup>2</sup>*

**Objective** Inflammatory bowel disease (IBD) is divided into ulcerative colitis (UC) and Crohn's disease (CD), and IBD is appeared more commonly in younger generation and there are



some occasions to manage pregnant women complicated with IBD. Patients with IBD have inflammatory and autoimmune background. The purpose is to investigate the perinatal outcome in pregnant patients complicated with IBD. **Methods** Twenty-nine pregnancies of 25 patients with IBD (21 cases ; UC, 4 cases ; CD) who delivered during 2006 and 2016 in our hospital were enrolled in this study. The perinatal outcomes were analyzed retrospectively, using medical records. As control, the pregnancy outcome was analyzed in 509 pregnancy cases with no complications including IBD. **Results** The developing rates of p-PROM, preterm delivery, or HPD were not significantly different between two groups. The body weight gain during pregnancy in patient group of IBD was significantly more than that in control group ( $11.6 \pm 4.0\text{kg}$  vs  $10.2 \pm 3.7\text{kg}$ ,  $p=0.023$ ). The body weight, Apgar score and pH of umbilical artery of neonates were not significantly different between the two groups. However, the admission rate of NICU in patient group was significantly higher compared with control group (24.1% vs 11.4%,  $p=0.041$ ). The causes for admission in patient group were massive aspiration syndrome, neonatal distress, neonatal bradycardia, or suspicion of GBS infection, etc. **Conclusion** Although the perinatal outcome of pregnant patients with IBD is not almost different from that of control population, it was considered that the careful observation to the neonate was important.

### ISP-50-3

**Live birth after intravenous treatment for uterine arteriovenous malformation, a case report** Kazumi Tada, Susumu Miyashita, Tatsuya Kuno, Ichio Fukasawa *Dokkyo Medical University*

**Introduction** Uterine arteriovenous malformation (U-AVM) is a rare complication with massive hemorrhage after uterine curettage or postpartum period, which can lead to life-threatening condition. We report a case of live birth after the interventional radiological (IVR) treatment for U-AVM. **Case** A 39-year-old woman, gravida 6, para 2, was referred because of massive uterine bleeding after three weeks of curettage for incomplete abortion. Pathological vessels and blood flow were noted in the low uterine segment by ultrasonography and MRI, which was compatible with U-AVM. Uterine bleeding was decreased spontaneously at that time, but massive hemorrhage appeared again eight months after and urgent IVR was indicated. Feeding vessels from the left uterine artery were suspected and selected embolus was carried out. She got pregnant spontaneously after the IVR treatment and gave birth 20 months afterward. The intrapartum hemorrhage was 1,302g. She discharged without pathological bleeding. Although abnormal bleeding did not appear after the delivery, continuous bleeding was observed after a complete abortion after 27 months. We carried out pelvic angiography 29 months after, and performed the right uterine-artery embolus. The patient got inserted an intrauterine contraceptive device with luteinizing hormone and under the follow-up. **Discussion** We reported a case of live birth after the IVR treatment for U-AVM. The massive hemorrhage from the U-AVM could lead a life-threatening condition, and aggressive IVR was rationalized.

### ISP-50-4

**Mild paroxysmal nocturnal hemoglobinuria in pregnancy, that was difficult to distinguish from hemolysis, elevated liver enzymes, and low platelet count syndrome : A case report** Youhei Tsunoda, Ikuno Kawabata, Eika Harigane, Yukiyo Harigane, Hiroki Shimamura, Manabu Shimada, Masahiko Kato, Yuri Shouda, Takehiko Fukami, Takashi Matsushima, Koichi Yoneyama, Toshiyuki Takeshita *Nippon Medical School*  
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare type of

hemolytic anemia, involving bone marrow failure and thrombosis. We present a case of PNH-complicated pregnancy that proved difficult to distinguish from hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. The patient was a 36-year-old nullipara with pregnancy initiated by assisted reproductive technology. At the gestational age of 35 weeks and 0 days, she developed severe proteinuria, fetal growth restriction, and thrombopenia. The findings at initial examination were Hb 10.0 g/dL, Plt 83,000, AST 64 U/L, LDH 1,201 IU/L, antithrombin III 98.3% and haptoglobin was less than 10 mg/dL. Hemoglobinuria or schizocytes were not found. As clinical findings suggested partial HELLP syndrome, we performed an emergency cesarean section. After the delivery, her platelet count normalized, but her AST and LDH levels remained high. We made a closer examination of LDH. We suspected hematological disease because LDH1 and LDH2 levels were abnormal. We finally diagnosed her with PNH because sugar-water test was positive, haptoglobin level was low, and high-sensitivity flow cytometry showed low levels of CD55 and CD59 on erythrocyte surfaces. As the patient's condition appeared mild, we monitored her without treatment. If there are no specific findings for HELLP syndrome, the possibility of PNH-complicated pregnancy should be considered. PNH-complicated pregnancy involves the high risk of thrombosis, and the risk of death for both the mother and fetus. It is important to establish a diagnosis of PNH for treatment during the next pregnancy.

### ISP-50-5

**Uterine prolapse during pregnancy : two case reports** Yuta Momono, Tetsuro Hoshiai, Kaou Tanoue, Kosuke Tanaka, Takahiro Minato, Michiyo Kurakata, Hidekazu Nishigori, Masatoshi Saito, Nobuo Yaegashi *Tohoku University Hospital*  
**Introduction** Uterine prolapse that develops during pregnancy is rare, and it is regarded as one case in 10,000 to 15,000 deliveries. There is no definite view on labor management. We report two cases in which uterine prolapse develops during pregnancy and has a different outcome. **Case 1** A 37-year-old woman, gravida 5, para 0. She developed uterine prolapse at 37 weeks and 2 days of gestation. On the next day, uterine prolapse worsened and became POP-Q stage III, which caused symptoms of urination difficulty and abdominal distension. However, the uterine vagina became highly congested and the cervix varied. We concluded that it was impossible to deliver vaginally, and caesarean section was performed. **Case 2** A 39-year-old woman, gravida 0. She developed uterine prolapse at 35 weeks of gestation. Based on the experience of the above cases, we decided to carry out planned delivery. At the 38 weeks 0 day of gestation, using the metroilintel, and induction of labor was started by oxytocin. Although descending of the fetal head was smooth, expansion and retraction of the uterine cervix was poor and it required manual opening of the cervical canal. The baby was born on natural birth. Cervical laceration was found at 8 o'clock direction and sutured. **Conclusion** There are many reports that cesarean section was performed as in case 1, in patients with uterine prolapse who developed during pregnancy. However, it is suggested that natural delivery may be performed if planned labor is carried out as in case 2.

### ISP-50-6

**Shakuyakukanzoto could be an effective treatment for a pregnant women with lumbar disk herniation and crampy pain** Miyuki Terata, Yuka Okada, Hanae Kawamura, Gen Haba, Yuri Sasaki, Tomonobu Kanasugi, Chizuko Isurugi, Rie Oyama, Akihiko Kikuchi, Toru Sugiyama *Iwate Medical University*  
**Introduction** Shakuyakukanzoto (SKT), which is composed of Kanzo (Glycyrrhiza radix) and Syakuyaku (Paeoniae radix),

is a kind of Japanese Kampo Medicine. A major effect of SKT is to improve symptoms of muscle cramps. We herein report a pregnant woman with lumbar disk herniation, to whom SKT was quite effective to relieve severe pain. **Case A** 33-year-old pregnant woman, Gravida 1, Para 0, was referred to our hospital at 24 weeks of gestation. MRI at 14 weeks at another hospital showed lumbar disk herniation. Her pain gradually worsened, and she became unable to walk by herself at 24 weeks. We started SKT without any other medication at 25 weeks of gestation. The pain score drastically dropped from 6/10 to 1-2/10 immediately after taking SKT for the first time, and we could finally cease SKT at 29 weeks of gestation with no recurring pain. **Conclusion** SKT has two important effects, that is, to keep balance and amendment of Ketsu (blood) and Sui (body fluid), and therefore it can mitigate the cramp in body and smooth muscles. Based on our experience, SKT maybe quite effective for treating a pregnant woman with a crampy pain caused by lumbar disk herniation. It might be considered as one of the possible first medication and an alternative to other treatment such as NSAIDs and a nerve block during pregnancy.

### ISP-51-1

**Predicting Data-based Induction Interval of Labor Induction with Titrated Oral Misoprostol Solution** Shi-Yann Cheng, Fung-Chang Sung, Cheng-Li Lin *China Medical University of Taiwan, Taiwan*

**Objective** Determine the dominant factors which affect the induction interval in labor induction with titrated oral misoprostol solution. **Methods** Women between 36 to 42 weeks of gestation under labor induction with titrated oral misoprostol solution were collected from March 2004 to August 2011. Women received basal unit of 20 ml misoprostol solution (1 µg/ml) every one hour for 4 doses, and then were titrated against individual uterine response. The recorded induction-to-vaginal delivery interval (IVDI) was the primary dependent variable. Nine independent variables including maternal age, maternal body height, maternal body weight, parity, gestational age at induction, birth weight of newborn, Bishop score, cervical length and cervical Os were also recorded. There were one hundred fifty-nine women in our database, 6 of them who underwent emergency cesarean delivery and 22 of them with poor response to misoprostol were excluded. Multivariable regression analysis was used to estimate the IVDI associated with all related factors. **Results** There were 55 nullipara women (42.0%) and 76 multipara women (58.0%) in our study. There were 3 factors significantly related to IVDI: Cx length, Cx Os, and maternal parity. The regression equation was acquired such as  $Y = (4.44 \pm 15.8) + (3.20 \pm 1.24) \times A - (1.22 \pm 0.44) \times B - (2.81 \pm 0.85) \times C$  [Y: IVDI (hrs); A: cervical length (cm); B: cervical os (cm); C: para, where value=0 for nullipara or value=1 for multipara] **Conclusion** The Bishop score, Cx length, Cx Os, and maternal parity are the dominant variables to evaluate labor induction and predict IVDI.

### ISP-51-2

**Comparison of maternal and perinatal morbidity in term breech presentation between elective and emergency cesarean section** Benjamas Kitnithee, Sanitra Anuwutnavin, Pharuhas Chanprapaph, Suanya Heamar, Pimnara Rongdech *Siriraj Hospital, Mahidol University, Thailand*

**Objective** To compare maternal and neonatal adverse outcomes between planned and emergency cesarean section for singleton term breech presentation. **Methods** In a retrospective cohort chart review, data were received from women with a singleton breech presentation who underwent elective or emergency cesarean section at term between 2007 and 2015 at Siriraj Hospital,

Bangkok, Thailand. The medical records of all women and their newborns were statistically analyzed. **Results** During the 9-year period, complete data were collected for 2,203 pregnant women. Of the 1,332 (60.5%) women underwent emergency cesarean delivery, 871 (39.5%) women were delivered by planned cesarean section. The significant predisposing factors (all  $P < 0.001$ ) associated with emergency operation included maternal age  $< 35$  years, gestational age  $< 38$  weeks, multiparity, no previous uterine surgery, and being non-private case. There was no maternal or perinatal death in either group. Maternal morbidity in both groups was comparable except for the longer hospital stay in the emergency group ( $P=0.047$ ). A 1-minute Apgar score ( $P=0.037$ ) was significantly lower in the emergency group. However, the Apgar score at 5<sup>th</sup> minute ( $P=0.825$ ) and admission to neonatal units ( $P=1.00$ ) were similar between the groups. Certain emergency indications, such as cord prolapse and placenta previa, were related to the adverse outcomes while cesarean delivery in advanced cervical dilatation ( $> 6$  cm) or low fetal station ( $> 0$ ) did not have any excesses of maternal and neonatal complications. **Conclusion** In singleton term breech presentation, emergency cesarean delivery in tertiary care setting was not associated with an increase in serious maternal and neonatal morbidity compared with planned cesarean section.

### ISP-51-3

**Uterine tonic contraction after initiation of oxytocin infusion for induction or augmentation of labor** Takahiro Yamashita, Shinichiro Otera, Yoko Gekka, Tomoko Shinohara, Taiki Samejima, Nobuko Akamata, Shinichiro Yabe, Yukiko Kawana, Yoshiharu Takeda, Tomoko Adachi, Takashi Okai, Masao Nakabayashi *Aiiku Hospital*

**Objective** We report 39 cases of uterine tonic contraction within 30 minutes after administration of oxytocin infusion. **Methods** Medical records, including fetal cardiocograms and partograms were investigated retrospectively. Cases of uterine tonic contraction occurring within 30 minutes after initiation of oxytocin infusion with two mIU/min were picked up. Character of tonic contraction, existence of fetal deceleration, treatment, prognosis of the newborns, etc. were analyzed. **Results** The number of deliveries after 22 weeks of gestation from November 2016 to September 2017 were 2,641, of which 1,256 cases were administered intravenous oxytocin and/or prostaglandin F<sub>2α</sub> (PG) infusion. 1,122 cases were administered oxytocin alone, 55 cases; PG alone, and 79 cases; both oxytocin and PG in a sequential order. Uterine tonic contraction was observed in 39 cases, all of which were after oxytocin infusion, 35 of which were accompanied deceleration of the fetal heart rate. The average and median interval between oxytocin initiation and tonic contraction was  $5.0 \pm 6.3$  and two minutes, respectively. The average and median interval between oxytocin initiation and fetal deceleration was  $8.7 \pm 7.5$  and 8 minutes, respectively. The bottom and duration of the deceleration were  $72 \pm 13$  bpm,  $6.7 \pm 2.4$  minutes, respectively. 27 cases were administered oxytocin again with one mIU/min and no cases observed tonic contraction. Vacuum delivery was performed in two cases after fetal deceleration. In all the 39 cases, the newborns' conditions were good. **Conclusion** Close observation is recommended for about 15 minutes after the initiation of oxytocin.

### ISP-51-4

**Can we stop Oxytocin after entering the active phase of labor for fetal growth restriction (FGR) babies; pros. or cons?** Sayuri Iwai, Kazuya Mimura, Tatsuya Miyake, Aiko Kakigano, Shinya Matsuzaki, Keiichi Kumasawa, Masayuki Endo, Tadashi Kimura *Osaka University*

**Objective** To investigate whether discontinuation of oxytocin

infusion increases the duration of the active phase of labor or reduces maternal and neonatal complications undergoing labor induction for fetal growth restriction. **Methods** This is a retrospective study involving 136 women with singleton pregnancy who underwent labor induction due to FGR at our institution, from January 2010 to August 2017. Two groups were compared: continuation of oxytocin (control) until delivery versus once discontinuation of oxytocin (DC) at the beginning of active phase of labor, which was determined as 4cm dilatation with active labor. At beginning, there was no abnormal FHR monitoring. Primary outcome was duration of the active phase. Secondary outcomes were total duration of labor, uterine hyperstimulation and FHR abnormalities rates, mode of delivery, and neonatal outcomes. **Results** Duration of the active phase was 6 min longer in the DC group, and the length of second stage was 22 min longer in the DC group; however, these were not statistically significant. The rate of FHR abnormalities was higher in the DC group, but it did not reach statistical significance (41.8% in control vs 57.3% in DC,  $P=0.08$ ). Uterine hyperstimulation was significantly higher in the control group (18.9% vs 4.9%;  $P=0.01$ ). Total C/S rate was 14.8% in the control group, whereas 24.5% in DC group ( $P=0.15$ ). **Conclusion** Discontinuation of oxytocin infusion at the beginning of active phase of labor for FGR elongated labor period. However, we can perform DC at the onset of active phase safely without increase uterine hyperstimulation and CS rate under strict monitoring.

#### ISP-51-5

**Risk factors for nonreassuring fetal status before labor in the presence of premature rupture of membranes** Urara Idei, Norikazu Watanabe, Mika Fukase, Akiko Sugiyama, Seiji Tsutsumi, Satoru Nagase *Yamagata University Hospital*

**Objective** This retrospective study examined risk factors for nonreassuring fetal status (NRFS) before labor in the presence of premature rupture of membranes (PROM). **Methods** We recorded continuous fetal cardiotocography (CTG) from PROM to initiation of labor. Patients with at least one level three or more deceleration, as defined by the Japan Society of Obstetrics and Gynecology, were considered NRFS. We compared the following factors in NRFS patients and others: age, gestational weeks, duration from PROM to initiation of labor, maternal or fetal complications, labor induction, mode of delivery, and recording duration of CTG. **Results** Among 54 women, preterm delivery occurred in six (11.1%). The median duration from PROM to initiation of labor was 14 hours, 10 minutes. The median CTG recording time was seven hours, one minute. There were 21 (39%) patients with NRFS from PROM to initiation of labor. The longer the duration, the more NRFS appeared during this time period (odds ratio 1.05; 95% confidence interval 1.00–1.10;  $p=0.032$ ). Induced delivery with NRFS during this period was only performed in one case with placental abruption. **Conclusion** The longer the duration from PROM to initiation of labor, the more NRFS appeared during this time period. A patient with NRFS who required induced delivery did not show an increase with time.

#### ISP-51-6

**A Potential Contribution of Bradykinin Receptor B1 Agonist to the Mechanism of Development of Myometrial Interstitial Edema** Yi Shen, Naoki Tamura, Tomoaki Oda, Kazuhiro Sugihara, Hiroaki Itoh, Naohiro Kanayama *Hamamatsu University School of Medicine*

**Objective** Myometrial interstitial edema is one of the most common histopathological diagnoses of uterine atony and its treatment options are limited. Kinins are important mediators of most kinds of inflammation that are released during injury, infection

and immune system activation. The effects of kinins are mediated by 2 type of receptors (B1 and B2 receptor) and induction of vascular hyperpermeability and edema. The objective of this study was to assess whether bradykinin receptor B1 agonist is involved in myometrial interstitial edema. **Methods** Tissues were collected by abdominal hysterectomy after the onset of postpartum hemorrhage. 10% buffered formalin-fixed specimens were embedded in paraffin, and cut into 3- $\mu$ m-thick sections. We selected the cases with myometrial interstitial edema. Control group is from normal pregnant women after receiving written informed consent. Primary antibodies of B1 and B2 receptor were used for immunohistochemistry staining. ImageJ was used for quantitative microscopy analysis for the IHC staining. **Results** Immunohistochemistry of B1R but not B2R showed a much stronger staining and an increased count of B1R-positive cells within the myometrial interstitial edema compared with controls. Significant differences were observed in the B1R+ area ratio/total cells in tissue sections using the unpaired  $t$ -test ( $P<0.05$ ). **Conclusion** Uterine atony is estimated to be responsible for 75–80% of postpartum hemorrhage, however, the etiology remains to be clarified. These data demonstrate that bradykinin receptor B1 agonist can promote myometrial interstitial edema and may open new avenues for postpartum hemorrhage treatment in future.

#### ISP-51-7

**Pregnancy outcomes subsequent to uterine arterial embolization for severe post-partum hemorrhage** Hitomi Imafuku, Mayumi Morizane, Tokuro Shirakawa, Kenji Tanimura, Masashi Deguchi, Hideto Yamada *Kobe University Hospital*

**Objective** To assess pregnancy outcomes subsequent to uterine arterial embolization (UAE) for severe post-partum hemorrhage (PPH). **Methods** Eighteen pregnancies after UAE from January 2003 to December 2016 in the single center were studied. **Results** During the study period, 88 women underwent UAE for severe PPH (blood loss  $>2,000$ ml) and 16 subsequently required hysterectomy due to uncontrolled hemorrhage (14/16) or infection (2/16). Sixteen women conceived subsequently to UAE including 2 women who conceived twice. Five of 18 pregnancies required infertility treatment. The median interval from UAE to the subsequent pregnancy was 25 months (13–77 months). The outcomes of 18 pregnancies were two miscarriages, two artificial abortions, one ectopic pregnancy, one invasive mole and 12 live births (7 cesarean and 5 vaginal delivery) including 2 preterm deliveries. Although pregnancy induced hypertension and fetal growth restriction occurred in one case, each growth of the other babies was appropriate for gestational age. One had placenta previa and 2 had placenta accreta. In one case of artificial abortion, cesarean section was performed at 20 weeks because of massive bleeding during the termination of a fetus with multiple malformation. The median blood loss at delivery of 13 cases including the case terminated at 20 weeks was 1991ml (395–8,500ml). There were 6 cases (2 cesarean and 4 vaginal delivery) of severe PPH in 18 pregnancies. Two were used Bakri tamponade, 4 underwent UAE and 3 subsequently required hysterectomy. **Conclusion** There was a high incidence of severe complications after UAE in subsequent pregnancies.

#### ISP-51-8

**Promotion of a new technique for cesarean section at full dilatation** Kotaro Shimura, Aiko Kakigano, Tatsuya Miyake, Tsuyoshi Takiuchi, Shinya Matsuzaki, Kazuya Mimura, Keiichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

**Objective** Incidence of cesarean sections (CS) has increased and we often encounter CS at full dilatation. Deeply impacted head

into the pelvis makes the procedure technically difficult and CS at full dilatation is associated with major maternal and fetal morbidity. Instead of a conventional method of pushing head through vagina, we introduced a new technique called reverse breech extraction technique from 2016, which has been reported to have less maternal complications. We evaluated maternal and neonatal morbidity of this new technique. **Methods** We retrospectively analyzed CS cases performed at full dilatation. We compared maternal and neonatal outcomes between cases delivered by pushing head through vagina (push group) and those delivered by reverse breech technique (pull group). **Results** We reviewed 601 CS reports and 298 emergent CS cases were included. Full dilatation was noted in 49 cases (16.4%). There is a trend that maternal complications including mean operative time and blood loss were lower in the pull group compared with the push group. Rate of another maternal complications including postpartum hemorrhage, blood transfusion, extension of the uterine incision and puerperal endometritis, or neonatal outcomes including birth asphyxia and NICU admission rate were not different significantly. **Conclusion** Reverse breech extraction technique might be safer and smoother than pushing technique for delivery of a deeply impacted head at emergent CS. Reverse breech extraction technique can minimize maternal complications.

### ISP-52-1

#### Non-Invasive Monitoring of the Cardiac Effects of Continuous Intravenous Oxytocin Infusion during Cesarean Delivery

Kayo Tanaka, Hiroaki Tanaka, Michiko Kubo, Masafumi Nii, Junko Watanabe, Kuniaki Toriyabe, Kazuhiro Osato, Yuki Kamimoto, Tomoaki Ikeda *Mie University*

**Objective** The effects of continuous intravenous oxytocin infusion on cardiac output (CO) and stroke volume (SV) have not been investigated. Therefore, we evaluated whether a continuous intravenous infusion of oxytocin had a major impact on CO and SV. **Methods** Ten pregnant women were recruited. Non-invasive monitor (EV1000/VolumeView) was used to measure CO, SV, heart rate (HR), and mean aortic pressure (mAP) during a 5 minute infusion of oxytocin during Caesarian sections. Data were analyzed using unpaired t-tests and the generalized linear model for repeated measures. **Results** The mean increase in CO was 123% (relative to baseline) after 60 seconds, which was a few seconds after the delivery of the baby. CO remained above baseline. We observed a minor increase in SV between baseline and the start of the intervention. SV increased approximately 8% after injection of oxytocin. There was an overall increase in HR, reaching a maximum 80 seconds after the intervention. Initially, there was a slight increase in mAP, which then slowly decreased remained under baseline. **Conclusion** Continuous intravenous infusion of oxytocin does not have a major effect on CO or SV, similar to its lack of a major effect on HR and blood pressure.

### ISP-52-2

#### Evaluation of circulatory dynamics during cesarean section using electrical cardiometry

Atsuko Hichijo, Takashi Kaji, Naoto Yonetani, Minoru Irahara *Tokushima University*

**Objective** Changes in the circulatory dynamics of pregnant women are significant. Cardiac output increases during pregnancy and especially changes due to uterine contraction and pain during delivery. In previous studies, we confirmed that cardiac output in vaginal delivery (VD) markedly increased during delivery, and high cardiac output status persisted for 2 hours thereafter using electrical cardiometry. On the other hand, the circulatory dynamics in caesarean section (CS) is predicted to be completely different from VD due to anesthesia etc. How-

ever, there is no report that continuously evaluated the variation. Therefore, we evaluate hemodynamics around delivery at CS by noninvasive continuous cardiac monitoring using electrical cardiometry. **Methods** We examined the transition of stroke volume, heart rate, and cardiac output from before operation to 2 hours after baby birth using electrical cardiometry in 15 healthy pregnant women who underwent CS. Atonic bleeding cases and hypertensive disorders of pregnancy cases were excluded. Analysis was evaluated for normality and compared with VD 15 cases by t test. **Results** In CS, stroke volume and cardiac output were found to increase significantly in 15 minutes after birth ( $P < 0.001$ ). Also in CS, the cardiac output in minutes was reduced to its original condition within 120 minutes after birth. These fluctuations were less compared with VD. **Conclusion** The circulatory dynamics in CS was different from in VD. By electrical cardiometry, fine evaluation of circulatory dynamics was also possible in CS.

### ISP-52-3

#### Outcome of twin delivery: A single center experience

Masami Hayashi, Hiroko Katayama, Ryo Uemura, Aki Takase, Natsuko Yokoi, Akihiro Hamuro, Takuya Misugi, Akemi Nakano, Daisuke Tachibana, Masayasu Koyama *Osaka City University*

**Objective** The aim of this study is to evaluate neonatal outcome of twin pregnancy by comparison between groups who planned to vaginal delivery and cesarean delivery. **Methods** We reviewed that all twin pregnancies delivered after 34 weeks of gestation during January 2014 and September 2017. The cases with obstetrical and fetal complications were excluded. **Results** The study population included 88 women with twin pregnancies. Forty women were selected vaginal delivery (Group A) and 48 women were selected cesarean delivery (Group B). In group A, 30 twin pregnancies (75%) delivered vaginally. Average gestational age was 36w6d in group A, and 36w4d in group B. Average Apgar scores of the first baby, and second baby (at 5 min) were 9.0 and 8.9 in group A respectively. Average Apgar scores of the first and second baby are 8.9 and 8.9 in group B. There is no significant difference between these groups. The number of neonates with transient tachypnea were similar between the groups (19% vs. 17%). There is no significant difference between MD and DD for failure of vaginal delivery in group A. In group B, emergent cesarean section was performed in 48% pregnancies because of labor onset and rupture of membranes. **Conclusion** The success rate of vaginal delivery is 75 percent regardless of chorionicity. There was no significant difference between groups who hope to vaginal delivery and cesarean delivery in neonatal outcome. We consider that vaginal delivery of twin pregnancy is a reasonable option.

### ISP-52-4

#### A study of factors associated with increased lactic acid levels in umbilical arterial blood

Ryuhei Kurashina, Yoshimitsu Kuwabara, Mirei Yonezawa, Nozomi Ohuchi, Tomoko Ichikawa, Rintaro Sawa, Shigeo Akira, Toshiyuki Takeshita *Nippon Medical School Hospital*

**Objective** This study aimed to identify risk factors associated with increased umbilical arterial blood lactic acid levels that reflect fetal acidosis. **Methods** We retrospectively studied the medical records of 459 patients with singleton vaginal deliveries at our hospital between August 2015 and March 2017. We analyzed the correlations between umbilical arterial blood gas and clinical parameters. Spearman's rank correlation coefficient, the Mann-Whitney U test, the t-test,  $\chi^2$  test, and logistic regression were used for statistical analysis. **Results** Umbilical arterial blood gas analysis showed negative correlations between lactic



acid levels, and 1 and 5 minute Apgar scores, pH, base excess, and HCO<sub>3</sub><sup>-</sup> also showed negative correlations. The duration of the first and second stages of labor were positively correlated with lactic acid levels. Lactic acid levels were significantly higher in groups in which the duration of the second stage of labor was 30-59 minutes, 60-119 minutes, or >120 minutes, compared to the group with a duration of 0-29 minutes. Univariate analysis showed that parity, duration of the first and second stages of labor, use of oxytocin, and vacuum extraction were significant risk factors associated with increased lactic acid levels. Multivariate analysis showed that prolonged first and second stages of labor were independent risk factors associated with increased lactic acid levels. **Conclusion** Prolonged first and second stages of labor are associated with increased lactic acid levels in umbilical arterial blood and may affect fetal acidosis.

### ISP-52-5

**The Origin of Inflammation in the Pathophysiology of Postpartum Acute Myometritis involved in Amniotic Fluid Embolism** Divyana Jain, Tomoaki Oda, Naoaki Tamura, Hiroaki Itoh, Kazuhiro Sugihara, Naohiro Kanayama *Hamamatsu University School of Medicine*

**Objective** There is massive infiltration of inflammatory cells including neutrophils and macrophages alongwith C5a receptor expression and mast cell degranulation, that is Postpartum Acute Myometritis (PAM), in the uterine myometrium after hysterectomy in Amniotic Fluid Embolism (AFE). However, uterine cervix is usually ripened during vaginal delivery with infiltration of inflammatory cells. Our aim is to investigate the origin and distribution of these inflammatory and immune cells related to anaphylactoid reaction in the uterine tissue affected with PAM in AFE. **Methods** Under the AFE registry program in Japan, these cases are registered and investigated in our institution. We investigate every uterine tissue at - body, isthmus and cervix with (vaginal delivery) and without (scheduled cesarean delivery) cervical maturation. We performed immunohistochemistry for inflammatory, immune cell markers- Neutrophil elastase, CD68, Mast cell tryptase, IL-8, MCP-1 and C5a receptor and observed their expression at these uterine sites. **Results** We investigated uterine tissues from two and three patients with and without cervical maturation respectively. Mast cell degranulation was observed in body, isthmus and cervix in both groups which is not seen in normal cervical maturation. Neutrophil elastase, CD68 and IL-8 were increased in body compared with isthmus or cervix in two cases without cervical maturation group indicating more inflammatory reaction in body. **Conclusion** There is a possibility that sudden activation of mast cells in all sites of uterine tissue may play an important role in PAM pathophysiology alongwith inflammatory changes in the body, which is independent of the cervical ripening and cervical inflammatory cells.

### ISP-52-6

**A case of unscarred uterine rupture : A rare and difficult diagnosis** Shihori Nishizawa, Satomi Tanaka, Shun Masaoka, Asako Kumagai, Sachi Sukekawa, Yoshiko Murase, Shotaro Yata, Hiroshi Kaneda, Yuka Yamamoto, Toshitaka Tanaka, Naoki Mitsuhashi *Juntendo University Shizuoka Hospital*

**Introduction** Unscarred uterine rupture is rare and it is often difficult to diagnose. We report a case of unscarred uterine rupture that we could not diagnose before surgery. **Case** A 31-year-old first gravid woman delivered a boy with 2,962g and Apgar score 8/9 by forceps at 40 weeks 5days gestation with induction of labor. After parturition, she became emergency transportation to our hospital due to the increase of vaginal hematoma and the hemorrhagic shock. On her arrival, her blood

pressure was 76/54 mmHg, heart rate was 140/min, Shock Index (SI) was 1.8. We suspected unscarred uterine rupture as one of the differential diagnosis, but ultrasonography showed no disruption of the uterine muscle layer. The vaginal examination showed vaginal hematoma and vaginal laceration. While applying transfusion to her, we performed a vaginal laceration suture under general anesthesia. Hematoma around uterus continuing from vaginal hematoma was confirmed by contrast CT examination after surgery, but there was no obvious abnormality in the uterus. The next day, because genital bleeding was persisting and hemostasis was difficult, transcatheter arterial embolization was performed. On the fourth day, since rebleeding occurred, we performed a total hysterectomy and found incomplete horizontal uterine rupture in lower urine segment. **Discussion** It seemed difficult to diagnose using images in case of incomplete horizontal unscarred uterine rupture. Even if diagnosis with images is difficult, it is necessary to consider uterine rupture as differential diagnosis of postpartum hemorrhage.

### ISP-52-7

**What kind of risk factors can foresee the postpartum hemorrhage after vaginal delivery in uncomplicated pregnancy?** Kazuhiro Nishioka<sup>1</sup>, Naoto Furukawa<sup>2</sup>, Seigo Imanaka<sup>1</sup>, Ayumi Tsuji<sup>1</sup>, Taketoshi Noguchi<sup>1</sup>, Hirotaka Kajihara<sup>1</sup>, Kiyoshige Horie<sup>1</sup> *Yamato Takada Municipal Hospital<sup>1</sup>, Nara Prefecture Western Medical Center<sup>2</sup>*

**Objective** Postpartum hemorrhage (PPH) is the leading cause of maternal morbidity after a vaginal delivery. As most coagulation factors increase during normal pregnancy, the prothrombin time (PT) and the activated partial thromboplastin time may be decreased, but the association between PPH and the coagulation profile is unclear. The present study aimed to identify risk factors for PPH in uncomplicated pregnancies. **Methods** Our retrospective cohort study included 396 pregnant women without complications from two institutions between Jan 1, 2015 and Dec 31, 2016. The logistic regression model was used to evaluate univariate and independent multivariate associations of the clinical parameters with PPH (blood loss > 800 ml). **Results** The incidence of PPH > 800ml was 11.6% (46/396). Univariate analysis using the logistic regression model revealed that PT/INR at 36-37 weeks of gestation, birth weight > 3,000g, episiotomy or laceration multipara, and age (>30) were significantly associated with PPH. Multivariate analysis revealed that independent risk factors for PPH were PT/INR, episiotomy or laceration, and birth weight (p=0.0103, 0.0042, and 0.0106, respectively). Based on receiver operating characteristic analysis, the cut-off value of PT/INR level to predict PPH > 800ml was 1.03. **Conclusion** The findings of the present study indicated that risk factors for PPH > 800ml were PT/INR at 36-37 weeks of gestation, episiotomy or laceration, and birth weight > 3,000 g. The PT/INR value at 36-37 gestational weeks > 1.03 is an independent predictor of severe PPH.

### ISP-53-1

**Clinical outcome of linear salpingotomy for a different lesion of tubal pregnancy** Toshimichi Oki<sup>1</sup>, Chie Oki<sup>2</sup>, Natsuko Uchida<sup>2</sup>, Sayuri Hiwatashi<sup>2</sup>, Yukiko Nakajo<sup>2</sup>, Hideki Yamasaki<sup>3</sup>, Ichiro Iwamoto<sup>4</sup>, Hiroaki Kobayashi<sup>1</sup> *Kagoshima University School of Health Sciences<sup>1</sup>, Kagoshima University Medical and Dental Hospital<sup>2</sup>, Kagoshima Medical Association Hospital<sup>3</sup>, Kagoshima University<sup>4</sup>*

**Objective** Recently, a few report has described about linear salpingotomy. We tried to preserve an impaired tube of tubal pregnancy after salpingotomy with fully informed consent. In this study, we retrospectively investigated clinical outcomes of liner salpingotomy in an individual site of tubal pregnancy.



**Methods** Subjects were as follows, 10 cases of fimbrial pregnancy (F group), 16 of isthmic pregnancy (I group), and 107 of ampullar pregnancy (A group) who underwent laparoscopic salpingotomy. Between three groups, findings of fallopian tubes, blood loss during surgery, and success rate of laparoscopic salpingotomy were compared. **Results** Intraoperative blood loss was greater in I group than F and A groups. Rupture rate of serous membrane : F group 0% (0/10), I group 18.8% (3/16), A group 1.9% (2/107). Rupture rate of muscle layer : complete : 0% (0/10), 37.5% (6/16), 1.9% (2/107), incomplete : 0% (0/10), 43.8% (7/16), 0% (0/107), respectively. The success rate of fallopian tube preservation was 90.0% (9/10), 50.0% (8/16), 93.5% (100/107), recovery rate of tubal patency after the surgery was 100% (9/9), 75.0% (6/8), 96.0% (96/100) respectively. **Conclusion** Isthmic pregnancy have negative impact to preserve an impaired tube by salpingotomy, because isthmus pregnancy often complicated with severe damage of tubal wall. However, an addition of end to end anastomosis to salpingotomy of isthmic pregnancy is a useful alternative.

### ISP-53-2

**Impact of parity on the transition of fetal presentation transition during pregnancy** Shogo Yamaguchi<sup>1</sup>, Takeshi Nagamatsu<sup>2</sup>, Rieko Shitara<sup>1</sup>, Hitomi Furuya<sup>1</sup>, Aki Hara<sup>2</sup>, Takahiro Seyama<sup>1</sup>, Toshio Nakayama<sup>1</sup>, Takayuki Iriyama<sup>1</sup>, Yutaka Osuga<sup>2</sup>, Tomoyuki Fujii<sup>2</sup> *The University of Tokyo Hospital<sup>1</sup>, The University of Tokyo<sup>2</sup>, Saitama Cancer Center<sup>3</sup>*

**Objective** Prediction of the final fetal presentation is important for the planning of delivery. This study aimed to clarify the characteristics of fetal presentation during pregnancy distinctively in primiparous and multiparous women. **Methods** This study was conducted under the approval of ethics committee of our facility. Perinatal records of 1,923 women {1,173 primiparous women (P) and 750 multiparous women (M)} who delivered at our hospital from 2015 to 2016 were retrospectively reviewed. The data on fetal presentation was confirmed by ultrasonography at prenatal visits between 30 and 34 weeks of gestation (WG). Correlation among non-cephalic delivery, Fetal presentation during this period and parity was statistically analyzed. **Results** The frequency of non-cephalic presentation from 30 to 34 WG was not significantly distinct between P and M (13.3% vs 14.0%,  $p=0.60$ ). However, P showed significantly higher non-cephalic rate than M at delivery at term (4.52% vs 2.67%,  $p<0.05$ ). The ratio of non-cephalic delivery was significantly higher in women without any findings of cephalic presentation from 30 to 34 WG, compared with those showing cephalic presentation at least one time during the same period in both P and M (P : 0.60% vs 47.1%,  $p<0.05$ , M : 1.08% vs 31.8%,  $p<0.05$ ). **Conclusion** The information on fetal presentation during the period from 30 to 34 WG is useful for the prediction of the final presentation. Transition to cephalic presentation is estimated to occur more frequently in M than in P.

### ISP-53-3

**A case review of methotrexate therapy in ectopic pregnancy** Yoshihide Inayama, Koji Yamanoi, Jumpei Ogura, Tsutomu Ohara, Mie Sakai, Haruka Suzuki, Koh Suginami *Toyooka Hospital*

**Objective** Methotrexate (MTX) treatment for ectopic pregnancy is common and effective. In some cases, however, it fails and subsequent surgeries are required. The aim of this study is to discuss pit-falls in MTX treatment. **Methods** In our hospital, MTX treatment is performed for un-ruptured ectopic pregnancies whose hemodynamic status is stable and initial serum hCG levels are less than 10,000 mIU/ml. Before MTX treatment we performed a diagnostic imaging test to identify the pregnancy

locations. We analyzed the clinical records of ectopic pregnancies who were initially treated with MTX in our hospital from April 2016 to September 2017. **Results** During the period, six patients were treated with MTX ; five were tubal pregnancies and one was interstitial pregnancy. The median age at diagnosis was 29 and one patient received assisted reproductive therapy. MTX treatment succeeded in five patients but failed in one patient. The serum hCG level of this patient at diagnosis, on MTX treatment day 3 and day 9 were 2,596, 4,132, 3,468 mIU/mL, respectively. Additional MTX injection was administered on day 9, but tubal rupture occurred and an emergent laparoscopic surgery was performed on treatment day 12. Two patients who were successfully treated with MTX got pregnant within a year. **Conclusion** MTX treatment may fail even in patients with relatively low serum hCG levels at diagnosis. It is important to observe symptoms, vital signs, and serum hCG levels carefully during MTX treatment. Surgery should be considered immediately when rupture is suspected.

### ISP-53-4

**Two cases of uterine rupture occurred during second trimester** Ryo Uemura, Takuya Misugi, Masami Hayashi, Megumi Fudaba, Aki Takase, Natsuko Yokoi, Hiroko Katayama, Akihiro Hamuro, Akemi Nakano, Daisuke Tachibana, Masayasu Koyama *Osaka City University*

Uterine rupture is rare for a pregnant woman without uterine operation or caesarean section. We report the two cases of uterine rupture occurred during second trimester. A 40-year-old gravidity-2, parity-1 patient without caesarean section was admitted to previous hospital due to threatened abortion at 17weeks of gestation. Sudden abdominal pain was occurred and transferred to our hospital at 18weeks of gestation. Moderate abdominal pain limited uterus was recognized, but the next day, pain became severe and shock index increased to 2.0. Contrast enhanced CT showed intraabdominal hemorrhage and we underwent exploratory laparotomy. In the operation, we recognized massive hemorrhagic ascites, uterine rupture at fundus uteri and placenta accrete, and performed supra-cervical hysterectomy. A 40-year-old gravidity-6, parity-4 patient without caesarean section was diagnosed complete abortion at another clinic at 8weeks gestation. Chorion membrane was not confirmed, but gestational sac was not detected in uterus by ultrasound, and clinical follow was over. After 6 weeks later, sudden abdominal pain was occurred and intraabdominal hemorrhage and fetus in uterus was recognized and transferred to our hospital. We diagnosed 13 weeks gestation by ultrasound and suspected interstitial portion of the right fallopian tubal pregnancy by MRI, so we underwent exploratory laparotomy. In the operation, we recognized massive hemorrhagic ascites and uterine rupture at interstitial portion of right fallopian tube, and performed total hysterectomy. Uterine rupture can occur even patient without uterine operation or caesarean section. When abdominal pain limited uterus was recognized, it is important to suspect uterine rupture.

### ISP-53-5

**Obstetric Outcome of Subsequent Pregnancy following Uterine Artery Embolization for postpartum hemorrhage** Mariko Jitsumori, Shinya Matsuzaki, Tatsuya Miyake, Aiko Kakigano, Tsuyoshi Takiuchi, Kazuya Mimura, Keiichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

**Objective** Uterine artery embolization (UAE) is used to treat uncontrollable postpartum hemorrhage. The obstetric outcome of subsequent pregnancy following UAE has been shown in a limited number of studies, with some reports showing a higher

rate of placenta accreta. However, there has been no case control study ; therefore, we conducted a case control study of subsequent pregnancy following UAE in our hospital. **Methods** In a retrospective analysis, data from deliveries in our hospital, between January 2012 and June 2017, was reviewed. The deliveries were divided into previous UAE (study group) and non-UAE (control group) groups. Placenta accreta was defined as confirmed by pathological examination. **Results** Data from 2,845 patients were included in the study. Fifteen patients were included in the study group, and 2,830 patients were included in the control group. Although our control group could contain significant bias of preterm birth rate as a referral hospital, there are no differences were observed between the study and control groups in the frequency of preterm delivery [2/15 (13.3%) vs 447/2,830 (15.7%) ; P=1.00]. However, placenta accreta was significantly more common in the study group than in the control group [5/15 (33.3%) vs 27/2,830 (0.95%) ; P=0.001]. **Conclusion** Our study suggested that previous UAE was a significant risk factor of placenta accreta.

### ISP-53-6

**Epidemiology of ectopic pregnancy : incidence, risk factors and outcomes in Mongolia** Tsevelmaa Baldan<sup>1</sup>, Munkhtsetseg Davaatseren<sup>2</sup>, Enkhtsetseg Jamsranjav<sup>2</sup> *Marie Stopes International Mongolia, Mongolia<sup>1</sup>, Mongolian National University of Medical Sciences, Mongolia<sup>2</sup>*

**Objective** We aimed to identify potential risk factors and to evaluate the contribution of the risk factors associated to EP. **Methods** This case-control study was conducted from 1998 to 2016 in the four Hospitals in UB, Mongolia. In case group there were a total of 121 women diagnosed with EP, while in the control group I ; 130 women who had normal pregnancy and in the control group II ; 129 women who had induced abortion. The basic recorded information and the laboratory method was determination of anti-chlamydia trachomatis IgG titer. The association between EP and the factors studied was analysed by Multivariate multinomial logistic regression and adjusted relative risk ratios (aRRR). **Results** EP group had higher IgG antibody titres than group I and group II. Then fitted as a trend variable, using log-base-2 (IgG titre) the association was highly significant (aRRR=1.1 95%CI : 1.0-1.3 and aRRR=1.2 95%CI : 1.1-1.4 ; P=0.0019). A history reproductive tract infection (RTI) was associated with increased risk of EP, even after adjustment for anti-chlamydial IgG titre with aRRR between 2.2 (95%CI : 0.96-7.0) and 4.2 (95%CI : 1.5-11.7) compared to ANC and IA controls. Also, cigarette smoking was a strong risk factor for EP with aRRR of 2.8 (95%CI : 1.3-6.2) and 4.4 (95%CI : 1.8-11.0). **Conclusion** In this UB city population, history of infection with Chlamydia trachomatis was independent, dose related risk factor for EP.

### ISP-54-1

**CD59 expression on human extravillous trophoblast may be regulated by surrounding microenvironment** Masashi Ueda<sup>1</sup>, Akihito Horie<sup>1</sup>, Yukiyasu Sato<sup>2</sup>, Hirohiko Tani<sup>1</sup>, Asuka Okunomiya<sup>1</sup>, Yusuke Sagae<sup>1</sup>, Masaki Mandai<sup>1</sup> *Kyoto University<sup>1</sup>, Japanese Red Cross Otsu Hospital<sup>2</sup>*

**Objective** In human placenta, although endovascular extravillous trophoblast (eEVT) makes direct contact with maternal complement components, eEVT is not eliminated by their activation. Previously, we found that expression of CD59, one of membrane-bound complement regulators, is higher on eEVT than on interstitial EVT invading the maternal decidua in vivo. In addition, we demonstrated that CD59 provides some protection against complement-dependent cytotoxicity to trophoblastic cell line in vitro. In this study, we investigate possible envi-

ronmental factors that regulate CD59 expression in the isolated EVT. **Methods** The first-trimester chorionic samples were obtained from artificial abortions and were subjected to the organ cultures to isolate the primary EVT (isolated EVTs). Possible effect of hypoxic culture or co-culture with platelets on CD59 expression in the isolated EVTs was assessed with q-PCR and/or flow cytometry. In addition, possible effects of treatment with various cytokines that are abundantly released from activated platelets (i.e., IL-1 $\beta$ , CCL5, TGF- $\beta$ 1, VEGF and PDGF) on their CD59 expression were examined with q-PCR. **Results** CD59 expression in the isolated EVTs was down-regulated under the hypoxic condition and up-regulated by co-culture with platelets. Among the various cytokines examined, only TGF- $\beta$ 1 could alter (up-regulate) CD59 expression in the isolated EVTs. **Conclusion** High CD59 expression on eEVT could be at least in part explained by the surrounding microenvironment such as high oxygen concentration in the maternal spiral artery and TGF- $\beta$ 1 released from the platelets that are activated following the deposition on eEVT.

### ISP-54-2

**Serum autotaxin level as a biomarker for placental function** Yumiko Nishimori<sup>1</sup>, Takeshi Nagamatsu<sup>1</sup>, Tatsuya Fujii<sup>2</sup>, Nobuko Mimura<sup>1</sup>, Takayuki Iriyama<sup>1</sup>, Yutaka Osuga<sup>1</sup>, Tomoyuki Fujii<sup>1</sup> *The University of Tokyo<sup>1</sup>, Kanto Rosai Hospital<sup>2</sup>*

**Objective** Autotaxin (ATX) is a major enzyme that produces lysophosphatidic acid, a phospholipid mediator. ATX is known to increase in malignant tumors, arteriosclerosis, pulmonary fibrosis. Placental production is a major source of serum ATX during pregnancy. This study aimed to examine the association of serum ATX concentration with the placental weight and fetal growth. **Methods** This study was conducted under approval of our facility ethics committee. We collected serum samples from 148 women with singleton pregnancy, including 116 women of uncomplicated pregnancy and 32 women complicated with preeclampsia (PE) and/or fetal growth restriction (FGR). The correlation of the serum ATX levels in the second and the third trimesters with placental weight, birth weight and BPR (birth weight to placental weight ratio) was evaluated. Serum ATX concentration in the second and the third trimester was determined by ELISA. **Results** The serum ATX levels increased along with the progression of gestation, reaching its peak at term pregnancy, and rapidly returned to pre-pregnancy level at postpartum period. In uncomplicated pregnant women, a significant negative correlation (R=0.72 P<0.001) was detected between BPR and the serum ATX level in the second trimester, but not in the third trimester. This negative correlation in the second trimester was canceled in the pregnancies with PE and/or FGR. **Conclusion** Our findings imply that placental ATX in normal pregnancy could be involved in the mechanism to adjust fetal growth to appropriate status. It is possible that dysregulation of ATX production is associated with the pathobiology of PE and FGR.

### ISP-54-3

**Transport mechanism of nicotine in BeWo cells** Takako Sadakane, Iemasa Koh, Yoshiki Kudo *Hiroshima University*

**Objective** Maternal nicotine exposure via smoking has been associated with birth complications, such as spontaneous abortion and fetal growth restriction. To understand the adverse effects of maternal smoking during pregnancy, it may be important to clarify the mechanism underlying the transplacental transfer of nicotine. In this study, we investigated the mechanism of nicotine uptake using BeWo cells as a model of the human placental trophoblast. **Methods** BeWo cells were cultured for 4 days and were used for the uptake study. BeWo cells were incubated

with [ $^3\text{H}$ ] nicotine, and the amounts taken up by the cells were measured by liquid scintillation counting. **Results** [ $^3\text{H}$ ] Nicotine uptake was time- and temperature-dependent and showed saturation kinetics with a Michaelis constant  $K_m$  of 300.6  $\mu\text{M}$  in the BeWo cells. In addition, the Eadie-Hofstee plots were linear, suggesting that a single transport system was involved in nicotine uptake in BeWo cells. [ $^3\text{H}$ ] Nicotine uptake in the BeWo cells showed clear pH dependence and was high at high pH. The uptake of [ $^3\text{H}$ ] nicotine was potently inhibited by organic cations such as clonidine, diphenhydramine, and pyrilamine, but was not affected by substrates and/or inhibitors of known organic cation transporters, such as carnitine, 1-methyl-4-phenylpyridinium, or tetraethylammonium. **Conclusion** These results suggest that a specific transport system is involved in the uptake of nicotine in BeWo cells.

#### ISP-54-4

**Accumulation of prostaglandin  $E_2$  in amniotic fluid and expression of PGE synthases and transporters during human labor** Nanase Takahashi, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Juntendo University Hospital*

**Objective** Metabolites of arachidonic acid (AA), especially prostaglandin  $E_2$  ( $\text{PGE}_2$ ), are known to induce labor.  $\text{PGE}_2$  production from AA is catalyzed by cyclooxygenases (COX)-1, 2, and PGE synthases (cPGES and mPGES-1, 2).  $\text{PGE}_2$  is transported to the extracellular space by the transporters such as SLCO2A1. However, the detailed mechanism of  $\text{PGE}_2$  production and transportation during human labor is largely unknown. **Methods** This study includes pregnant women at term who were classified into the following groups: women who delivered at term in labor (TLB) and at term not in labor (TNL). All patients provided written, informed consent before the collection of subjects, which were approved by the Ethics Committee. **Results** We revealed that the concentrations of  $\text{PGE}_2$  in amniotic fluid of subjects at TLB are much higher than those of TNL by LC-MS. By RT-qPCR, we found significantly higher expressions of cPGES both in TLB villus tissue and fetal membrane than TNL. The same results were also shown by western blotting analysis. Immunohistochemistry revealed that expressions of COX-2, cPGES, and SLCO2A1 were observed in syncytiotrophoblast, chorion trophoblast, and amnion epithelium. Finally, we performed human membrane transwell model analysis which showed significantly higher  $\text{PGE}_2$  production in TLB membranes both in fetal and maternal sides than those of TNL. **Conclusion** In summary, we showed that  $\text{PGE}_2$  in amniotic fluid is possibly produced mainly by COX-2 and cPGES in syncytiotrophoblast, chorion trophoblast, and amnion epithelium during labor and may induce uterine contraction directly or indirectly. Our studies are the first to reveal the unknown function of cPGES in labor.

#### ISP-54-5

**Expression of TrkB isoforms in FGR and non-FGR** Akane Kondo<sup>1</sup>, Daichi Nakaoku<sup>1</sup>, Mikio Yamasaki<sup>1</sup>, Yumiko Goto<sup>2</sup>, Kazumi Takahashi<sup>2</sup>, Mikio Morine<sup>1</sup>, Kenji Hinokio<sup>1</sup>, Kazuhisa Maeda<sup>1</sup> *Shikoku Medical Center for Children and Adults<sup>1</sup>, Tokai University<sup>2</sup>*

**Objective** Brain-derived neurotrophic factor (BDNF) and its receptor Tropomyosin related kinase B (TrkB) are expressed in placenta. TrkB has a basic function of inducing invasion and cell survival. However, their function in the placenta is not clear yet. Trophoblasts remodel blood vessels by replacing the vascular endothelium infiltrating the decidua after the epithelial-mesenchymal transition (EMT). Cytotrophoblast (CT) becomes Extravillous Cytotrophoblast (EVT) and Syncytiotrophoblast (STB). TrkB is expressed on these cells and may involve the re-

modeling of the vessels by EMT, which is essential for fetal growth. **Methods** We analysed expression of TrkB and BDNF, a ligand of TrkB in the group of 27 cases of FGR and 31 normal pregnancy. Since there is a possibility of the defect of TrkB isoforms in FGR samples of human, we analyzed all isoforms in FGR to reveal the correlation between BDNF signal deficient isoforms and FGR. The expression of isoforms were confirmed by using RT-PCR with primers of corresponding TrkB exons. **Results** 12 out of 14 FGR placenta showed multiple defect of exons. Within FGR group, 35-41w groups showed more defects than earlier gestation, 28-34w. This was similar tendency compared to non-FGR Groups. Compared to FGR and non-FGR, more sample showed expression of less lesion within non-FGR Group. **Conclusion** Expression of binding site of BDNF and intracellular domains were lower in FGR-35-41w Group. This alteration was shown in all gestation non-FGR group. From this result, placental TrkB showed insufficient downstream signaling in late gestational period.

#### ISP-54-6

**Effects of TNF- $\alpha$  and IGF-I on proliferation and angiogenesis of BeWo cells** Kei Tanaka, Miho Matsushima, Tomoko Izawa, Shinji Tanigaki, Seishi Furukawa, Yoichi Kobayashi, Mitsutoshi Iwashita *Kyorin University*

**Objective** Circulating levels of TNF- $\alpha$  and IGF-I are elevated in obesity and obesity is considered as chronic inflammation. Placental hypertrophy and macrosomia are often observed in pregnancy with obesity. However, it is not elucidated yet whether TNF- $\alpha$  and IGF-I are involved in pathogenesis of placental hypertrophy. We investigated the effects of TNF- $\alpha$  and IGF-I on proliferation and angiogenesis of trophoblast cells by using BeWo cells. **Methods** After incubating BeWo under the presence of TNF- $\alpha$  ( $10 \times 10^2$  pg/ml) and IGF-I ( $10^2$  ng/mL), we assessed cell number and proliferation by WST-1 assay and BrdU uptake assay, respectively. Apoptosis was evaluated by TUNEL assay and caspase-3, 8 activity assay. We also measured the concentrations of VEGF, PIGF, and FGF in the conditioned media by ELISA. **Results** Under the presence of IGF-I ( $10^2$  ng/mL), cell number and BrdU uptake of BeWo was dose-dependently enhanced by TNF- $\alpha$  ( $10 \times 10^2$  pg/ml), while no such effects were detected without IGF-I. The number of TUNEL positive cells were decreased and caspase activities were suppressed by  $10^2$  pg/ml of TNF- $\alpha$ . IGF-I ( $10^2$  ng/mL) also decreased the number of TUNEL positive cells and suppressed caspase activities. The concentrations of PIGF and VEGF were significantly higher in the presence of  $10 \times 10^2$  pg/ml of TNF- $\alpha$ , while TNF- $\alpha$  showed no significant effects on FGF. Addition of IGF-I ( $10 \times 10^2$  ng/mL) dose-dependently suppressed PIGF secretion and enhanced VEGF secretion. **Conclusion** TNF- $\alpha$  and IGF-I stimulate proliferation synergistically and regulate apoptosis and angiogenesis by independent mechanisms, which suggests that TNF- $\alpha$  and IGF-I are responsible for placental hypertrophy in pregnancy with obesity.

#### ISP-54-7

**The study for the effect of different diameter in bilateral umbilical arteries on the formation of umbilical twist** Masamitsu Nakamura, Tomohiro Oba, Tatsuya Arakaki, Mayumi Tokunaka, Minako Goto, Ryu Matsuoka, Akihiko Sekizawa *Showa University*

**Objective** To clarify the effect of the difference of diameters in bilateral umbilical arteries on formation mechanism of umbilical twist. **Methods** Cross-sectional cohort study was performed. The subjects measured the umbilical arteries diameter from 19 to 22 weeks after determining gestational age at 9-10 weeks were enrolled between January and December in 2016. The di-

rection of umbilical twist was diagnosed by ultrasound, and the degree of umbilical twist was assessed using antenatal coiling index (ACI) at free loop of the umbilical cord. The cases with fetal anomaly and single umbilical artery were excluded in this study. **Results** One-hundred nine cases were included in the present study. The median (range) gestational age measured diameter of umbilical vessels was 20 (19–22) weeks. The frequencies of cases with left umbilical twist were significantly higher than those of right twist [left 81.7% (89 cases) vs 18.3% (20)]. The diameters of left and right umbilical arteries (mean  $\pm$  SD) were  $1.7 \pm 0.4$  and  $1.9 \pm 0.4$  ( $p=0.024$ ). Cases with right umbilical artery thicker than left were 63.3% (69), with right umbilical artery thinner than left were 24.8% (27), and with right equaled left were 11.3% (13). The frequency of cases with left twisted umbilical cord which had right umbilical artery thicker than left were 92.8% (64/89) significantly more than 48.1% (13/27) with right artery thinner than left ( $p<0.01$ ). **Conclusion** It is revealed that the frequency of left umbilical twist was more than 70%. The difference of diameter in right and left umbilical artery might be related to the direction of umbilical twist.

### ISP-55-1

**Soluble endoglin-inhibited autophagy enhances LPS-inducing inflammasome production in peripheral blood of pregnant women** Akitoshi Nakashima, Tae Kusabiraki, Aiko Aoki, Azusa Sameshima, Tomoko Shima, Osamu Yoshino, Shigeru Saito *University of Toyama*

**Objective** Autophagy plays an important role for inflammasome removal, resulting in control of inflammation. We have reported that soluble endoglin (sENG), mRNA of which are elevated in early onset of PE, inhibited autophagy in trophoblasts. It is, meanwhile, still unknown the mechanism how systemic inflammation could be induced in preeclampsia. This study examined whether sENG enhanced inflammasome derived IL-1 $\beta$  by LPS in peripheral blood mononuclear cells (PBMCs) of pregnant cases. **Methods** Informed consent was obtained from all participants ( $n=23$ ). The secreted IL-1 $\beta$  levels were measured in PBMCs in the presence of sENG with LPS by ELISA. **Results** The concentration of IL-1 $\beta$  was significantly higher in PBMCs with LPS than that without LPS ( $180 \pm 168$ ,  $1.3 \pm 0.9$  pg/ml). The IL-1 $\beta$  levels were no difference in PBMCs between pregnant and non-pregnant women, or between under normoxic and hypoxic conditions. To firstly investigate the effect for IL-1 $\beta$  production by autophagy inhibition, 3MA, a PI3K inhibitor, was treated in PBMCs with LPS. The IL-1 $\beta$  levels were increased 5.7-fold in the presence of 3MA ( $p=0.002$ ). In addition, the LPS-mediated IL-1 $\beta$  expression levels were also significantly higher in PBMCs with 100, 500, or 1,000 ng/ml sENG, compared with that with LPS alone ( $p=0.008$ ,  $0.0002$  or  $<0.0001$ ). **Conclusion** We firstly showed that autophagy inhibition by 3-MA or sENG enhanced IL-1 $\beta$  production by LPS in PBMCs. Soluble endoglin-mediated autophagy inhibition might be involved in not only anti-angiogenesis, but also dysregulation of inflammasome, resulting in onset of preeclampsia.

### ISP-55-2

**Association between birth weight and subsequent risk for hypertensive disorders of pregnancy** Maiko Wagata<sup>1</sup>, Yasuhiro Kurosawa<sup>2</sup>, Hirotaka Hamada<sup>2</sup>, Michiyo Kurakata<sup>2</sup>, Tetsuro Hoshiai<sup>2</sup>, Hidekazu Nishigori<sup>2</sup>, Masatoshi Saito<sup>2</sup>, Hirohito Metoki<sup>3</sup>, Nobuo Yaegashi<sup>2</sup>, Junichi Sugawara<sup>2</sup> *Tohoku University Tohoku Medical Megabank Organization<sup>1</sup>, Tohoku University<sup>2</sup>, Tohoku Medical and Pharmaceutical University<sup>3</sup>*

**Objective** To clarify the association between woman's own birth weight and her subsequent risk for hypertensive disorders of pregnancy (HDP) in each subtype and assess the risk for HDP

among women born small and overweight in adulthood. **Methods** In this study, 4,770 singleton pregnant women were included. We analyzed the association between women's birth weight and HDP by multivariate logistic regression analysis adjusting for age, pre-pregnancy body mass index (BMI) and family history of hypertension in each subtype. We also constructed a composite variable that combined birth weight ( $<2,500$ ,  $2,500-3,500$ ,  $>3,500$ g) and pre-pregnancy BMI ( $<18.5$ ,  $18.5-22$ ,  $22-25$ ,  $>25$ kg/m<sup>2</sup>), providing 12 categories and performed multivariate logistic regression analysis. **Results** In total, 497 women were affected by HDP (10.4%). The prevalence of HDP was 17.65%, 14.41%, 10.41%, 9.95%, 11.11%, and 4.88% in birth weight  $<2,000$ g,  $2,000-2,500$ g,  $2,500-3,000$ g,  $3,000-3,500$ g,  $3,500-4,000$ g, and  $>4,000$ g group, respectively ( $p$  for trend=0.07). In birth weight  $<2,500$ g group, the adjusted odds ratio (OR) for HDP was 1.73 (95% confidence interval : 1.16–2.57) in whole HDP, 1.75 (0.96–3.17) for gestational hypertension, 3.42 (1.76–6.65) for preeclampsia, compared with  $2,500-3,500$ g group. In the combination of birth weight and pre-pregnancy BMI, birth weight  $<2,500$ g and pre-pregnancy BMI  $>25$ kg/m<sup>2</sup> group had the highest adjusted OR : 6.60 (1.84–23.60) for gestational hypertension, and 21.18 (7.19–62.41) for preeclampsia. **Conclusion** A significant association exists between birth weight and subsequent HDP, whereas this association differs by HDP subtypes. Women born small and overweight in adulthood have particularly high risk for HDP and weight control is important.

### ISP-55-3

**A role of Sonic hedgehog pathway in preeclamptic placenta** Hiroshi Takai, Eiji Kondoh, Haruta Mogami, Yosuke Kawamura, Shingo Io, Mai Sato, Yoshitsugu Chigusa, Masaki Mandai *Kyoto University*

**Objective** We previously reported that Sonic hedgehog (Shh) pathway was involved in preeclamptic placentas. Insulin like growth factor 1 receptor (IGF1R) is known to be a key role in fetal growth and placental function. The aim of this study is to elucidate the association between Shh pathway and IGF1R in placenta. **Methods** The study protocol was approved by the Ethics Committee. Twenty placental samples were collected from normal and preeclamptic singleton pregnancies ( $n=10$ , respectively). The expressions of Patched homolog 1 (PTCH1), a Shh receptor, and IGF1R were examined by qPCR. Clinical data including placental weight and fetal birth weight were collected from medical records to investigate their association with PTCH1 or IGF1R expression. Primary cytotrophoblasts (CTBs) were treated with or without cyclopamine, a Shh pathway inhibitor or si-Gli2, one of the transcriptional factors in Shh pathway. CTBs were treated with or without recombinant Shh (rShh). **Results** PTCH1 and IGF1R expressions were significantly down-regulated in preeclamptic placentas (both  $P<0.001$ ). PTCH1 expressions were correlated with IGF1R expressions ( $R=0.4821$ ,  $P=0.0313$ ). PTCH1 expressions were highly correlated with fetal birth weight ( $R=0.7807$ ,  $P<0.001$ ) and placental weight ( $R=0.5839$ ,  $P=0.0069$ ). PTCH1 and IGF1R expressions in CTBs were significantly down-regulated by cyclopamine ( $n=6$ ,  $P=0.010$ ,  $P=0.032$ ) and si-Gli2 ( $n=6$ ,  $P=0.001$ ,  $P=0.017$ ). The protein expressions of IGF1R in CTBs treated with rShh was increased and not increased treated with rShh and Cyclopamine compared with control. **Conclusion** Shh pathway may contribute to the regulation of IGF1R expression in the placenta.

### ISP-55-4

**Correlation between intracranial imaging by MRI and development at age of 3 in the children born from mothers with hypertensive disorders of pregnancy or spontaneous preterm birth** Tae Kusabiraki, Noriko Yoneda, Satoshi Yoneda, Mutsumi



Kobayashi, Kaori Fukuta, Arihiro Shiozaki, Shigeru Saito *University of Toyama*

**Objective** We evaluated the correlation between intracranial imaging by MRI (Kidokoro score : KS) and development at age of 3 in the children born from mothers with hypertensive disorders of pregnancy (Child-HDP) or spontaneous preterm birth (Child-PTB). **Methods** Eighteen cases of Child-HDP and 41 cases of Child-PTB managed in our hospital from 2006 to 2015 were selected. They were all evaluated intracranial abnormality by MRI before discharge from NICU and development at age 3 by Bayley-III. Poor development was defined as cerebral palsy, mental retardation, and low score of Bayley-III. KS which can accurately evaluate intracranial lesions was used in this study. **Results** 1) The rate of KS was 12.2% (Normal), 41.5% (Mild), 31.7% (Moderate) and 14.6% (Severe) in Child-PTB, while that was 50.0%, 14.6%, 11.1% and 0% in Child-HDP. 2) In Child-PTB, delivery weeks of gestation tended to correlate according to severity of KS (28.9 of Normal, 28.2 of Mild, 27.3 of Moderate and 25.9 of Severe,  $p=0.082$ ), and the frequency (%) of poor development also tended to correlate (0, 11.8, 7.7 and 50.0,  $p=0.058$ ), but not in Child-HDP. 3) There was a significant difference between development and KS in Child-PTB ( $7.0 \pm 0.8$  of good development vs  $13.7 \pm 1.8$  of poor,  $p<0.01$ ), but not in Child-HDP. **Conclusion** The interesting relationship was observed between intracranial imaging by MRI and long-term prognosis at age of 3 in children born from PTB mothers, while there was no correlation in HDP cases. In HDP cases, neurodevelopment might be recognized as functional damage rather than organic damage.

#### ISP-55-5

**A novel of biomarker profiles in experimental aged maternal mouse with hypertensive disorders of pregnancy** Kiichiro Furuya, Keiichi Kumasawa, Hitomi Nakamura, Tadashi Kimura *Osaka University*

**Objective** Advanced maternal age (AMA) has increased and related to fetomaternal mortality and morbidity. One major complication of AMA is hypertensive disorders of pregnancy (HDP). We established a mouse model that mimics the phenotypes of human AMA. **Methods** Aged pregnant Jcl : ICR mice were used as AMA model mice and analyzed their phenotypes. We also examined their blood pressure and some biomarkers that are associated with the pathogenesis of HDP : soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), the key factors of HDP. **Results** The significant findings of our investigation are : 1) The AMA model mice manifested the same phenotypes of human AMA including maternal obesity, declining fertility, small gestational age (SGA), and higher percentage of intrauterine fetal death (IUFD), 2) The AMA mouse model represented increasing blood pressure at late gestation ( $108.2 \pm 7.7$  vs  $92.7 \pm 5.7$  mmHg,  $P<0.01$ ) and normalization of it after delivery similar to human HDP patients, and 3) While HDP and placental dysfunction are complicated, AMA mice and human HDP AMA patients manifested a low serum level of sFlt-1 in late gestational period (mice ;  $16,800.0 \pm 10,709.5$  vs  $26,611.9 \pm 8,702.0$  pg/mL,  $P<0.01$ , human ;  $8,507.6 \pm 3,298.7$  vs  $14,816.9 \pm 5,413.5$  pg/mL,  $P<0.05$ ). **Conclusion** AMA model mice resembled human AMA. AMA model mice was complicated with HDP : however, the serum sFlt-1 level displayed a low level in late gestational period. Our findings provide the evidence that the serum sFlt-1 level does not necessarily reflect the conventional pathogenesis of HDP in aged human and murine pregnancies, and may contribute to the future management of HDP in AMA.

#### ISP-55-6

**Risk Factors for Bleeding Complications after Cesarean Sec-**

**tion among Preeclampsia Cases Followed by Postoperative Prophylactic Anticoagulation** Naoya Tsujimoto, Hironobu Hyodo, Satoshi Nitta, Saho Fujino, Miho Saito, Norihiko Nakazato, Etsuko Saito, Midori Funakura, Sorahiro Sunagawa, Koji Kugu *Tokyo Metropolitan Bokutoh Hospital*

**Objective** Preeclampsia is reported to increase bleeding complications with prophylactic anticoagulation. The objective of this study was to identify risk factors for bleeding complications among cases of preeclampsia with prophylactic anticoagulants after cesarean section. **Methods** Sixty-eight cesarean cases of preeclampsia (including superimposed preeclampsia) with postoperative prophylactic anticoagulation were reviewed retrospectively at a tertiary perinatal center between 2012 and 2017. Bleeding complications were defined as subcutaneous hematoma, subfascial hematoma, and intraperitoneal hematoma detected by ultrasonography or computed tomography. Age, body mass index, preoperative 24-hour urine protein, 24-hour urine volume, and other clinical and laboratory data were studied about the association with bleeding complications by univariate and multivariate analysis. **Results** Among a total of sixty-eight cases, bleeding complications were recorded in nine cases : subcutaneous hematoma in four, subfascial hematoma in four, and intraperitoneal hematoma in one. Univariate analysis showed that preoperative platelet count and preoperative 24-hour urine protein were associated with bleeding complications. Multivariate logistic regression analysis revealed that a preoperative decreased platelet count was an independent risk factor for bleeding complications (OR, 0.852 ; 95% CI, 0.73-0.99 ;  $P=0.04$ ). **Conclusion** A preoperative platelet count was significantly related to bleeding complications in cases of preeclampsia after cesarean section followed by postoperative prophylactic anticoagulation even the count was not abnormally low.

#### ISP-56-1

**Examination of the influence of infectious stress in postnatal period on sexual behavior of male rats in adulthood** Mayila Yiliyasi, Toshiya Matsuzaki, Rie Yanagihara, Kiyohito Yano, Takeshi Iwasa, Minoru Irahara *Tokushima University*

**Objective** We examined the influence of infectious stress exposure in early postnatal period on sexual behavior of male rats. **Methods** SD male rats were divided into 3 groups : control group ( $n=17$ ), PND10LPS group ( $n=31$ ) and PND25LPS group ( $n=16$ ). Lipopolysaccharide (LPS) ( $100 \mu\text{g}/\text{kg}$ ) was injected to PND10LPS and PND25LPS groups on the 10th and 25th days of age, respectively. Sexual behavior was observed for 30 minutes in 10 to 12 weeks. We checked hypothalamic mRNA expression levels of sexual behavior related factors and serum testosterone (T) concentration. Thereafter, the testes were removed at 14 weeks, and a silicone tube containing T was placed in the back of the neck and sexual behavior was observed. **Results** The sexual behavior of the PND10LPS group was significantly less than the control group. PND10LPS and PND25LPS groups showed significant lower serum T and mRNA expression of progesterone receptor B (PRB) and GnRH than in control group. After supplementation of T, sexual behavior of the PND10LPS and PND25LPS groups still was significantly less than that of the control group. **Conclusion** That attenuation of sexual behavior in adult male rats which were exposed to infectious stress in neonatal period could not be recovered by testosterone supplementation and might be brought by lower expression of PRB in hypothalamus.

#### ISP-56-2

**The influence of early life psychological stress on sexual maturation and on sexual activity in female rats** Kiyohito Yano, Toshiya Matsuzaki, Rie Yanagihara, Mayila Yiliyasi,



Takeshi Iwasa, Minoru Irahara *Tokushima University*

**Objective** The influence of early-life psychological stress induced by maternal separation (MS) on the sexual maturation and the sexual activity was examined in female rats. **Methods** Female rats were divided into control (C) and maternal separation (MS) groups, respectively (n=24 per group). Pups in MS groups were placed in isolated cages during 240min/day from postnatal day (PND) 2 to PND11. Onset of vaginal opening (VO) in rats were monitored from PND29 to PND40. Thereafter, estrous cycle were monitored from PND62 to PND72. We collected the ovaries at 11-week age and observed sexual behaviors at 12- and 14-week ages. We injected progesterone (1mg) in the rat's back at 48 and 24 hours before the sexual behavior test, and estradiol (10 $\mu$ g) 4 hours before the test. Female rats were put in a cage with male rats and monitored for 30 minutes. **Results** Body weight at PND 14 was significantly lower in MS group than in C group, respectively ( $p < 0.05$ ). VO and number of estrous did not differ between the groups. Parameters of sexual behavior at 12-week did not differ between C group and MS group; Number of darts (C:  $41.3 \pm 12.2$ times, MS:  $36.5 \pm 10.1$ ), Number of ear wiggles (C:  $20.2 \pm 6.0$ , MS:  $23.3 \pm 8.2$ ), Lordosis quotient (LQ) (C:  $56.8 \pm 10.2\%$ , MS:  $52.4 \pm 10.6$ ), Lordosis rating (LR) (C:  $0.86 \pm 0.21$ , MS:  $0.77 \pm 0.18$ ). The sexual behavior at 14-week also did not differ between the groups. **Conclusion** Psychological stress in early life did not influence on sexual maturation and sexual activity in female rats.

### ISP-56-3

**Nine cases of Turner syndrome with differences in menstrual abnormality and physical findings** Makiho Ishibashi<sup>1</sup>, Takafumi Watanabe<sup>1</sup>, Miki Ohara<sup>1</sup>, Toshifumi Takahashi<sup>2</sup>, Hiromi Komiya<sup>1</sup>, Hideki Mizunuma<sup>2</sup>, Keiya Fujimori<sup>1</sup> *Fukushima Medical University<sup>1</sup>, Fukushima Medical Center of Children and Women<sup>2</sup>*

The structural abnormality of the X chromosome is characterized by phenotypes such as short stature and amenorrhea, depending on the site of the abnormalities. We here report the diagnostic indications and phenotypes of nine cases of Turner syndrome observed in our department. Regarding the diagnostic indications, two patients were diagnosed at school age due to short stature. One patient was diagnosed in her late teens due to lack of secondary sex characteristics. Six patients were over the age of 20 years at the time of their respective diagnoses, which were made because of infertility and primary amenorrhea. In patients with short stature and external malformations such as underdevelopment of the external genitalia, and in case of infertility and no response to ovulation induction, the period until the execution of until chromosome analysis was short. On the other hand, the period until diagnosis tended to be longer in the six patients, who did not have desire of pregnancy, and were treated for secondary amenorrhea. Regarding menstruation abnormality and karyotype, primary amenorrhea was found in five cases, and their karyotype were monosomy, disomy and ring chromosome (with mosaicism), or the breakpoint of X-autosomal chromosome was Xq21.1. Secondary amenorrhea was observed in three cases, and the breakpoint of the X-autosomal chromosome and deletion were regions of Xq22-qter. One patient with first-degree secondary amenorrhea had unbalanced X-autosomal translocation, and her phenotype and menstrual disorder were mild because of the inactivation of the derivative X chromosome and the small deletion such as Xq28-qter.

### ISP-56-4

**Five patients with vaginal agenesis treated using non surgical vaginoplasty using uterine cervical dilators** Akiko Kawasaki<sup>1</sup>, Hiroko Jjiri<sup>1</sup>, Hiroyuki Yoshikawa<sup>2</sup>, Iku Gamada<sup>1</sup>, Yoko

Tsukuda<sup>1</sup>, Yuki Mori<sup>1</sup>, Toyomi Satoh<sup>1</sup> *University of Tsukuba<sup>1</sup>, Ibaraki Prefectural Central Hospital<sup>2</sup>*

For the patients with vaginal agenesis, vaginoplasty is an essential treatment. Vaginoplasty includes both nonsurgical and surgical treatments. The nonsurgical method is safe and easy to perform; therefore it is considered as a firstline treatment. In our hospital, vaginal dilation using uterine cervical dilators named Hegar dilators is performed on patients with Mayer-Rokitansky Kuster Hauser syndrome, and on patients undergoing vaginoplasty to prevent vaginal stenosis after the procedure. This study reports five patients successfully treated with this method. Out of four patients with MRKH syndrome, two lacked a vagina completely, and two had a shallow vagina. Gynecologists initiated dilation with an adequately sized cervical dilator, which made a 3 cm deep cavity in the external genital area. After the examination, they instructed patients on how to use the dilator, and patients continued self dilation daily at home. Patients visited the hospital every month for further instructions. The size of the dilator was gradually increased, until the vaginal cavity extended to 6 cm in depth with a No.30 dilator. The duration needed to achieve the end point was between 5 and 20 months. One patient had a congenital vaginal aplasia with a normal uterus. Following surgical vaginoplasty, she underwent a vaginal dilation to prevent vaginal stenosis. After other types of vaginal dilators failed at vaginal dilation, Hegar dilator proved effective. All patients were successfully treated without complications. However, a large scale study is required to confirm the efficacy of this method.

### ISP-56-5

**The retrospective analysis of 53 patients of primary amenorrhea** Yuri Miyahara<sup>1</sup>, Yasuhiko Kamada<sup>1</sup>, Hirofumi Matsuoka<sup>1</sup>, Shiho Fujita<sup>1</sup>, Kotaro Kubo<sup>1</sup>, Ai Sakamoto<sup>1</sup>, Sayoko Kotani<sup>1</sup>, Hisashi Masuyama<sup>1</sup>, Mikiya Nakatsuka<sup>2</sup> *Okayama University<sup>1</sup>, Faculty of Health Sciences, Okayama University<sup>2</sup>*

**Objective** Primary amenorrhea is defined as the absence of menstruation at the age of 18 years. It may be caused due to various conditions. This study aimed to identify those conditions and assess their diagnosis and management. **Methods** A retrospective study was conducted between January 2004 to July 2017, during which 53 cases were analyzed. In this analysis, we also included patients with delayed menarche. **Results** The median age of patients at their first visit was 19 years [15-35 (median, range)], which is greater than that in the existing reports. The chief complaint of 48 patients was amenorrhea. Out of the 53 cases, 27 had uterine amenorrhea (Mayer-Rokitansky-Kuster-Hauser syndrome), 13 had hypothalamic and pituitary disease, 6 had ovary-related amenorrhea, 4 had outflow tract disorders, 2 had polycystic ovarian disease, 2 had symptomatic amenorrhea, and 1 had gonadal dysgenesis. There is some overlapping. 24 patients were analyzed based on chromosomal tests, and 3 abnormalities were detected. 19 patients received hormone replacement therapy, and 21 patients underwent surgical and nonsurgical techniques for vaginal reconstruction. **Conclusion** Some patients with primary amenorrhea, depending on their disorders, face difficulty in conception. Sometimes, their sex differs from their perceived gender. Therefore, careful physical examination and systematic evaluation are imperative for a proper diagnosis. Additionally, we should pay proper attention to the provision of physical and/or mental support to such patients.

### ISP-57-1

**The role of endometrial and uterine vascular status measurement in predicting pregnancy outcome in frozen thawed embryo transfer cycles** Byung Kyoo Park, Moo Sung Jo, Jong-Kil

Joo, Kyu Sup Lee, Byung Su Kwon, Yoon Hwa Kim, Sul Lee, Ka Yeong Yun, Dong Soo Suh, Ki Hyung Kim, Hyun Joo Lee, Sieun Han *Pusan National University Hospital, Korea*

**Objective** An appropriate endometrial condition and vascular supply are usually known as essential for implantation of embryo. This study was performed to assess the role of endometrial and uterine vascularity status measurement in predicting pregnancy outcome during frozen-thawed embryo transfer (FET) cycles. **Methods** After endometrial preparation, vitrified blastocysts were thawed and assisted hatching by zona dissection was performed. On the day of embryo transfer (ET), endometrial thickness (EMT), resistance index (RI) and pulsatility index (PI) of sub-endometrial artery (SEA) and uterine artery (UA) were obtained by transvaginal sonography (TVS). All women were divided into pregnant or not groups, and these variables were compared between 2 groups. **Results** Patients' general demographic characteristics weren't different statistically between pregnant and nonpregnant groups. The overall implantation rate, clinical pregnancy rate, and ongoing pregnancy rate were 31.1%, 41.4% and 28.6%, respectively. 29 Patients who conceived had average EMT, RI of SEA, PI of SEA, RI of UA, and PI of UA values of 9.15mm, 0.91, 2.42, 0.95, and 3.37, respectively. 41 Patients who didn't conceive had average EMT, RI of SEA, PI of SEA, RI of UA, and PI of UA values of 9.31mm, 1.01, 2.56, 0.94, and 3.00, respectively. In two groups, all variables were not statistically different ( $p > 0.05$ ). **Conclusion** Measurement of endometrial thickness and blood flow index of uterus and endometrium by transvaginal sonography during frozen-thawed embryo transfer (FET) cycles can't seem to predict the pregnancy outcome. But endometrial receptivity is thought to be still important factor in successful implantation of FET cycle and many studies agree that high degrees of endometrial perfusion shown by Doppler sonogram suggests more receptive endometrium.

### ISP-57-2

**Endometrial Receptivity Array : Retrospective Review of Reproductive Outcomes Among Patients with Personalized Embryo Transfer (pET)** Justin Tan<sup>1</sup>, Arohummam Kan<sup>1</sup>, Samer Tannus<sup>3</sup>, Gary Nakhuda<sup>1,2</sup> *University of British Columbia, Canada<sup>1</sup>, Olive Fertility Centre, Canada<sup>2</sup>, McGill University Health Care Centre, Canada<sup>3</sup>*

Human implantation is an intricate process that requires synchronous dialogue between a healthy embryo and a receptive endometrium. In the context of in vitro fertilization (IVF), aneuploid embryos which lack developmental competence likely account for the most common cause of implantation failure : however, even euploid, morphologically normal blastocysts fail to implant in about 1/3 of transfers. Endometrial receptivity represents another potential cause of implantation failure and through advances in proteomic analysis, an endometrial receptivity array (ERA) has been developed to accurately and reproducibly identify endometrial receptivity status. The clinical benefit of such an assay, however, is still undergoing further investigation. In this retrospective review, we investigated whether the contribution of the endometrial factor could be identified with the ERA test, particularly in patients with a history of euploid blastocyst implantation failure. Among 88 patients who underwent ERA testing at a private clinic in Vancouver, Canada, between October 2014-January 2017, 81 (92.1%) had a history of implantation failure, 48 underwent euploid embryo transfer with CCS, and 19 (40%) were determined to have an unreceptive endometrium on initial ERA biopsy. After personalized embryo transfer (pET), we found that implantation and ongoing pregnancy rates were improved (73.7% vs. 54.2% and 63.2% vs. 41.7%, respectively) compared to patients without pET, although differences were not statistically significant owing

to small sample size. Hence, larger prospective studies are required to validate our findings. Nevertheless, our experience demonstrates that pET among patients with a non-receptive endometrium yields improved reproductive outcomes. Hence, there is likely clinical benefit to identifying the personal window of implantation (WOI) with ERA.

### ISP-57-3

**Retrospective study on the clinical efficacy of single embryo transfer (SET) for IVF-adverse cases ; a single IVF center** Kaori Shinya, Chuyu Hayashi, Erina Kato, Remi Hasegawa, Yuki Okuma, Erina Hashimoto, Akiko Kasuga, Atsushi Komatsu, Yasuji Miyagawa, Shinichi Takada, Fumihisa Chishima, Kei Kawana *Nihon University*

**Objective** Single embryo transfer (SET) is recommended to avoid multiple pregnancy following IVF-ET. Double embryo transfer (DET) has been also acceptable only for repeated IVF failures or elder cases. Indication of SET could extend to such adverse cases because of recent technical innovation. We here examined whether SET including frozen embryo transfer is effective for the cases. **Methods** Under the informed consents, 212 cycles of SET during 2013-2017 in our hospital were investigated. Clinical pregnancy and live birth rates were compared with the nationwide IVF-ET data (2014) reported by JSOG using Fisher's exact test. Cumulative pregnancy rates after SET were also investigated focusing on over 40 years-old cases. **Results** Clinical pregnancy rates following SET were 20.2%, 22.4% and 10.2% for all, 35-39, and 40-45 years-old cases, respectively, which were worse than JSOG data. In turn, live birth rates following SET were 16%, 15.8% and 7.1% for all, 35-39, and 40-45 years-old cases, respectively, which were equivalent to JSOG data. The cumulative pregnancy rates at third and fifth SET were 51% and 79%, respectively. As for over 40 years-old cases, the rates at third and fifth SET were 35% and 74%, respectively. There was no difference in the rate at fifth SET between all and over 40 years-old cases. **Conclusion** Live birth rate following SET was equivalent to that of JSOG data regardless of age. The cumulative pregnancy rates caught up at fifth IVF even though over 40 years-old cases. These data suggested that SET might be effective for IVF-adverse cases.

### ISP-57-4

**Cases that needed GnRH agonist in artificial FET cycle** Yuri Yamamoto<sup>1</sup>, Akira Kuwahara<sup>1</sup>, Ayaka Tachibana<sup>1</sup>, Kenji Hinokio<sup>2</sup>, Minoru Irahara<sup>1</sup> *Tokushima University<sup>1</sup>, Shikoku Medical Center for Children and Adults<sup>2</sup>*

**Objective** Recently, it has reported that GnRH agonist does not influence clinical pregnancy rate, but there were sometimes cancellation cycles due to premature ovulation. Therefore we extracted the cases which had spontaneous ovulation during HRT-FET cycle and examine the case considered that addition of GnRH agonist was appropriate. **Methods** Between January 2016 and December 2016, data from HRT-FET cycles involving 164 cycles, 115 cases were analyzed. Estradiol patch gradually was increased and on day 14, endometrial thickness was measured. After that, Chlormadinone Acetate was started, and FET was performed 6 days after progestin initiation. If follicle growth or premature ovulation were detected by ultrasound scan, serum hormone levels were analyzed. Serum P level over 1.5ng/ml, the cycle were cancelled. We compared follicle growth group (group A, n=5) and ovulation group (group B, n=4) and non-follicle group (group C, n=106) about age, basic FSH level, the oocyte collection number. **Results** Mean age and basal FSH level were significantly higher in group A ( $41.4 \pm 2.1$  years,  $14.7 \pm 12.4$  IU/ml) and group B ( $40.5 \pm 2.6$  years,  $17.9 \pm 6.0$  IU/ml) than group C ( $36.5 \pm 4.3$  years,  $6.3 \pm 2.5$  IU/ml). Oocyte col-

lection number were  $10.2 \pm 5.1$  in group A,  $7.5 \pm 7.1$  in group B,  $13.3 \pm 7.8$  in group C.  $\text{FSH} > 15 \text{ IU/ml}$  was only two cases in group C. **Conclusion** It was revealed that premature ovulation tended to be easy to happen during HRT-FET without GnRH agonist in advanced age, the ovarian failure such as  $\text{FSH} > 15 \text{ IU/ml}$  and desirable for use GnRH agonist.

### ISP-57-5

**Impact of ovarian stimulation protocols on perinatal outcomes in fresh single-embryo transfers : Analysis of 36,469 singleton deliveries in Japanese Assisted Reproductive Technology Registry between 2007 and 2013** Seungchik Jwa<sup>1</sup>, Akira Nakashima<sup>2</sup>, Akira Kuwahara<sup>2</sup>, Kazuki Saito<sup>3</sup>, Minoru Irahara<sup>2</sup>, Osamu Ishihara<sup>1</sup>, Hidekazu Saito<sup>4</sup> *Saitama Medical University<sup>1</sup>, Tokushima University<sup>2</sup>, Tokyo Medical and Dental University<sup>3</sup>, National Center for Child Health and Development<sup>4</sup>, Sora no Mori Clinic<sup>5</sup>*

**Objective** To investigate whether ovarian stimulation protocols affect perinatal outcomes in fresh embryo transfer (ET) cycles. **Methods** A retrospective cohort study was conducted using Japanese assisted reproductive technology (ART) registry between 2007 and 2013. A total of 36,469 singleton deliveries born after fresh single ET were included. Ovarian stimulation protocols include natural ( $n=3,942$ ), clomiphene citrate (CC) ( $n=4,594$ ), CC+gonadotropin ( $n=5,218$ ), Gonadotropin releasing hormone (GnRH) agonist ( $n=15,651$ ) and GnRH antagonist ( $n=7,064$ ). Main outcomes were still birth, Cesarean section (CS), preterm delivery (PTD), low birth weight (LBW), very low birth weight (VLBW), small for gestational age (SGA) and large for gestational age (LGA). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a generalized estimating equation adjusting for correlations within institutions and confounders of year, maternal age and infertility diagnosis. **Results** Compared with natural cycle, ovarian stimulation cycles were associated with significant increased risk for PTD, LBW and SGA ( $p < 0.01$ ). Especially, ovarian stimulations using CC+gonadotropin demonstrated highest increased risks for LBW and SGA (adjusted OR [95% CI] : 1.68 [1.48 to 1.92] for LBW ( $p < 0.001$ ), and 1.82 [1.57 to 2.11] for SGA ( $p < 0.001$ )), and further associated with significant increased risk for stillbirth (2.52 [1.30 to 4.91],  $p < 0.006$ ), CS (1.13 [1.02 to 1.24],  $p < 0.017$ ) and VLBW (2.65 [1.51 to 4.6],  $p < 0.001$ ). Ovarian stimulation using CC without gonadotropin demonstrated similar significant associations except stillbirth. **Conclusion** Ovarian stimulation was associated with adverse perinatal outcomes of PTD, LBW and SGA. Ovarian stimulations using CC may have adverse effect on perinatal outcomes in fresh ET.

### ISP-57-6

**A long-term cohort study on 3,509 babies born through assisted reproductive technology (ART) for 6 years of age** Kensuke Akitsu, Tomoya Hasegawa, Akina Yamanaka, Keiko Ueno, Naoaki Kuji, Hirotaka Nishi *Tokyo Medical University Hospital*

**Objective** There are still few clear studies that investigate long-term prognosis of children born from ART. Therefore, this study aimed to investigate that the difference between the growth and development of singleton children conceived after different infertility treatments and those conceived naturally at 6 years of age. **Methods** A total of 4,095 mothers who conceived through ART at 26 clinics in Japan, participated in the study between October 1, 2008 and November 30, 2009, and informed consent was obtained from all patients before entering the study. Each baby was born after frozen embryo transfer (FET,  $n=1,223$ ), fresh embryo transfer (FrET,  $n=1,005$ ), or natural conception (NC,  $n=1,281$ ). The data on their growth and develop-

ment (Weight, height, KIDS scale) at 18 months and 6 years of age were obtained using a questionnaire. **Results** Finally, 1,582 (45.1%) participants undertook the follow-up survey. The birth weight of singleton children conceived via FET, FrET, and NC was 3,071, 3,017, and 2,998 g ; that at 6 years of age was 20.3, 20.4, and 19.7 kg, respectively. The birth height of singleton children conceived via FET, FrET, and NC was 49.1, 49.0, and 48.5 cm ; that at 6 years of age was 114.8, 115.3, and 114.2 cm, respectively. On the other hand, there was no significant difference in the KIDS score between each treatment group at 6 years of age ( $p < 0.05$ ). **Conclusion** At 6 years of age, the weight and height of children conceived through ART are higher than those of children conceived naturally.

### ISP-57-7

**Hysteroscopy performed at mid-luteal period of previous cycle of ART treatment did not improve the uterine receptivity for embryo but might cause the over invasive examination** Kyoko Nishimura<sup>1</sup>, Jun Kawagoe<sup>1</sup>, Koki Matsuo<sup>1</sup>, Isao Takehara<sup>1</sup>, Jun Matsukawa<sup>1</sup>, Hideki Igarashi<sup>2</sup>, Satoru Nagase<sup>1</sup> *Yamagata University<sup>1</sup>, Kyono ART Clinic<sup>2</sup>*

**Objective** Though several methods are reported that may improve the uterine receptivity for embryo and the success ratio of artificial reproductive technologies (ART), their usefulness is still controversial. Since hysteroscopy was one of those reported methods, we evaluated if the hysteroscopic examination is practically useful or not. **Methods** Between May, 2016, and April, 2017, we performed 180 cycles (129 in-vitro fertilization (IVF) cycles and 51 frozen embryo transfer (FET) cycles) of hysteroscopy at the mid-luteal period of the previous cycle of ART treatment and compared their outcome of ART with the immediate treatment cycles which did not undergo hysteroscopy. We also examined the adverse outcome of hysteroscopy. Patient allocation depended on the choice of each patients after the information was provided. Statistical analysis was performed by Student's t-test. Approval of the ethics committee was obtained. **Results** Among the hysteroscopy group for IVF, 73 cycles (56.6%) could undergo fresh embryo transfer (ET), but 56 cycles could not (26 performed all embryo freezing ; 21 did not acquire embryos ; 9 canceled IVF). Within the hysteroscopy group for FET, 42 cycles (82.4%) could undergo ET, but 9 canceled ET. Endometrial polyp was found in 2 cycles (1.1%). One cycle developed the pelvic inflammatory disease. There were no statistical differences in age of patients, treatment number, pregnancy ratio, and miscarriage ratio between hysteroscopy group and immediate treatment group. **Conclusion** Hysteroscopy does not improve pregnancy rates. Moreover, almost half of cycles can't undergo ET after hysteroscopy cycle. Therefore, routine hysteroscopy has less reasonability for recommendation.

### ISP-57-8

**Treatment outcome of In Vitro Fertilization—Embryo transfer in patients who have treated abnormal thyroid function** Chiaki Heshiki, Keiko Mekaru, Maho Miyagi, Kozue Akamine, Yoichi Aoki *University of the Ryukyus*

**Objective** It is known that an abnormal thyroid function increases the risk of infertility and miscarriage, although it remains unclear whether a treated abnormal thyroid function affects the treatment outcomes of IVF-ET. We therefore evaluated the treatment outcomes of IVF-ET in patients with an abnormal thyroid function. **Methods** We retrospectively analyzed the first IVF-ET cycle of 209 women from 2009 to 2015. Three analyses were conducted : (1) treated abnormal thyroid function vs. normal thyroid function ; (2) TSH level of  $< 2.5 \mu\text{U/mL}$  vs. that of  $> 2.5 \mu\text{U/mL}$  ; and (3) hypothyroidism with autoim-

munity positive vs. negative. **Results** In analysis (1), there were no significant differences in clinical pregnancy rate, miscarriage rate, and birth weight between women treated for abnormal thyroid function (n=34) and those with a normal thyroid function (n=175). No woman in the treated abnormal thyroid function group had perinatal complications. In analysis (2), there were no significant differences in the clinical pregnancy rate, miscarriage rate, and birth weight between women with hypothyroidism with TSH levels of <2.5 µU/mL (n=22) and >2.5 µU/mL (n=7). In analysis (3), there were no significant differences in the clinical pregnancy rate, miscarriage rate, and birth weight of women with hypothyroidism who were either thyroid autoimmunity positive (n=10) or negative (n=19). **Conclusion** If treated, abnormal thyroid function will not compromise the IVF-ET treatment outcomes or perinatal outcomes, regardless of TSH threshold or thyroid autoimmunity.

### ISP-58-1

**The comparison between mechanical and laser assisted hatching in Frozen-thawed blastocyst transfer cycles : A retrospective study of clinical outcomes** Moosung Jo, Hyunjoon Lee, Kayeong Yun, Hyunyoung Jo, Seungchul Kim, Sul Lee, Hyekyung Noh, Seoyoon Hwang, Lee Youngjoo, Lee Sieun, Jong-Kil Joo, Kyusup Lee *Pusan National University Hospital of Korea, Korea*

**Objective** We widely had used either mechanical assisted hatching (MAH, partial zona dissection) or laser assisted hatching (LAH) in frozen-thawed embryo transfer program. Therefore we decided conduct a retrospective study, aiming to compare clinical outcomes after MAH or LAH in women of frozen thawed blastocyst transfer undergoing ART. **Methods** A total of 206 AH cycles (101 MAH and 105 LAH) were performed from the January 1, 2014 until the December 31, 2016 at infertility center, Pusan National University Hospital in Busan, Korea. All AHs were included by autologous single or double frozen-thawed blastocysts transfer. **Results** The implantation rates per ET cycle was 55.1% in MAH group and 49.5% in LAH group (p=0.40). The clinical pregnancy rates per ET cycle was 42.6% in MAH group and 43.8% in LAH group (p=0.86), and the ongoing pregnancy rates was 37.6% in MAH group and 33.3% in LAH group (p=0.52). In our all clinical outcomes, the implantation rates, clinical pregnancy rates, ongoing pregnancy rates were not showed differences between MAH and LAH groups. **Conclusion** No significant differences were noted in implantation, clinical and ongoing pregnancies between the two test group, laser and mechanical techniques. Although not significant, both implantation and ongoing pregnancy rates were higher in MAH group, but clinical pregnancy rates were higher in LAH group.

### ISP-58-2

**The efficacy of in vitro Fertilization (IVF) in treating vaginismus causing infertility : a retrospective analysis of 13 cases** Ying-Wen Wang, Kuo-Chung Lan *Kaohsiung Chang Gung Memorial Hospital, Taiwan*

**Objective** The purpose of this study was to retrospectively review the cases of severe vaginismus causing infertility and the outcome after receiving IVF treatment at Kaohsiung Chang Gung Memorial Hospital. We analyzed the demographic features, average oocyte pick-up number, embryo quality, pregnant outcome and way of delivery among these patients. **Methods** We reported a case series of women suffering from severe vaginismus and infertility. In this retrospective study, 13 patients with vaginismus treated with IVF between 1998 and 2017 at our hospital were analyzed. **Results** The mean duration of infertility before their seeking intervention was 5.3 years at the average age of 34.5. The average oocyte pick-up number was

6.5. 11 out of the 13 patients became pregnant after IVF treatment with pregnancy rate 54.2% per cycle. Most of these women choose cesarean section when delivery. **Conclusion** Cognitive-behavioral therapy seems to be the mainstay treatment for vaginismus based on current literature review. However, if a women visited Obstetrics/Gynecology doctor directly for infertility, IVF is also a solution for women with severe vaginismus causing infertility based on the satisfactory outcome.

### ISP-58-3

**Shall we "Pause" PGS?** Shizuko Takahashi<sup>1</sup>, Pasquale Patrizio<sup>2</sup> *The University of Tokyo<sup>1</sup>, Yale University, USA<sup>2</sup>*

**Objective** Japan, just began preimplantation genetic screening (PGS) this year since there seems to be increasing evidence and is performed in the US and Europe. In the US, approximately 22-33% of all cycles utilize PGS. Marketed for several decades, PGS advocates are pressuring and criticizing those restricting PGS as unethical. However, while PGS is increasingly performed worldwide, some institutions in the US are beginning to put PGS on "pause." We explore the ethics of performing tests without sufficient evidence. **Methods** A review of the previous publications on PGS, focusing on controversies. Comparing publications from the US and from Europe. **Results** Two major factors contribute to this "pause" : the ongoing absence of a convincing randomized control trials using appropriate populations and outcome measures, and human failure to presume that technology can accurately predict an embryo's intrinsic nature to err and self-repair during its development. For patients to discard or transfer what has been diagnosed "abnormal" of a developing embryo can mean embryo loss or burden the pregnancy. For providers, distress of ethically providing a test that has limited evidence, and explaining what abnormal truly means without inflicting a patient is challenging. **Conclusion** Countries and institutions should always consider sufficient evidence prior to incorporating testing, even if it has been marketed over decades and seem less controversial with technological advancements. Despite demands from patients and pressures from society, institutions and countries should boldly put a testing on "pause." Results from the pilot study will help to reveal the truth.

### ISP-58-4

**A comparative retrospective study between controlled hyper-stimulation and mild-stimulation protocol for women with low AMH value** Rena Toriumi, Takashi Nagashima, Yukiko Matsuzawa, Yoichi Kobayashi, Mitsutoshi Iwashita *Kyorin University Hospital*

**Objective** Despite small number of oocytes in oocyte retrieval and low clinical pregnancy rates, there is no consensus about ovarian stimulation protocol for women with low Anti-Müllerian hormone (AMH) value, which has been studied about the potential clinical utility for assessment of follicle reservation. The purpose of this study was to assess clinical outcomes and clarify appropriate stimulation protocol for women with low AMH value. **Methods** In cases of oocyte retrieval in our hospital, we assessed 78 cycles, 34 from younger than 40 years and 44 cycles from older than 40 years, with low AMH value. The cycles were also divided two groups ; controlled hyper-stimulation group and mild-stimulation group. We compared total number of obtained oocytes and clinical pregnancy rates of these groups depending on the age. **Results** In the cycles from younger than 40 years, the total number of obtained oocytes and clinical pregnancy rates were not differences between controlled hyper-stimulation group and mild-stimulation group. Meanwhile, in the cycles from older than 40 years, there were also no differences between controlled hyper-stimulation group and mild-stimulation group in the total number of obtained oocytes and



clinical pregnancy rates. **Conclusion** From our results, it is indicated that there was no change about the total number of obtained oocytes and pregnancy rates between controlled hyperstimulation and mild-stimulation in case of low AMH value.

### ISP-58-5

**The interval between oocyte retrievals was not correlated with the number of eggs retrieved** Takeshi Fukunaga, Isao Takehara, Jun Kawagoe, Kyoko Nishimura, Jun Matsukawa, Michi Nishi, Koki Matsuo, Hideki Igarashi, Satoru Nagase *Yamagata University*

**Objective** In assisted reproductive technology (ART), patients often undergo repeated oocyte retrievals because of the failure of their treatment. People have thought that the extension of interval between oocyte retrievals may increase the number of retrieved oocytes compared to shorter period. However, the appropriate interval between oocyte retrievals is unclear. Therefore, we examined whether the interval between oocyte retrievals should be increased to improve ovary function. **Methods** We used the ART database of our Hospital (May 1989 to September 2016) and evaluated 392 cycles in 157 patients who underwent two or more consecutive ovarian hyperstimulation using the long protocols of GnRH agonist. Intervals of more than 6 months were excluded to avoid the effects of ovarian aging. We measured the correlation between the interval period of oocyte retrievals and 1) the changes of oocyte number of second or third oocyte retrievals from the one of the first treatment, 2) the volume of injected gonadotropin, or 3) the success of pregnancy. We used Spearman's rank-order correlation and Mann-Whitney U tests for statistical analysis. Approval of the ethics committee was obtained. **Results** There were no significant relationships between the interval of oocyte retrievals and the number of retrieved oocytes (correlation coefficient:  $-0.04$ ,  $p=0.52$ ), the total volume of injected gonadotropins ( $p=0.83$ ), or pregnancy outcomes ( $p=0.08$ ). **Conclusion** The interval between oocyte retrievals may not affect the number of retrieved oocytes. Extending the interval of oocyte retrieval to wait for recovery of ovary function may not be required.

### ISP-58-6

**Successful delivery in a 44-year-old woman using vitrified human oocytes taken from the woman at 41 years of age** Miyako Funabiki<sup>1</sup>, Sagiri Taguchi<sup>1</sup>, Masako Karita<sup>1</sup>, Yoshihiro Tada<sup>1</sup>, Terumi Hayashi<sup>1</sup>, Yuri Iwaki<sup>1</sup>, Takashi Matsubara<sup>1</sup>, Takeharu Ohta<sup>2</sup>, Kazunori Maeda<sup>1</sup>, Yoshitaka Nakamura<sup>1</sup> *Oak Clinic<sup>1</sup>, Oak Clinic GINZA<sup>2</sup>*

Successful pregnancies and deliveries are rare in women over 40 years of age. To date, no case report has been published about a successful delivery in a woman over 40 years of age using vitrified oocytes obtained through social egg freezing from a woman over 40 years of age. Here we report a case of a successful live birth from a 44-year-old woman using vitrified oocytes taken from the woman at 41 years of age. In addition, the technique using vitrified oocytes was used for social reasons. The 44-year-old patient delivered a 2,534 g female infant by Caesarean section in the 37th week of pregnancy. The Apgar scores for the female infant were 9 at 1 min and 9 at 5 min. The female infant exhibited no anomalies and is developing normally under the close surveillance of pediatricians. In addition, the 44-year-old patient provided written informed consent. And, the clinical study was approved by Institutional Review Board (IRB) at our clinic. However, the concept of social egg freezing has medical, ethical and social problems. Furthermore, the rate of live births differs among clinics or hospitals due to variations in the vitrification and warming techniques used. Therefore, information from individual clinics or hospitals about the risks, the rates of

successful live births and the cost of social egg freezing should be provided to patients to aid in the decision making process of the patients.

### ISP-58-7

**Effect of resveratrol supplementation during embryo transfer on IVF outcomes in infertile women: a cross-sectional study** Asako Ochiai<sup>1</sup>, Keiji Kuroda<sup>1</sup>, Yuku Ikemoto<sup>1</sup>, Rie Ozaki<sup>1</sup>, Keisuke Murakami<sup>1</sup>, Makoto Jinushi<sup>1</sup>, Koji Nakagawa<sup>2</sup>, Rikikazu Sugiyama<sup>2</sup>, Mari Kitade<sup>1</sup>, Atsuo Itakura<sup>1</sup> *Juntendo University Hospital<sup>1</sup>, Sugiyama Ladies Clinic<sup>2</sup>*

**Objective** Resveratrol is a polyphenolic compound and natural activator of sirtuin (SIRT) 1. Based on animal experiments, resveratrol has been mooted as a potentially therapeutic and preventive agent for cell senescence including ovarian aging. Clinical trials have not been performed to evaluate the impact of resveratrol on implantation and pregnancy outcome in humans. Recently, we showed that resveratrol inhibits decidualization of human endometrial stromal cells in vitro. This study was performed to clarify the impact of resveratrol supplementation on in vitro fertilization (IVF) outcomes in embryo transfer (ET) cycles. **Methods** This single-center, cross-sectional retrospective study (2012 to 2014) was designed to compare the outcomes of ET in women with taking resveratrol supplementation (200 mg/d) during luteal phase or not. Out of 7,520 ET cycles, we excluded 1,097 cycles with poor prognostic factors: 44 years-old and over and ET with morphologically poor quality embryos (Veeck classification, grade 4 and 5). We compared the resveratrol (RES) group (205 cycles in 101 women) and control (non-RES) group (6,218 cycles in 3,831 women). Odds ratios (OR) and 95% confidence intervals (CI) were calculated by multivariate logistic regression after controlling potential confounders: patient age and transferred embryo grade. **Results** Statistical analysis showed significantly lower implantation rate (OR=0.72; 95% CI 0.49-1.06), lower clinical pregnancy rate (OR=0.54; 95%CI 0.34-0.85) and higher miscarriage rate (OR=2.6; 95%CI 1.06-6.34) in the RES group compared to the non-RES group. **Conclusion** In line with the adverse effect of resveratrol on decidualization of primary endometrial cultures, supplementation during luteal phase appears detrimental for IVF outcomes, although additional studies are warranted.

### ISP-58-8

**A Study on the usefulness of hysteroscopy for ET repeated failure cases in ART** Yusuke Fukuda, Yukiko Katagiri *Toho University Omori Medical Center*

**Objective** Chronic endometritis is one of reason for implantation failure. We studied on the usefulness of hysteroscopy for ET repeated failure cases in ART. **Methods** We investigated 18 cases of ET repeated failure which were conducted from January 2016 to March 2017. Olympus HYF TYPEV was used as hysteroscopy. They were treated by internal use of antibiotic for two weeks and more after hysteroscopy. Dividing them into pregnancy and non-pregnancy groups who got and didn't get pregnant after hysteroscopy, respectively, hysteroscopy findings were compared and treatment cycle until pregnancy as well as pregnancy rate were calculated for pregnancy group. Square test and t-test were used. **Results** Of 18 cases in total, 6 and 12 cases were pregnancy group and non-pregnancy group, respectively. The average number of ET failure were 4.3 (2-11). Age of pregnancy group (median value: 35.0) was significantly younger than that of non-pregnancy group (median value: 39.0). **Conclusion** Hysteroscopy is useful for ET repeated failure cases in ART with relatively less age factor. In consideration of the fact that pregnancy has been achieved in pregnancy group during the first treatment cycle after hysteroscopy, it is be-



lieved that other cause should be sought for cases with hysteroscopy findings that pregnancy has not been achieved even after treatment. It is believed to be necessary to review whether hysteroscopy should be positively introduced before starting ART.

### ISP-59-1

**The regulation of endoplasmic reticulum stress improved the development of aged oocytes** Isao Takehara<sup>1</sup>, Hideki Igarashi<sup>2</sup>, Jun Matsukawa<sup>1</sup>, Satoko Suzuki<sup>1</sup>, Koki Matsuo<sup>1</sup>, Jun Kawagoe<sup>1</sup>, Satoru Nagase<sup>1</sup> *Yamagata University<sup>1</sup>, Kyono ART Clinic<sup>2</sup>*

**Objective** In assisted reproductive technology, the number of treatment cycles required for aged women is increasing. Advanced maternal age results in the deterioration of oocyte quality, but the exact cause is unknown. We focused on the endoplasmic reticulum stress (ERS) reported in various aging-related diseases and examined the relationship of ERS with the quality of aged oocytes and whether the control of ERS improved oocyte quality. **Methods** We used 5-week-old B6C3F1 female mice and 10-week-old ICR male mice. We defined oocytes released from the oviduct at 13 h and 19 h after hCG induction as “fresh” and “aged,” respectively. We compared (A) embryo development and (B) GRP78 expression (a chaperone protein increased by ERS) in fresh and aged oocytes and embryos. Furthermore, using aged oocytes treated with salubrinal (to control the effects of ERS on the PERK pathway), we compared (C) embryo development, (D) the expression of GRP78 and p-eIF2a (phosphorylated via the PERK pathway), and (E) the rate of dead cells in blastocysts with untreated aged oocytes. **Results** (A) The development of aged embryos was significantly poorer. (B) GRP78 expression was higher in aged oocytes. (C) Salubrinal-treated aged embryos showed improved development. (D) In salubrinal-treated aged oocytes, lower GRP78 and higher p-eIF2a expression were observed. (E) In salubrinal-treated aged blastocysts, fewer dead cells were found. **Conclusion** Aged oocytes were more influenced by ERS than fresh oocytes were. Salubrinal improved the development of aged embryos. The regulation of ERS can be a breakthrough treatment for the aged oocytes.

### ISP-59-2

**Novel antigens involved in ovarian autoimmunity in POI (primary ovarian insufficiency), and their localization and function in the human ovary** Satoko Osuka, Akira Iwase, Yukiyo Kasahara, Sayako Yoshita, Ayako Muraoka, Shotaro Hayashi, Natsuki Nakanishi, Takashi Nagai, Tomohiko Murase, Maki Goto, Fumitaka Kikkawa *Nagoya University*

**Objective** Previous studies indicated an association between POI and autoimmunity. We analyzed the sera of POI patients with thyroid autoimmunity (TA), in order to identify the antigens involved in ovarian autoimmunity (OA) and analyze their biological functions. **Methods** IP products of patients (POI patients with/without TA, and control patients) sera and protein from the granulosa cell line (HGrC1) were analyzed using mass spectrometry to identify the antigens involved in OA. We confirmed the expression of the identified antigens in the ovary samples. HGrC1 were used for evaluating the functions of these antigens. The recombinant antigens were produced using HEK 293T. **Results** POTE E/F were identified as the candidate antigens using mass spectrometry. POTE (prostate, ovary, testis and placenta) genes expressions in ovaries has been reported but the functions weren't well established. Immunohistochemistry of the human ovary revealed POTE E/F staining in granulosa cells and oocytes, moreover, the intensity were changed in different stages of follicle development. TSH treatment in HGrC 1 increased POTE expression and decreased proliferation ac-

tivity than control subject. POTE siRNA transfection in HGrC 1 downregulated POTE gene expression, meanwhile, proliferation activity was increased. Recombinant human POTE protein were produced from whole length cDNA. **Conclusion** Proteomic analysis identified POTE proteins as candidate antigens involved in OA. POTE expression levels were changed in different stages of follicle development, and may affect the proliferation activity of HGrC1. In future, revealing the functions of POTE proteins may help in elucidating POI pathogenesis, furthermore, quantification of the antibody using recombinant protein could be a marker for detecting pre-POI patients.

### ISP-59-3

**The effects of chronic testosterone administration on body weight, food intake, and fat weight were changed age-dependently** Takeshi Iwasa, Toshiya Matsuzaki, Rie Yanagihara, Mayila Yiliyasi, Kiyohito Yano, Minoru Irahara *Tokushima University*

**Objective** To examine whether androgens effects on body weight (BW), food intake (FI) and body composition might be changed age-dependently, the effects of chronic testosterone (T) administration were evaluated in rats of different ages. **Methods** Young (10 weeks of age) and middle-aged (12 months of age) rats were randomly assigned to either the T-administered or the non-administered group. Silastic tube filled with crystalline T and empty tube was implanted in T-administered group and non administered group, respectively. BW and cumulative FI were assessed every week, and the rats were sacrificed by decapitation at 4 weeks after the implantation. The weights of visceral and subcutaneous fat were assessed, and blood and brain were harvested. Serum leptin and hypothalamic NPY mRNA levels were measured to evaluate leptin resistance. **Results** Although chronic T administration increased BW gain, FI, and feed efficiency in both young and middle-aged rats, it increased visceral fat weight only in middle-aged rats. Therefore, it is possible that T promotes the conversion of energy to adipose tissue and exacerbates fat accumulation in older individuals. In addition, although the administration of T increased the serum leptin level, it did not alter hypothalamic neuropeptide Y mRNA level in middle-aged rats. On the contrary, such T-induced changes were not observed in young rats. Thus, T might induce hypothalamic leptin resistance, which could lead to fat accumulation in older individuals. **Conclusion** T might disrupt the mechanisms that protect against adiposity and hyperphagia and represent a risk factor for excessive body weight and obesity, especially in older females.

### ISP-59-4

**Impact of vitamin D supplementation on preconception immune tolerance in infertile women** Yuko Ikemoto<sup>1</sup>, Keiji Kuroda<sup>1</sup>, Koji Nakagawa<sup>2</sup>, Asako Ochiai<sup>1</sup>, Rie Ozaki<sup>1</sup>, Keisuke Murakami<sup>1</sup>, Makoto Jinushi<sup>1</sup>, Rikikazu Sugiyama<sup>2</sup>, Satoru Takeda<sup>1</sup> *Juntendo University Hospital<sup>1</sup>, Sugiyama Clinic<sup>2</sup>*

**Objective** Successful pregnancy is favor of T-helper (Th) 2 cells (Th2), and Th1 is related to embryonic rejection. Vitamin D (VD) is an important immune modulator via inhibition of proliferation of Th1 and promotion of Th2. VD deficiency is associated with reproductive failure and pregnancy complications. The aim of this study is to investigate the clinical efficacy of VD in infertile woman for preconception care in maternal immune tolerance. **Methods** Serum 25-hydroxyvitamin D3 (25(OH)VD), Th1 (CD4+/IFN- $\gamma$ +) and Th2 (CD4+/IL-4+) levels were measured in 276 infertile women from 2014 to 2016. We categorized VD deficiency (25(OH)VD < 20ng/ml), insufficiency (21-30ng/ml) and sufficiency (>30ng/ml), and compared T-helper cell among 3 groups. We additionally examined detailed immu-

nological test pre- and post-VD supplementation (1,000IU/d) in 8 patients with VD deficiency. This study was approved by the Local Ethics Committee. **Results** Our data shows 87.3% of infertile women were lacking 25(OH)VD levels. In immunological profiles, the number of patients with aberrant high Th1/Th2 ratio ( $>10.3$ ) in sufficient group was significantly smaller than other 2 groups ( $p=0.046$ ). After supplementation, 25(OH)VD were increased in all patients ( $p=0.008$ ), levels of Th1 were significantly decreased ( $p=0.016$ ), leading to reduction of Th1/Th2 ratios ( $p=0.023$ ). There were no complications or adverse effects. **Conclusion** Most of infertile women were lack of VD status. Preconception VD supplementation with VD deficiency may sufficiently optimize maternal immune rejection to embryo via Th1/Th2 ratio, leading to prevention against proinflammatory obstetrical complications during pregnancy.

### ISP-59-5

**Effect of metformin on androgen receptor expression in endometrial epithelial/stromal cell lines** Miki Ohara<sup>1</sup>, Akiko Yamaguchi<sup>1</sup>, Fumiko Saito<sup>1</sup>, Satoshi Suzuki<sup>1</sup>, Ryota Suganuma<sup>1</sup>, Toshifumi Takahashi<sup>2</sup>, Hideki Mizunuma<sup>2</sup>, Hiromi Komiyai<sup>1</sup>, Kei-ya Fujimori<sup>1</sup> *Fukushima Medical University<sup>1</sup>, Fukushima Medical Center for Children and Women<sup>2</sup>*

**Objective** There are few studies focusing on the effect of metformin on the endometrium in patients with polycystic ovary syndrome (PCOS). Our previous study showed that expression of endometrial androgen receptor (AR) decreased and HOXA10 increased with administration of metformin to PCOS patients. In this study, to examine whether the metformin effects on PCOS endometrium may be direct or not, we utilized endometrial epithelial/stromal cell lines. **Methods** After culturing the Ishikawa cells and Human Endometrial Stromal cells (HESCs) from each respective subculture for 24 hours, we added testosterone (T group), or both testosterone and metformin (T+M group) to the culture medium. For control, we also cultured cells without testosterone and metformin (C group). Protein was extracted from the cells after culturing for 48 hours from addition of the preparations. We analyzed the AR expression levels using Western blotting. **Results** In the T group, the expression levels of AR in both cell lines increased as compared to the C group. The levels of AR in the T+M group were lower than those in the T group. **Conclusion** Addition of testosterone increased AR expression in both Ishikawa cells and HESCs, while addition of metformin to testosterone reduced AR expression. Based on these findings, metformin may reduce AR expression by acting directly on the endometrium in the presence of testosterone.

### ISP-59-6

**The Effectiveness of a New Comprehensive Numerical Multi-Scoring System for Endometriosis** Masao Ichikawa, Shigeo Akira, Hanako Kaseki, Kenichiro Watanabe, Shuichi Ono, Toshiyuki Takeshita *Nippon Medical School Hospital*

**Objective** To evaluate the diagnostic effectiveness of a new Numerical Multi-Scoring System for Endometriosis (NMS-E). **Methods** In this prospective observational research, we included 94 women diagnosed with endometriosis at our hospital. The NMS-E combines internal examination and transvaginal ultrasonography to evaluate the adnexa, adhesions, pain, and the uterus. The E-score then gives an idea of the overall severity of endometriosis (out of 40 points; 10 per item in the NMS-E). The diagnostic accuracy of each evaluated item of the NMS-E was verified by comparison with intraoperative findings, and the usefulness of the E-score was evaluated by comparison with the revised American Society for Reproductive Medicine (r-ASRM) score. **Results** The average overall E-score and r-ASRM score were  $17.7 \pm 5.8$  and  $69.0 \pm 32.6$ , respectively. A posi-

tive correlation ( $r=0.662$ ) was observed between the E-score and the r-ASRM score. The accuracies of adnexal, adhesional, and uterine evaluation by transvaginal ultrasonography were 91.8%, 83.0%, and 90.6%, respectively. Compared with the lesion-free group, the pain score was significantly higher in the group with endometriotic lesions in the pouch of Douglas ( $4.34 \pm 2.7$  vs.  $1.84 \pm 2.06$   $p=3.0E-04$ ), right uterosacral ligament ( $4.26 \pm 2.63$  vs.  $2.29 \pm 1.97$   $p=1.0E-04$ ), and left uterosacral ligament ( $3.88 \pm 2.56$  vs.  $2.27 \pm 2.56$   $p=2.4E-03$ ). **Conclusion** The NMS-E accurately diagnosed the overall status and severity of endometriosis, and would be useful as an index for medical and surgical strategy.

### ISP-59-7

**Efficacy of individualized dose of FSH in ovarian stimulation for unexplained sterility** Toshiya Matsuzaki, Rie Yanagihara, Kiyohito Yano, Takeshi Iwasa, Minoru Irahara *Tokushima University*

**Objective** The ovarian stimulation to unexplained infertility frequently induces multiple pregnancy. In this study, we evaluated individualized initial dose of FSH by BMI in patients of unexplained infertility. **Methods** Twenty one patients who were diagnosed unexplained infertility or luteal insufficiency were treated with self injection of recombinant FSH in a low dose. Patients with BMI $<20$  injected 50IU, while patients with BMI $>20$  injected 62.5IU. They started self injection on cycle day 3~6. We measured follicle size using transvaginal ultrasonography. If no follicle developed, dose of FSH was increased by 12.5IU per time (up to 4 times). When follicle diameter reached 18mm, hCG 5,000IU was injected. **Results** The ovulation rate was 100%. The number of growing follicle was  $1.29 \pm 0.63$  (mean  $\pm$  SD). The monofollicular development was seen in 85.7% (BMI $<20$ ) and 78.6% (BMI $>20$ ). Number of follicle were 1~3 and there were no cycle with follicle number over 3. No pregnancy achieved. **Conclusion** The method of individualizing initial dose of FSH by BMI got high rate of ovulation and monofollicular development. This method seemed safe while no pregnancy happens. We need to clarify whether monofollicular development cycles using FSH are useful as treatment of unexplained sterility.

### ISP-59-8

**Comparison of Anti-Müllerian-Hormone levels between pregnant women with natural conception and sterile women in assisted reproductive technology** Kento Usui, Yukiko Katagiri, Yusuke Fukuda, Akiko So, Mamoru Kitamura, Azusa Moriyama, Ayumu Ito, Yuko Hayashi, Yuko Tamaki, Takehiko Tsuchiya, Mineto Morita *Toho University Omori Medical Center*

**Objective** Anti-Müllerian-Hormone (AMH) is a well-established marker of the ovarian reserve. Ovarian reserve is one of the important factors in assisted reproductive technology (ART) especially for controlled ovarian hyperstimulation. However, it has not been clear the relation between AMH concentration and fertility. We assessed the AMH levels in pregnant women conceived naturally, and compared to sterile women in ART. **Methods** The pregnant women in 6 to 14 gestational weeks, who conceived naturally, were recruited for this study. Their AMH levels were assessed by AMH Gen II ELISA kit and were compared to the AMH levels of infertile women treated by ART in our center. **Results** A total of 320 pregnant women (19-44 years old) and 496 infertile women (25-50 year old) were assessed. The cases with polycystic ovarian syndrome, passed history of operation on ovaries, and the FSH level is  $<14$  mIU/ml, were excluded. The AMH levels were decreased according as their age in the both groups. However, there were not significant the levels between pregnant women and infertile women. **Conclusion** It has been suggested that AMH is not a marker to

estimate the woman who will get pregnancy or not.

### ISP-59-9

**Individualized initial dose in low-dose FSH therapy for WHO group 2 patients** Rie Yanagihara, Toshiya Matsuzaki, Takeshi Iwasa, Kiyohito Yano, Minoru Irahara *Tokushima University*

**Objective** Incidences of multiple pregnancy by ovulation induction has been a problem to be solved for the long time. FSH treatment in a low-dose step up method can reduce the frequency of multiple pregnancy, but the rate is still higher than natural pregnancy. In this study, we evaluated our protocol of low-dose FSH therapy with individualized initial dose by BMI. **Methods** Twenty nine patients who were diagnosed WHO group 2 ovarian insufficiency were treated with self injection of recombinant FSH in a low dose step up protocol. Patients with BMI<20 and BMI>20 were injected 50IU and 62.5IU as initial dose. If no follicle is developed, dose of FSH was increased by 12.5IU per time (up to 4 times). When follicle diameter reached 18mm, hCG 5,000IU was injected. We evaluated ovulation rate and monofollicular development and compared with reported best results of which the ovulation rate was over 90% and monofollicular development was over 70%. **Results** The ovulation rate was 100% (BMI<20) and 90.9% (BMI>20). The monofollicular development was seen in 80% (BMI<20) and 77.3% (BMI>20). The average of number of growing follicle was  $1.07 \pm 0.47$  (mean  $\pm$  SD) and there were no cycle with follicle number over 2. The pregnancy rate was 60% (3/5 BMI<20) and 18.2% (4/22 BMI>20). No multiple pregnancy achieved. **Conclusion** The method of individualizing initial dose of FSH by BMI got high rates of ovulation and monofollicular development. This method could reduce multiple pregnancy in ovulation induction.

### ISP-60-1

**Dominant expression of angiotensin 1-7 receptor (MAS1) in the eutopic endometrium in the endometriosis patients** Takahiro Nakajima, Fumihisa Chishima, Takehiro Nakao, Chuyu Hayashi, Akiko Kasuga, Kaori Shinya, Takuo Nakayama, Hiromitsu Azuma, Go Ichikawa, Atsushi Komatsu, Tatsuo Yamamoto, Kei Kawana *Nihon University Itabashi Hospital*

**Objective** Tissue renin-angiotensin system (RAS) plays important roles in the tissue remodeling. We have demonstrated AT1 and AT2, receptors of angiotensin II, are expressed and both pathways balance RAS system in endometriosis by their opposing effects to each other. MAS1, a specific receptor of angiotensin1-7, also oppose AT1 pathway relating tissue remodeling. Here we examined whether MAS1 has any effect on pathogenesis of endometriosis. **Methods** Under informed consents, ovarian endometriotic tissues and eutopic endometrial tissues (endo-Em) were obtained from 32 patients with endometrial cyst. As control, normal endometrial tissues (cont-Em) were obtained from patients undergoing hysterectomy for benign diseases. Immunohistochemical staining were performed for MAS1, AT1 and AT2. The mRNA levels of the MAS1, AT1 and AT2 were examined by quantitative RT-PCR. **Results** Immunohistochemistry revealed that MAS1 was immune-positive at the apical side of glandular epithelium in endometriotic lesions. RT-qPCR revealed that MAS1 mRNA level in ovarian endometriosis was significantly higher than that cont-Em whereas not different from those in endo-Em. In the endometrium at proliferative phase, MAS1 mRNA level in endometriosis cases was significantly higher than that in controls. MAS1/AT1 mRNA ratio in the endometrium at proliferative phase was increased predominantly in endometriosis cases when compared with controls. **Conclusion** MAS1 was expressed not only in the ovarian endometriosis but in the eutopic endometrium. The expression of MAS1 in the eutopic endometrium was not observed in the

non-endometriosis patients at all. Inhibition of RAS system by MAS1 may characterize microenvironment of the eutopic endometrium in the endometriosis patients.

### ISP-60-2

**Clonal expansion and diversification of cancer-associated mutations in endometriosis and normal endometrium** Kazuaki Suda<sup>1</sup>, Kosuke Yoshihara<sup>1</sup>, Tatsuya Ishiguro<sup>1</sup>, Ryo Tamura<sup>1</sup>, Kaoru Yamawaki<sup>1</sup>, Yutaro Mori<sup>1</sup>, Hiroaki Kase<sup>2</sup>, Takayuki Enomoto<sup>1</sup> *Niigata University<sup>1</sup>, Nagaoka Chuo General hospital<sup>2</sup>*

**Objective** Endometriosis is characterized by ectopic endometrial-like epithelium and stroma. The aim of this study is to clarify molecular characteristics of endometriosis leading to development of better treatments. **Methods** After ethical committee approval and written informed consents, we performed whole-exome and target-gene sequencing for 107 ovarian endometriotic epithelium samples from 54 endometriosis patients and 82 normal uterine endometrial epithelium samples from 32 non-endometriosis patients. All samples were isolated from frozen sections by laser-microdissection. We also performed target-gene sequencing for 109 single endometrial glands obtained from three patients. **Results** In both endometriotic and uterine endometrial epithelium samples, numerous somatic mutations were identified within genes, including *KRAS* and *PIK3CA*, frequently mutated in endometriosis-associated ovarian and endometrial cancers. Analysis of mutant allele frequency (MAF) in endometriotic epithelium revealed a unique mutational landscape, wherein *KRAS* was frequently mutated, with a higher MAF accompanied by arm-level copy number alterations, leading to clonal expansion of cells carrying these changes. MAF distributions in normal uterine endometrium were lower than in endometriotic epithelium. To show that each endometrial gland was clonal in origin, we sequenced single endometrial glands and found that each gland carried a clonal state of distinct mutations, proving how heterogeneous genomic architecture of endometrial epithelium is. **Conclusion** We clarified that endometriosis and normal endometrium samples had already harbored cancer-associated mutations which were considered as driver mutations in endometriosis-associated ovarian and endometrial cancers. Combined with retrograde menstruation, overlapping in somatic mutations between endometriosis and uterine endometrium might be the molecular evidence that endometriosis derives from uterine endometrium.

### ISP-60-3

**Treatment with a selective estrogen receptor modulator, SR-16234 results in regression of endometriosis-like lesions in a murine model** Khine Yinmon, Fuminori Taniguchi, Kei Nagira, Yukihiro Azuma, Takashi Uegaki, Tasuku Harada *Tottori University*

**Objective** SR-16234 (SR) (Nobelpharma Co.) is a newly developed selective estrogen receptor modulator (SERM), which has an estrogen receptor (ER)  $\alpha$  pure antagonist and ER  $\beta$  partial agonist activity. We investigated the efficacy of SR-16234 on endometriosis-like lesions in the murine model of endometriosis. **Methods** A mouse endometriosis model was established by transplanting autologous endometrial tissue. Ovariectomized, estradiol replaced, 6-week-old BALB/c mice with surgically induced endometriosis (n=30) were injected with lipopolysaccharide (LPS) with or without SR (1mg/kg/day) treatment or vehicle, over a period of 4 weeks. Upon treatment completion, the endometriosis-like lesions that developed in the abdominal cavity of mice were counted, measured, and collected. Gene expression of inflammatory cytokines in the lesions was assessed by real time RT-PCR. Immunohistochemical analysis was used to

evaluate the effect of SR on cell proliferation, angiogenic activity, and inflammation. **Results** Treatment with SR significantly reduced the total number, weight and surface area of lesions per mouse. In addition, SR downregulated LPS enhanced *Vegf*, *Il-6*, *Ptgs-2* and *Ccl-2* mRNA expression in endometriosis-like lesions. Immunohistochemical analysis demonstrated a decrease in percentage of positive cells of Ki-67, and intensity and rate of positive cells of CD3, F4/80, and PECAM by SR treatment. **Conclusion** SR-16234 had a regressive effect on the development of murine endometriosis-like lesions. It may be used as a novel agent for the treatment of endometriosis.

#### ISP-60-4

**Role of Focal Adhesion Kinase (FAK) in development of endometriosis** Takashi Nagai, Akira Iwase, Chiharu Ishida, Shotaro Hayashi, Ayako Muraoka, Tomohiko Murase, Satoko Osuka, Maki Goto, Fumitaka Kikkawa *Nagoya University*

**Objective** The effect of cell adhesion itself on endometriosis has been hardly explored. Integrins, the cell adhesion molecules, have been demonstrated to regulate cell survival, proliferation and invasion via focal adhesion kinase (FAK) in many types of cells including endometriosis. Monocyte chemoattractant protein-1 (MCP-1) is one of the highly upregulated chemokines in endometriotic tissues. The purpose of this study is to investigate the role of FAK in endometriosis and to test the effect of FAK-inhibitor on a surgically induced endometriosis mouse model. **Methods** FAK, MCP-1, CD68 and TGF- $\beta$ 1 expression was assessed by immunohistochemistry in endometriotic cyst. We assayed the concentrations of MCP-1 in the culture media of endometrial stromal cells with or without endometriosis (eESC and ESC, respectively) and endometriotic cyst-derived stromal cells (CSC). TGF- $\beta$ 1 was measured by co-culture with CSCs and macrophages. In a mouse of endometriosis, FAK-inhibitor treatment was evaluated for lesion of ectopic endometrium. **Results** IHC showed that FAK, MCP-1 were enhanced on endometriotic cysts compared to endometrium. The MCP-1 concentration of CSC was higher than that of ESC, and secretion of MCP-1 was inhibited by FAK-Inhibitor. In a mouse model, FAK-inhibitor treatment significantly reduced number of lesion per mouse. **Conclusion** In conclusions, increased secretion of MCP-1 from endometriotic stromal cells was mediated via FAK which was stimulated by integrin-extracellular matrix adhesion. These results suggest that inflammatory response and cell adhesion is interrelated and implicated in the development endometriosis.

#### ISP-60-5

**Peritoneal NK cell suppression for cytotoxicity and chemotaxis in women with endometriosis** Shimpei Yamamoto, Takashi Ushiwaka, Chiaki Izumiya, Tamami Tsuzuki, Kayo Taniguchi, Nagamasa Maeda *Kochi University*

**Objective** In women with endometriosis, immunologic suppression by natural killer (NK) cells and macrophages in peritoneal fluid (PF) is considered to be associated with the pathogenesis of endometriosis. In this paper, we investigate the immunologic behavior of peritoneal NK cells from women with endometriosis by time-lapse imaging system. **Methods** PF samples obtained at laparoscopic surgery from women with endometriosis were compared to without endometriosis. We investigated the immunocompetent PF cell movement and behavior by time-lapse imaging under microscope incubator. The cell movement speed was calculated as a chemotaxis index. This study was approved by IRB at own affiliation. **Results** During the menstrual period, we can observe retrograde endometrial cells in PF. Interestingly, immunocompetent cells from women without endometriosis were cytotoxic to retrograde endometrial cells. In particular,

peritoneal NK cells are most cytotoxic and retrograde endometrial cells were damaged and collapsed by surrounding NK cells and finally disappeared. On the contrary, in women with endometriosis, retrograde endometrial cells were hardly damaged and they remained after menstrual period. The cell movement speed of NK cells from women with endometriosis was significantly decreased compared to control. On the other hand, the cell movement speeds of both macrophages and lymphocytes were not significantly difference between with and without endometriosis. **Conclusion** In women with endometriosis, peritoneal NK cell has not only decreased cytotoxicity but also has decreased chemotaxis assessed by cell movement speed. This immunologic suppression of NK cells in women with endometriosis may be associated with the pathogenesis of endometriosis.

#### ISP-61-1

**Healthcare for young gynecologic malignant tumor patients at our hospital** Kanako Yoshida, Yuri Kadota, Kana Kasai, Takako Kawakita, Takeshi Kato, Minoru Irahara *Tokushima University*

**Objective** 30 to 40% of gynecologic malignant tumor patients are women under the age of 50. Most of the patients are undergoing surgery including bilateral oophorectomy, chemotherapy or radiation therapy, resulting in ovarian dysfunction. Total health care after cancer treatment is important, even for gynecological cancer being relatively good prognosis. **Methods** We examined ovarian deficiency symptoms, dyslipidemia, bone mineral density and treatment method of 13 patients with ovarian dysfunction after cancer treatment at our hospital. **Results** Diagnosis were 4 cervical cancers (2 squamous cell carcinomas and 2 adenocarcinomas), 5 endometrial cancers (5 endometrioid adenocarcinomas) and 4 ovarian cancers (3 endometrioid adenocarcinomas, 1 mucinous tumor of borderline malignancy). The average age at treatment was 40 (31-47) years old. For ovarian deficiency symptoms, hot flash was the most common in 8 cases, followed by complaints of symptoms such as malaise, insomnia, anxiety. Dyslipidemia was found in 7 cases, bone mineral density was normal in 7 cases, osteopenia in 3 cases, osteoporosis in 2 cases. For cervical cancer and ovarian cancer, Hormone Replacement Therapy (HRT) was started from the early stage of treatment. In contrast, HRT was performed carefully in endometrial cancer, and treatment was done with Kampo and vitamin D as necessary at the early stage of cancer treatment. In 5 of 7 patients in which HRT was initiated, improvement in ovarian deficiency symptom was observed. **Conclusion** Management of young gynecologic malignant tumor patients requires not only the presence or absence of recurrence, but also management with attention to the total health care including HRT.

#### ISP-61-2

**Intraoperative Surgical Apgar Score predicts 30-day morbidity in elderly gynecological patients** Kazumi Kurata, Yoko Chino, Akiko Shinagawa, Tetsuji Kurokawa, Yoshio Yoshida *University of Fukui*

**Objective** The aim of this study was to determine whether a preoperative health status index and intraoperative data could predict perioperative morbidity and mortality in women over the age of 65 years undergoing surgery for gynecologic disorders. **Methods** The medical records of 70 female patients who were >65 years of age and who underwent surgery under general anesthesia in our university hospital from January 2014 to December 2015 were retrospectively reviewed. Preoperative data were extracted from a database and included comorbidities, American Society of Anesthesiologists physiological status classification, the Charlson Comorbidity Index, the Subjective



Global Assessment 2011 revision, the subjects' risk of falling, body mass index, and age. The intraoperative factors investigated included the type of surgery and the Surgical Apgar Score (SAS). Major postoperative complications were defined as >Grade 3 based on the Clavien-Dindo classification version 2.0. **Results** Of the 70 elderly gynecological patients, 6 (8.6 percent) developed serious Grade 3 or worse complications within 30 days of surgery. The only factor that significantly affected postoperative complications was the SAS, an index of the patient's intraoperative condition. The optimum cut-off SAS for the occurrence of complications was determined by the receiver operating characteristic curve to be >6 points. A score >6 points predicted the development of postoperative complications with 66.7 percent sensitivity and 85.9 percent specificity. **Conclusion** In this study, the SAS predicted the development of serious complications in elderly gynecological patients within 30 days of surgery more accurately than did other comorbidities, preoperative assessments, and type of surgery.

### ISP-61-3

**The comparison of lower urinary tract symptoms after various surgeries for pelvic organ prolapse** Kaori Hoshino<sup>1</sup>, Mai Myouga<sup>1</sup>, Kazuaki Yoshimura<sup>1</sup>, Toru Hachisuga<sup>2</sup> *Wakamatsu Hospital of the University of Occupational and Environmental Health<sup>1</sup>, University of Occupational and Environmental Health<sup>2</sup>* **Objective** Most of the patients of pelvic organ prolapse (POP) have some lower urinary tract symptoms (LUTS) and gynecologists should consider the changes of LUTS. There are few reports that analyze the changes of LUTS between different types of POP surgeries. In this study, we analyzed pre and post-operative LUTS in various POP surgeries. **Methods** Seventy-two patients who underwent POP surgeries in our hospital from March 2016 to March 2017 were enrolled in this study. The types of surgeries were transvaginal mesh (TVM, n=33), laparoscopic sacrocolpopexy (LSC, n=18), laparoscopic uterosacral ligament suspension (L-USLS, n=12), and transvaginal non-mesh surgery (n=9). Voided volume (VV), average and maximum flow rate (Qave and Qmax), and post-void residual urine (PVR) were measured by uroflowmetry and ultrasound before and 1, 3, 6 months after the surgeries. Core urinary tract symptoms score (CLSS) and quality of life (QOL) score was simultaneously obtained. **Results** There was no significant difference between the groups in the backgrounds. VV and Qave of LSC group were significantly higher than those of TVM group until 3-month after the surgeries. PVR of TVM group was greater than LSC group at 1-month after the surgeries and reduced at 3-month. Regarding stress urinary incontinence (SUI), CLSS of LSC was significantly worse than that of TVM. L-USLS wasn't any significant difference compared with the other surgeries. QOL score significantly improved after all surgeries. **Conclusion** TVM tended to cause voiding difficulty, however, it recovered after 6months. On the other hand, LSC caused more possibility of SUI. QOL improved after all POP surgeries.

### ISP-61-4

**The restoration of vaginal front and posterior wall together is necessary with Native Tissue Repair in the case of grade III and IV of Pelvic Organ Prolapse** Tetsuya Oishi, Hiroki Kato, Takashi Shibata, Hisato Tokuda, Fumikazu Kotsuji *Takatsuki General Hospital* **Objective** In announcement until the last time, we reported usefulness of Native Tissue Repair of vaginal front wall using "Pubocervical Fascia Pulling Up Method" and of vaginal posterior wall using "Rectovaginal Fascia Pulling Up Method" for Pelvic Organ Prolapse (POP). Here we introduce the results that examined the need of the restoration of vaginal posterior wall

for POP. **Methods** From July 2012 to May 2016, for the case of grade III Pelvic Organ Prolapse, we checked the emergence of vaginal vault of posterior wall at the end of operation for the vaginal front wall. If not there, we did not perform the restoration of vaginal posterior wall. **Results** In 209 cases of grade III and IV of POP, 192 cases were able to be followed up for over one year. Of the 192 cases, 14 of the 147 cases where restoration of only the vaginal front wall were performed had vaginal vault of posterior wall after operation. All gradually begins enlarging from 6 months post operation and some have become beyond the hymen ring in 1-2 years. On the other hand, none of the 26 cases observed during the same period where restoration of vaginal front and posterior wall were performed together have vaginal vault of posterior wall. **Conclusion** The restoration of pubocervical fascia and rectovaginal fascia together is necessary in the case of grade III or higher of POP, because existence of damage of not only pubocervical fascia but also rectovaginal fascia should be considered.

### ISP-61-5

**Four cases of Pelvic Organ Prolapse (POP) complicated with uterine cancer or precancerous lesion** Ayuko Ootoshi<sup>1</sup>, Hiromi Kashiwara<sup>1</sup>, Mai Temukai<sup>1</sup>, Yuri Kamino<sup>1</sup>, Yoshimi Tokugawa<sup>1</sup>, Chikako Tsukahara<sup>1</sup>, Takeshi Hisamatsu<sup>1</sup>, Takashi Miyatake<sup>1</sup>, Koji Hisamoto<sup>1</sup>, Masahiko Tsujimoto<sup>2</sup>, Yukihiko Nishio<sup>1</sup> *Osaka Police Hospital<sup>1</sup>, Department of Pathology, Osaka Police Hospital<sup>2</sup>*

Recently, with the aging of the population, patients with POP are increasing, and it seems that cases complicated with uterine malignancy will increase in the future. Before the POP surgeries, we check the cervical cytology and endometrial thickness. With these examinations, we decide the type of surgery. We present four cases of POP patients with co-existing uterine malignancy or precancerous lesion who underwent surgery. Case 1 is an 84-year-old woman with uterine prolapse. Her cervical cytology was HSIL, the colposcopy biopsy showed CIN1, therefore total vaginal hysterectomy and all vaginal excision were performed. The diagnosis was cervical squamous cell carcinoma stage IA. Case 2 is an 82-year-old woman with uterine prolapse. She had endometrial thickening, biopsy and MRI were performed and the diagnosis was uterine corpus clear cell adenocarcinoma stage IA. Total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentum resection, USL fixation were performed. Case 3 is a 77-year-old woman with uterine prolapse. Her cervical cytology was SCC. The colposcopy biopsy showed CIS, however PET-CT showed abnormal uptake in the cervixes. Semi-radical hysterectomy, BSO and USL fixation were performed. Case 4 was a 69-year-old woman with cystocele. Endometrial cancer was suspected by biopsy. TAH, BSO and USL fixation were performed. From the reflection that we should predict the carcinoma before the surgery of case 1, in other cases, procedure of the surgeries were mainly for the carcinoma, for the POP only USL fixation was performed. Therefore there is a possibility of cystocele recurrence in the future.

### ISP-61-6

**Repair of the Stage 3 POP That a Ring Pessary Made Giant Rectovaginal Fistulas and the Rectal Mucosa Covered the Posterior Vaginal Wall Beyond the Fistula : Operative Technique** Hiroki Kato, Tetsuya Oishi, Takashi Shibata, Hisato Tokuda, Satoshi Nakago, Fumikazu Kotsuji *Takatsuki General Hospital*

We experienced a repair of the stage 3 POP that a ring pessary made giant rectovaginal fistulas and the rectal mucosa covered the posterior vaginal wall beyond the fistula. We thought that



broad separation of the rectal wall from its neighboring tissues and the order of a surgical procedure were the vital for the success of the operation. For accurate separation of the rectal wall, the perineal skin was transversely cut and the edge of the posterior vaginal wall was grasped and stretched. This made the precise separation of the rectal wall possible. When the separation of the rectal wall reached to the fistula, the rectal mucosa overlying the vaginal mucosa was removed. Then, the rectal wall above the fistula was removed from the vaginal wall. Followings are the operative order : 1) the separation of the pubocervical fascia from the anterior vaginal mucosa, 2) repair of the rectal fistula, 3) hysterectomy, 4) reconstruction of the pubocervical fascia, and 5) repair of the anterior and posterior vaginal mucosa. We thought about this surgical order due to the followings. Firstly, when we perform hysterectomy and anterior colporrhaphy before syringeal repair, the position of the fistula moves to deep in the vaginal canal. This makes repair of the fistula difficult. Secondly, if syringeal restoration is preceded, vaginal traction during the POP repair may produce a stress to the sutured rectal wall. Tertiary, the hysterectomy prior to repairing the fistula makes the separation of the rectum from the vagina difficult.

### ISP-61-7

**Effects of drospirenone on adhesion molecule expression and monocyte adherence in human endothelial cells** Fumitake Ito, Osamu Takaoka, Yukiko Tanaka, Akemi Koshihara, Hiroshi Tatsumi, Taisuke Mori, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** A major concern in hormone replacement therapy is the associated increased risk of cardiovascular diseases. A progestogen without the unfavorable effects on cardiovascular disease should be explored. Monocyte adhesion to endothelial cells is an important initial event in atherosclerosis. In this study, the effects of the alternative progestogen drospirenone (DRSP) on monocyte adhesion in human umbilical venous endothelial cells (HUVECs) were examined. **Methods** In HUVECs treated with estrogens and progestogens, including DRSP and medroxyprogesterone acetate (MPA), the expression of the adhesion molecules E-selectin, P-selectin, ICAM-1, and VCAM-1 were examined by real-time PCR and using an enzyme-linked immunosorbent assay. A flow chamber system was used to investigate the effects of DRSP on U937 monocytoid cell adherence to HUVEC monolayers. All experimental data were compared using one-way Analysis of Variance. **Results** Upregulation of adhesion molecule mRNA or protein was not seen in HUVECs treated with DRSP alone or with 17 $\beta$ -estradiol+DRSP. DRSP alone, 17 $\beta$ -estradiol+DRSP or ethinylestradiol+DRSP did not increase the number of adherent monocytoid cells to HUVECs in the flow chamber system. However, MPA significantly enhanced the monocytoid cell adherence ( $P < 0.05$ ). **Conclusion** DRSP did not increase the expression of adhesion molecules or monocytoid cell adherence to endothelial cells, indicating that DRSP could reduce the risk of atherogenesis caused by MPA. These results suggest that DRSP may be an alternative to MPA in hormone replacement therapy.

### ISP-61-8

**Levonorgestrel intrauterine system for previous delivery scar defect related postmenstrual bleeding management** Ying-Yi Chen<sup>1</sup>, Yu-Che Ou<sup>1,2</sup> *Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan<sup>1</sup>, Chang Gung Memorial Hospital at Chiayi and Chang Gung University College of Medicine, Taiwan<sup>2</sup>*

**Objective** Abnormal uterine bleeding associated with previous cesarean delivery scar defect (PCDS) have become a serious

problem with the increasing cesarean section rate. The most common bleeding pattern is postmenstrual bleeding. The aim of the present study is to evaluate the efficacy of levonorgestrel (LNG) intrauterine system (IUS) for postmenstrual bleeding treatment. **Methods** This was an observational study performed between May 2007 and February 2017. For patients who experienced postmenstrual bleeding after receiving cesarean section, we performed transvaginal ultrasound and hysteroscopy for evaluation. Treatment options including surgical intervention and LNG-IUS insertion were provided once the PCDS related postmenstrual bleeding was impressed. Total 22 patients chose LNG-IUS were enrolled. The basic background history and the gynecological symptoms of the patients were recorded. Written informed consent was obtained from the participants. **Results** The mean number of previous cesarean sections was  $1.91 \pm 0.61$ . The mean age of the study population was  $43.1 \pm 4.7$  years. 91.3% participants reported clinical improvement. The mean time to improvement was  $7.4 \pm 7.9$  months. The duration of postmenstrual bleeding significantly shortened after LNG-IUS use ( $10.41 \pm 5.98$  days and  $1.09 \pm 3.21$  days,  $p < 0.001$ ). Four patients (18.2%) became amenorrhea after 12 months. No headache, pelvic pain, or increased vaginal discharge was complained by the participants during the observation periods. **Conclusion** LNG-IUS is an effective treatment for PCDS related postmenstrual bleeding. We recommend LNG-IUS usage for patients in perimenopausal status, young patient who desire for childbearing in the future or anyone who asks for conservative treatment instead of surgery.

### ISP-62-1

**Clinical features of Thoracic endometriosis : a series of 25 cases from a single facility** Shinya Fukuda, Tetsuya Hirata, Kazuaki Neriishi, Akari Nakazawa, Miyuki Harada, Yasushi Hirota, Kaori Koga, Osamu Hiraie, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Thoracic endometriosis (TE) is one of the extra-genital endometriosis characterized by the presence of endometrial tissue in thoracic cavity. To clarify the clinical features of TE, we retrospectively studied 25 cases with TE in our hospital. **Methods** Twenty-five cases of TE were diagnosed from 2000 to 2016 in our hospital. The clinical features and management (age, symptom, laterality, prior operation, hormonal therapy and the frequency of relapse) were analyzed retrospectively by reviewing the records of our hospital. This study was approved by the Institutional Review Board of our hospital. **Results** Eighteen cases had catamenial pneumothorax (CP) and seven cases had catamenial hemoptysis (CH). The age of patient was significantly higher in CP compared to CH (36.8 vs 29.6 years old,  $P < 0.05$ ) and 16 cases (88.9%) of CP were right-sided, but CH cases showed no significant tendency in laterality. Nine cases (50%) in CP relapsed and one (14%) in CH. As for CP, the recurrence rate was 66.7% (2/3) in the patients without operation and 46.6% (7/15) even after operation. Hormonal therapy was performed in 16 cases with CP (89.9%). And four cases (4/16, 25%) relapsed in the patients with hormone therapy, whereas seven cases (7/16, 43.8%) relapsed in the patients without hormone therapy. **Conclusion** Considering the difference between CP and CH, we might hypothesize that pathogenesis of CP and CH can be distinctly categorized. Improvement of management strategy in CP is required because the recurrence rate of CP symptoms after treatment is high.

### ISP-62-2

**Alteration of coagulation status in the patients with endometriotic cysts** Kanoko Shoji, Fumihisa Chishima, Takahiro Nakajima, Takehiro Nakao, Erina Kato, Hiromitsu Azuma,

Chuyu Hayashi, Go Ichikawa, Atsushi Komatsu, Yasuji Miyakawa, Shinichi Takada, Kei Kawana *Nihon University Itabashi Hospital*

**Objective** Occurrence of cardiovascular morbidity ; myocardial infarction, and angina has been reported in the patients with endometriosis. Slight alteration in coagulation and fibrinolysis parameters have been noted in patients with endometriosis supports a potential hypercoagulable status in the patients with endometriosis. It has not been obtained confirmative views association of hypercoagulation in the patients with endometriosis, although some researchers suggests that active phase of the disease is associated with blood hypercoagulability. This study aimed at evaluating some variables of coagulation status and inflammatory markers in patients with endometriosis. **Methods** In a case control study, 39 patients with endometriosis and 17 patients without endometriosis were evaluated. Informed consent were obtained from all patients. The routine preoperative included complete blood count parameters, C-reactive protein, platelet (Plt), Plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), PT, PT ratio, APTT, APTT ratio. **Results** In patients with endometriosis, White blood cell counts, values of MPV, and PT were significantly higher when compared to control group ( $p < 0.05$ ,  $p < 0.0001$ , and  $p < 0.05$ , subsequently). **Conclusion** Alteration of the local coagulation system, in addition to inflammation may have an important role in the pathogenesis of endometriosis.

### ISP-62-3

**Laparoscopic cystectomy of endometrioma (LC) followed by oral contraceptives (OC) until conception is desired ; will this sustain later fecundability?** Arisa Takeuchi, Kaori Koga, Erina Satake, Tomoko Makabe, Mariko Miyashita, Gentaro Izumi, Masashi Takamura, Miyuki Harada, Tetsuya Hirata, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

**Objective** Laparoscopy enhances fecundability in patients with endometriosis ; however, the effect declines as the post-operative time goes by, and this decline discourages patients with endometrioma who do not wish immediate childbearing from undergoing laparoscopy. Post-operative use of oral contraceptives (OC) reduces recurrence of endometrioma after laparoscopic cystectomy (LC) ; however, its effect on later fecundability is unknown. To test our hypothesis : LC followed by OC sustains later fecundability, we conducted the following study. **Methods** Under IRB approval, 107 patients who underwent LC between 2009 and 2012, and have wished conception, and were followed-up for at least 24 months after LC, were retrospectively analyzed. According to the point of arising a wish for pregnancy, patients were divided into two groups : right after LC (Group A, n=83), and right after the discontinuation of post-operative OC (Group B, n=24). The cumulative pregnancy rate and the time to pregnancy were compared between groups. **Results** The cumulative pregnancy rate in Group B (54.2%) was equivalent to that in Group A (56.6%). Similarly, the time to pregnancy in Group B ( $12.8 \pm 7.3$  months, mean  $\pm$  SEM) was comparable with that in Group A ( $11.7 \pm 9.3$ ). **Conclusion** The pregnancy rate and the time to pregnancy were comparable between two groups, which suggests that the fecundability did not decline after LC followed by post-operative OC. This finding encourages patients with endometrioma who do not wish immediate childbearing to undergo LC followed by OC.

### ISP-62-4

**Dienogest therapy at the early stages of recurrence of endometrioma following primary surgery suppresses the aggravation of the disease** Akemi Koshihara, Taisuke Mori, Hiroyuki

Okimura, Hisashi Kataoka, Osamu Takaoka, Fumitake Ito, Izumi Kusuki, Jo Kitawaki *Kyoto Prefectural University of Medicine*

**Objective** In management of patients with endometriosis, preventing the recurrence of lesions and symptoms after primary conservative surgery is important to avoid additional surgeries and preserve fertility. The purpose of this retrospective study was to evaluate whether endocrine therapy immediately after post-surgical recurrence of ovarian endometrioma suppresses aggravation of the disease and reduce the necessity of second-line surgeries. **Methods** We enrolled 146 patients treated for endometrioma at our hospital between 2009 and 2015. After laparoscopic cystectomy using the stripping technique, opening of cul-de-sac obliterations, and complete resection of deep infiltrating endometriosis lesions, the patients received no treatment (n=83), an oral contraceptive (OC, n=32), or dienogest (n=27) depending on their medical background, and were followed up every 3 months. Those that developed recurrence of endometrioma immediately received dienogest, OC, or gonadotropin-releasing hormone agonist. **Results** Of the 16 cases with endometrioma recurrence (12 in the non-treatment group, 3 in the OC group, and 1 in the dienogest group), complete or partial resolution was achieved in 10 of the 11 cases treated with dienogest and one case with gonadotropin-releasing hormone agonist. However, there was no improvement in the 3 patients who received OC, and 1 of whom underwent secondary surgery. **Conclusion** Dienogest therapy at the early stage of post-surgical endometrioma recurrence appears to be a viable option to reduce the necessity of repeated surgery. It may also aid with conserving the ovarian reserve and maintain fertility in patients with endometriosis.

### ISP-62-5

**Validity of management against the endometriotic cyst : a retrospective study** Takeharu Kido, Tomoko Tsuzuki, Naoko Kida, Maiko Kobayashi, Yoji Hisamatsu, Hiromi Murata, Tomomi Mizokami, Masato Kita, Hidetaka Okada *Kansai Medical University*

**Objective** Endometriosis causes dysmenorrhea, infertile and malignancy in reproductive women. The aim of this study was to investigate the factors that indicate clinical management against the endometriotic cyst. **Methods** We researched retrospective records of 104 patients (mean age : 36) with the endometriotic cyst between June 2014 and December 2016. A surgery group was 41 patients and a non-surgery group was 63 patients. In the surgery group, 24 patients received medication before surgery and 21 patients received medication after surgery. **Results** Maximum diameter of the endometriotic cyst was significantly larger in the surgery group than in the non-surgery group ( $74.2 \pm 44.8$ mm vs  $45.6 \pm 18.9$ mm,  $p < 0.05$ ). Age was also higher ( $38.8 \pm 8.1$ years old vs  $33.2 \pm 5.9$  years old,  $p < 0.05$ ). There was no differences between the presence of subjective and maximum diameter of the endometriotic cyst ( $57.1 \pm 36.8$ mm vs  $57.7 \pm 28.5$ mm,  $p=0.6$ ). No significant association was observed between the presence of subjective and medication before surgery ( $p=0.91$ ). Medication after surgery was also no differences ( $p=0.54$ ). **Conclusion** The results of present study showed surgical indication is affected by tumor size and age because of malignancy risk. Management of endometriosis treatment is needed to select medication before and after surgery whether desiring to bear children.

### ISP-62-6

**Long-term dienogest administration in patient with symptomatic adenomyosis** Kazuaki Neriishi, Tetsuya Hirata, Shinya Fukuda, Gentaro Izumi, Akari Nakazawa, Miyuki Harada,

Yasushi Hirota, Kaori Koga, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*

**Objective** Adenomyosis is a common gynecological disorder that causes dysmenorrhea, hypermenorrhea, and metrorrhagia. Previously, we reported that 24 weeks of dienogest treatment is highly effective for pain in symptomatic adenomyosis. In this retrospective cohort study, we investigated the course of long-term dienogest treatment in patients with symptomatic adenomyosis. **Methods** The study protocol was approved by the Institutional Review Board of our hospital. This was a retrospective cohort study. The outcomes of a total of 18 cases were investigated using the medical records. Dienogest was continuously administered at a dose of 1mg twice daily. The main study variables were the visual analog scale score of adenomyosis associated pain, blood test (levels of hemoglobin (Hb), CA125, and E<sub>2</sub>) and the size of uterus. MRI was performed at baseline in all cases, which were categorized according to previously reported criteria based on the MRI exam (Kishi et al.). **Results** Twelve of 18 patients (66.7%) received dienogest until menopause or for a period of >80 months. Four cases (22.2%) discontinued dienogest treatment because of severe metrorrhagia. A comparison between cases with long-term use and those who discontinued treatment because of severe metrorrhagia showed a significant difference in hemoglobin level at baseline, pain score for dysmenorrhea at baseline, and the frequency of type 2 adenomyosis. Moreover, long-term dienogest use showed that serum estradiol level did not decrease. **Conclusion** Our report suggests that dienogest is tolerable for long-term use and may be an alternative treatment option in some patients to avoid hysterectomy.

### ISP-62-7

**Unusual hyper-inflammatory degeneration of adenomyosis after cesarean section** Atsushi Fusegi, Yoshie Oka, Yuno Ariyama, Osamu Yasui, Minako Matsuda, Momoko Ozawa, Kotoi Tsurane, Tsutomu Ida, Kazunori Koike, Yoshimi Taniguchi, Akira Kohyama *Tokyo Metropolitan Tama Medical Center*

Although pregnancy rates in patients with adenomyosis have risen due to the progress of infertility treatment, the adverse pregnancy outcomes associated with adenomyosis are unclear. We report a case in which unusual degeneration of adenomyosis occurred after a cesarean section (CS) and caused hyper-inflammatory. A 40-year-old (gravida 1, para 0) Japanese woman who was 27 weeks pregnant was transferred to our hospital due to premature threatened delivery. Ultrasound disclosed a 6 cm thickness of the uterine anterior wall. We diagnosed adenomyosis during pregnancy based on magnetic resonance imaging. We tried to maintain the pregnancy using tocolytic agents. At 31 weeks the patient had hypertension and the baby's growth was restricted. At 33 weeks and 3 days we conducted a CS due to non-reassuring fetal status. A 1,334 g infant was delivered. Postsurgically, the patient's hyper-inflammatory status and tendency to bleed continued. Uterine enlargement and a hematoma around the CS wound were found on computed tomography. Antibiotics were ineffective in reducing the inflammation. We performed a hysterectomy and removed the hematoma on postoperative day 5. Thereafter the patient's inflammatory status improved quickly. On histological examination decidual change in the adenomyosis with invasion of inflammatory cells was detected in a wide area of the uterus, part of which had become necrotic. Our case demonstrated an unusual degeneration of the adenomyosis occurring after delivery and causing hyper-inflammatory. Hysterectomy was a fast and effective treatment method. This case showed that degeneration of adenomyosis should be included in the differential diagnosis of post-CS hyper-inflammatory.

### ISP-62-8

**Analysis of clinical problems in medical treatment for adenomyosis** Minako Koizumi, Takahiro Hino, Yu Takahashi, Masakazu Sato, Nao Itaoka, Chiharu Ueshima, Maki Nakata, Yoko Hasumi *Mitsui Memorial Hospital*

**Objective** Although medical treatment for adenomyosis has not been established, Dienogest and levonorgestrel-releasing intrauterine system (LNG-IUS) are often chosen for symptoms including pain and abnormal uterine bleeding. We aimed to clarify the clinical problems of both treatments. **Methods** A retrospective study was designed covering 38 patients who were treated with Dienogest (Group A : 18 cases) or LNG-IUS (Group B : 21 cases) between January 2015 and August 2017. We investigated the clinical backgrounds and the reasons of discontinuation. Only one patient received both treatments. **Results** Patients' age in group A and B was  $43.8 \pm 4.9$  and  $42.7 \pm 6.8$ , respectively. The observation period was  $11.9 \pm 7.2$  months in group A and  $11.6 \pm 10.1$  months in group B. The number of patients who were treated previously was as follows : 13 cases (72.2%) in group A (GnRHa : 10 cases, LEP : 3 cases), and 9 cases (45%) in group B (GnRHa : 3 cases, Dienogest : 6 cases). Three patients in group A (16.7%) and six patients in group B (30%) discontinued the medication due to the following reasons : we observed 3 cases with severe atypical bleeding in group A, including one case in which transfusion and hysterectomy was required. We also observed 4 cases with atypical bleeding in group B, including 3 cases in which hysterectomy was required and one case in which transfusion was required. Furthermore, we ceased LNG-IUS treatment because of general fatigue in 2 cases. **Conclusion** We experienced several cases of severe atypical bleeding during medical treatment for adenomyosis. It is necessary to consider and inform the benefits and limitations.

### ISP-62-9

**Cystic adenomyoma uteri confused with LEGH in Diagnosis** Yoko Tsuzuki, Shinichiro Wada, Masae Yamamoto, Kanako Takimoto, Kaoru Minowa, Risa Tsunematsu, Kazuaki Imai, Hajime Ota, Ayako Nakajima, Takuma Matsuda, Yoshiyuki Fukushi, Takafumi Fujino *Teine Keijinkai Hospital*

Cystic lesions of uterus are rarely seen, in approximately 0.035% of all uterine tumors. A cystic adenomyoma is one of them and a benign neoplasm composed of endometrial-type glands and stroma with well-formed smooth muscle bundles. We report a case of multiple cystic uterine adenomyoma confused with Lobular endocervical glandular hyperplasia (LEGH) in diagnosis before operation with a review of the literature. A 36-year-old woman (gravida 4, para 1) presented to our hospital complaining of abdominal distension without dysmenorrhea. MRI revealed multiple cystic lesions, approximately 8cm in diameter, were located at corpus uteri to upper side of cervix uteri. Those cysts showed a high intensity on T2 weighted image and a low intensity on T1. Diffusion weighted image and apparent diffusion coefficient map did not show malignant findings. The result of uterine cervical biopsy was cervical squamous intraepithelial neoplasia 3 (CIN3). We preoperatively diagnosed it as LEGH and CIN 3. As she did not desire fertility preservation, we performed total laparoscopic hysterectomy and bilateral salpingectomy. The pathological diagnosis was adenomyoma of corpus uteri and CIN 3. She discharged uneventfully on the postoperative third day in good condition.

### ISP-63-1

**The size of endometrial polyps as predictors of spontaneous vanishing prior to surgical procedures : a retrospective analysis of hysteroscopic endometrial polypectomy** Eriko Yano, Wataru Isono, Yasunori Komatsu, Michiko Honda, Hiroko

Tsuchiya, Reiko Matsuyama, Akira Tsuchiya, Akihisa Fujimoto, Osamu Nishii *Teikyo University Hospital, Mizonokuchi*

**Objective** It is sometimes observed that endometrial polyps become unclear or even vanish by the time of operation when they were previously visible at the time of diagnostic hysteroscopy in the office setting. The objective of our study is to elucidate the clinical factors that influence the vanishing of endometrial polyps. **Methods** The medical records of 300 cases of hysteroscopic endometrial polypectomy from January 2015 to December 2017 in our hospital were retrospectively reviewed following the approval of our institution's review board. We defined cases of interest as "vanished polyp," in which the target polyp was not detected clearly by transvaginal ultrasound just before operation. As factors that contribute to "vanished polyp," we extracted the following 10 characteristics: "advanced age" ( $\geq 40$  years), "small polyp size" ( $\leq 10$  mm), "large body mass index" ( $\geq 22$ ), "multiparity," "presence of multiple polyps," "infertility," "dysmenorrhea," "abnormal bleeding," and "hormonal drug use." Statistical multivariate analysis was performed. **Results** From the 300 cases, we extracted data of 184 cases, in which the size of polyps from both before and after hospitalization were available. Ten cases of "vanished polyp" were identified. In a multivariate analysis of the 10 factors, only "small polyp size" showed a significant difference (odds ratio=6.8,  $P < 0.05$ ). **Conclusion** Our study revealed the possibility that endometrial polyps smaller than 10 mm may spontaneously vanish without surgical assistance, regardless of the number of the polyps or symptoms present. This insight may contribute to reducing the unnecessary scheduling of surgery.

### ISP-63-2

**Analysis of the effect of microwave endometrial ablation for dysmenorrhea** Yoshinobu Hamada<sup>1</sup>, Teppei Ichikawa<sup>1</sup>, Yasumasa Koroku<sup>1</sup>, Kanami Saito<sup>1</sup>, Naoki Yoshikawa<sup>1</sup>, Yoko Saito<sup>1</sup>, Taichi Irie<sup>1</sup>, Kayo Suzuki<sup>1</sup>, Makoto Iizuka<sup>1</sup>, Kouhei Sugimoto<sup>2</sup>, Shuichi Sakamoto<sup>1</sup>, Satoshi Takakura<sup>1</sup> *Dokkyo Medical University Saitama Medical Center<sup>1</sup>, Reproduction Center Dokkyo Medical University Saitama Medical Center<sup>2</sup>*

**Objective** Microwave endometrial ablation (MEA) alleviates the symptoms of menorrhagia. The efficacy of MEA for dysmenorrhea is controversial. We performed the retrospective analysis to evaluate the efficacy of MEA for dysmenorrhea. **Methods** Twelve patients who were treated with MEA for menorrhagia between April 2012 and June 2017 and could be checked the condition of menorrhagia and dysmenorrhea 3-6 months after MEA according to medical records were investigated. We compared age, preoperative hemoglobin, uterine length, times of ablation, vertical diameter, anteroposterior diameter and transverse diameter of uterine body between the patients with alleviation of dysmenorrhea and the patients with no alleviation. Mann-Whitney U test was used. **Results** Menorrhagia was improved in all patients. In 9 patients dysmenorrhea was alleviated, diffuse adenomyosis was present in 6 patients and uterine myoma was present in 3 patient. The rate of improvement of dysmenorrhea was 75% (9/12). Between 9 patient with alleviation of dysmenorrhea and 3 women without alleviation, no significant difference was observed in age ( $45.1 \pm 2.4$  vs  $41.0 \pm 2.6$ ), preoperative hemoglobin ( $9.3 \pm 1.9$  g/dl vs  $9.8 \pm 1.9$  g/dl), uterine length ( $8.4 \pm 1.4$  cm vs  $8.8 \pm 1.3$  cm), times of sounding ( $6.4 \pm 2.8$  vs  $8.0 \pm 1.7$ ), anteroposterior diameter ( $61.4 \pm 20.7$  mm vs  $74.9 \pm 20.7$  mm), transverse diameter ( $66.0 \pm 12.3$  mm vs  $70.2 \pm 5.0$  mm). The vertical diameter of patients with alleviation of dysmenorrhea was shorter than that of patients without alleviation, significantly ( $56.4 \pm 8.5$  mm vs  $79.7 \pm 17.3$  mm,  $p < 0.01$ ). **Conclusion** In case of menorrhagia with short vertical diameter of uterine body, the short-term efficacy of MEA for dysmenorrhea may be

expected.

### ISP-63-3

**Two cases of combined medical and surgical management of rudimentary uterine horn pregnancy** Daisuke Suzuki<sup>1</sup>, Toshifumi Takahashi<sup>1</sup>, Satoshi Suzuki<sup>2</sup>, Manabu Kojima<sup>2</sup>, Shu Soeda<sup>2</sup>, Hideki Mizunuma<sup>1</sup>, Keiya Fujimori<sup>2</sup> *Fukushima Medical Center for Children and Women<sup>1</sup>, Fukushima Medical University<sup>2</sup>*

**Background** A pregnancy within a noncommunicating rudimentary uterine horn pregnancy (NCRHP) is a rare entity, with a frequency of 0.24% to 0.6% of all ectopic pregnancies. We report two cases of noncommunicating rudimentary horn pregnancy that were medically terminated, with the patients subsequently undergoing uterine horn and fallopian tube resection. **Case report** Case 1. The patient was a 19-year-old nullipara. She was considered to have a missed abortion, and had 2 gestational sacs (GSs) without heartbeats at 8 weeks' gestation. Because the gestational sacs remained intact during curettage, she was diagnosed with NCRHP. Her serum level of human chorionic gonadotropin (hCG) was 40,199 mIU/ml. After methotrexate injections into the GSs, 2 courses of systemic methotrexate were administered. Laparoscopic surgery was performed on day 106 after the initial methotrexate treatment. The left rudimentary horn and fallopian tube were successfully excised, with minimal bleeding. Case 2. The patient was a 30-year-old nullipara. She was diagnosed with a left unicornuate uterus with right noncommunicating rudimentary uterine horn by hysterosalpingography and magnetic resonance imaging. As 1 GS with heartbeat was observed in the right rudimentary uterine horn at 6 weeks' gestation, she was diagnosed with NCRHP. Her serum level of hCG was 104,619 mIU/ml. A single methotrexate injection into the GS was administered. Laparoscopic surgery was performed on day 50 after the initial methotrexate treatment. The right rudimentary horn and fallopian tube were successfully excised with minimal bleeding. **Conclusion** Combined methotrexate treatment and laparoscopic surgery for patients with NCRHP is safe and effective.

### ISP-63-4

**Less invasive and easier vaginoplasty using laparoscopy and atelocollagen sponge** Yoshiya Miyahara, Mizuki Uenaka, Satoshi Nagamata, Kaho Suzuki, Senn Wakahashi, Yasuhiko Ebina, Hideto Yamada *Kobe University*

**Objective** The purpose of this study was to validate the therapeutic efficacy of the innovative surgical approach using laparoscopy and atelocollagen sponge, and the commercialized mould on the achievement of a satisfactory neovagina in patients with vaginal agenesis. **Methods** The current study involved six patients diagnosed as having Mayer Rokitansky Kuster Hauser syndrome. At first, the exploration of the pelvic and abdominal organs was performed carefully by laparoscopy. Then, after creating a vaginal tunnel, the commercialized mould wrapped with atelocollagen sponge was placed within the neovagina. The mould was started to insert into the neovagina at 7 days after operation. Since this mould was easier to manage compared with the previous methods using colon, it was less stressful for the patients and doctors to master the procedure after operation. **Results** Median operation time was 116 minutes and median blood loss was 75 ml. Median hospital stay was 22 days. The median length of the neovagina at discharge was 8 cm with two fingers in width in all patients. No remarkable postoperative complications were noted. At two months after surgery, the neovagina was confirmed to be completely epithelialized in all patients, assessed by Schiller test. **Conclusion** This innovative surgical procedure using laparoscopy and the mould



wrapped with atelocollagen sponge may be a more useful and easier approach for the treatment of vaginal agenesis.

### ISP-63-5

**The efficacy of laparoscopic omentectomy in patients with gynecological cancer** Risa Yoshimoto, Hatsuo Isogai, Takuji Ueno, Takuma Yamada, Takehiko Takeda, Kaname Uno, Sho Tano, Mayu Ukai, Tepei Suzuki, Toko Harata, Yasuyuki Kishigami, Hidenori Oguchi *TOYOTA Memorial Hospital*

**Objective** Omentectomy should be performed in patients with ovarian cancer and borderline ovarian tumor. But laparotomy with omentectomy often requires extending abdominal incision. The purpose of this study was to evaluate the efficacy of laparoscopic omentectomy (LOM). **Methods** This was a single center prospective cohort study. Patients with gynecologic cancer between January 2016 and March 2017 were eligible for this study. We analyzed the operative time, omental weight, the amount of blood loss, and complications. **Results** Twenty-four patients were enrolled for this study. The mean age was 51.3 years, and the mean BMI was 22.2 kg/m<sup>2</sup>. The prevalence of ovarian cancer, borderline ovarian tumor, cervical cancer, ovarian and cervical cancer, peritoneal cancer, and ovarian and endometrial cancer were 12, 5, 2, 2, and 1, respectively. Laparoscopic surgery was performed in 8 patients and the other 16 patients underwent both laparotomy and LOM. All patients were performed laparoscopic subtotal omentectomy, and visualization and magnification of small lesions such as hepatic and splenic flexure were better than laparotomy. The mean operative time of LOM was 41.5 minutes, the omental weight was 189.5g, and the estimated blood loss during LOM was small amount. All surgery could be accomplished without extending the incision to the upper abdomen, and no patient experienced intraoperative and postoperative complications. The mean hospital stay was 7.6 days. One patient of serous borderline tumor had peritoneal implant. **Conclusion** LOM is comparatively safe and an effective treatment for the patients with ovarian cancer and borderline ovarian tumor.

### ISP-63-6

**Two cases of surgically treated genital chronic graft-versus-host disease in females** Yasuhiko Kamada<sup>1</sup>, Yuri Miyahara<sup>1</sup>, Hirofumi Matsuoka<sup>1</sup>, Shiho Fujita<sup>1</sup>, Kotaro Kubo<sup>1</sup>, Toru Hasegawa<sup>1</sup>, Ai Sakamoto<sup>1</sup>, Sayoko Kotani<sup>1</sup>, Mikiya Nakatsuka<sup>2</sup>, Hisashi Masuyama<sup>1</sup> *Okayama University Hospital<sup>1</sup>, Okayama University<sup>2</sup>*

Allogenic hematopoietic stem cell transplantation (HSCT) is a crucial treatment for hematological malignancy. Gonadal dysfunction occurs at an early stage after HSCT, and such cases may require hormone replacement therapy (HRT). Genital chronic graft-versus-host disease (GVHD) is another complication post-HSCT. It starts with vulvar discomfort and dysuria due to erosions, fissures, and ulcers, subsequently progressing to dyspareunia and difficulty with penetration due to vaginal stenosis and obstruction. Surgical interventions are occasionally necessary in women with genital chronic GVHD to enable continuation of HRT and facilitate sexual intercourse. We report on two women who underwent surgery for vaginal obstruction due to genital chronic GVHD. **Case 1** A 22-year-old Japanese woman was referred to us for treatment of hematoocolpos. She had received HSCT for acute myelogenous leukemia at the age of 19 years. Her labia minora were fused in the midline. Magnetic resonance imaging (MRI) revealed that the lower two-thirds of the vagina were closed. She underwent vaginoplasty using an artificial dermis (an atelocollagen sponge). She could have sexual intercourse 4 months after surgery. **Case 2** A 24-year-old Japanese woman was referred to us for hematometra

and hematoocolpos. She had received HSCT for acute lymphoblastic leukemia at the age of 18 years. Her vulvar synechia was firm. MRI revealed that the lower one-third of the vagina was closed. She underwent vulvar adhesiolysis and removal of vaginal blood. Laparoscopically assisted vaginal reconstruction by Granjon's method was performed three months later. We believe that her condition has resolved.

### ISP-63-7

**A retrospective review of re-laparoscopy cases due to post-operative bleeding after laparoscopic surgery : Sequential monitoring of intra-abdominal drainage volume and vital sign trend for prompt diagnosis and intervention** Keisuke Murakami<sup>1</sup>, Rie Ozaki<sup>1</sup>, Ayako Masuda<sup>1</sup>, Shinichiro Ikuma<sup>1</sup>, Makoto Jinushi<sup>1</sup>, Keiji Kuroda<sup>1</sup>, Jun Kumakiri<sup>2</sup>, Mari Kitade<sup>1</sup> *Juntendo University Hospital<sup>1</sup>, Tokyo Women's Medical University Hospital<sup>2</sup>*

**Objective** Postoperative bleeding is rare, but one of a serious complication. Prompt diagnosis and intervention are crucial. In this study, we aimed to identify signature of re-laparoscopy cases and then clarify value of monitoring drainage volume and vital sign trend for prompt diagnosis and intervention. **Methods** Among 5,438 cases who underwent laparoscopic surgery for gynecologic benign pathologies at our institution between 2009 and 2016, twelve cases (0.2%) required re-laparoscopy for postoperative bleeding. Initial surgical findings and postoperative drainage volume and vital sign trends were reviewed. Relatively large drainage volume cases (total drainage volume at postoperative 12 hours >300ml) who did not necessitate re-laparoscopy were included for comparison (n=107, 2009-2016). **Results** Initial surgery of re-laparoscopy cases were uterine surgery (n=8, myomectomy ; 7, hysterectomy ; 1), adnexal surgery (n=3), uterus and adnexal combined surgery (n=1). Bleeding sites were uterus (n=6), adnexa (n=4), trocar wound (n=1), mesentery suspected to be injured by first trocar approach (n=1). Ten cases were successfully controlled hemorrhage by re-laparoscopy, however, two cases in shock vital required further intervention (laparotomy or arterial embolization). Continuous excessive drainage was observed in re-laparoscopy cases, whereas excessive drainage was transient in cases without re-laparoscopy. Vital sign monitoring could not distinguish both groups in early stage. **Conclusion** Re-laparoscopy is useful approach for postoperative bleeding. In cases with continuous excessive drainage, intervention should be undergone immediately before going into hemorrhagic shock.

### ISP-63-8

**Two cases of perineal plastic operation for patients of persistent cloaca** Mayu Nagata<sup>1</sup>, Kana Hiasa<sup>1</sup>, Keiko Kawamura<sup>1</sup>, Teruhiko Kawamura<sup>1</sup>, Natsuko Yokota<sup>1</sup>, Katsuko Egashira<sup>1</sup>, Kiyoko Kato<sup>1</sup> *Kyushu University<sup>1</sup>, University of Occupational and Environmental Health<sup>2</sup>*

**Objectives** Persistent cloaca is rare congenital anorectal malformation. Usually, multiple surgical procedures are required during the childhood for the correction of complicated problems. We herein report two cases of perineal plastic surgery during the long-term follow of persistent cloaca. **Case1** A 27-year-old woman had undergone proctoplasty and vaginal plastic surgery as an infant. After menarche, vaginal dilation was performed by prosthesis. Before her marriage, she elected to receive dilatation of vaginal and perineal plastic surgery. First, we designed bilateral gluteal fold flaps, 8×3 cm, along with preserved perforating branch of the perineal artery. We then rotated the flaps 120° and covered around the vaginal introitus. The postoperative course was normal. **Case2** A 23-year-old woman had undergone urethral and a vaginal plastic surgeries many times in childhood.



After menarche, vaginal dilation was performed by prosthesis. She received vaginal and perineal plastic surgery similar to case1, with a gluteal fold flap designed at the left side of body. After operation, the wound was ravaged and antibiotics was administered, due to the infection of the wounded area. The subsequent postoperative course was normal. **Conclusion** The case of infant persistent cloaca aims to achieve bowel control and urinary control. It is important to consider the prospect of a patient's marriage or their sexual function.

### ISP-63-9

**Tumorectomy for gynecological cancer recurrence : case series** Sen Wakahashi, Yasuhiko Ebina, Kaho Suzuki, Yoshiya Miyahara, Hideto Yamada *Kobe University Hospital*

**Objective** We report single-institution clinical outcomes of women treated with tumorectomy for gynecological cancer recurrence. **Methods** From 2004 to 2016, 20 patients were treated with tumorectomy and retrospectively analyzed. Primary cancer diagnoses were 9 ovarian, 4 endometrial, 4 cervical, 1 tubal, and 2 uterine sarcomas. The median age of the patients was 65 years (range, 38 to 83 years). The complete resection rate and survival were analyzed. Progression-free survival (PFS) was determined using Kaplan-Meier analysis. **Results** Median follow-up was 17 (range, 2-55) months. Recurrence locations were 40% pelvic cavity, 15% lung, Liver, 15% paraaortic node, and 5% inguinal node. We achieved in 75% a complete resection, and 55% of patient underwent treatment with after resected chemotherapy. In univariate analysis, age, cancer type (cervix, endometrial or ovary) were not associated with PFS. Whereas chemotherapy-free interval (defined as the time from the date of last chemotherapy to that of tumolectomy for recurrence) and received or not after resected chemotherapy tended to be associated with prognosis ( $P < 0.01$ , and  $P = 0.06$ , respectively). **Conclusion** The tumorectomy is effective local treatment modality in patients with gynecological cancer recurrence. Distant progression remains the primary mode of failure in this patient population. In carefully selected patients, a combination of systemic treatment and tumorectomy may offer long-term PFS.

### ISP-63-10

**Women with Acute Abdomen and its Laparoscopic Management — Senerio in Developing country** Jyoti Chaube<sup>1</sup>, Mahendra Bhusari<sup>1</sup>, Sanjay Chaube<sup>1</sup>, Manish Jain<sup>2</sup>, Rajkumar Verma<sup>2</sup> *St. Jude's Hospital, India<sup>1</sup>, M L B Medical College, Jhansi, India<sup>2</sup>*

Gynecological emergency are majority four diseases ectopic gestation, torsions of adnexa, rupture of ovarian tumour and ovarian bleeding. Diagnostic modalities are inconclusive some time or not available. laparotomy was the main option for the treatment. Laparoscopy was used to confirm the findings of the imaging modalities and as therapeutic option in patients of gynecological emergency. Laparoscopic management was performed in 98 cases during a period of five years. In majority of cases ectopic gestation was the cause. In 8 patients twisted adnexa was there. Except two all were managed with laparoscopic method. Laparoscopy is a good modality to tackle the patients of acute abdomen of gynecological causes.

### ISP-64-1

**Subserosal Leiomyoma Complicated with Peritoneal Cysts Difficult to Differentiate from Brenner tumor of the Ovary** Masafumi Katakura<sup>1</sup>, Takehiko Tsuchiya<sup>1</sup>, Tomoko Taniguchi<sup>1</sup>, Junya Sakuma<sup>1</sup>, Masaru Nagashima<sup>1</sup>, Youhei Takano<sup>2</sup>, Yoshihiro Yoshida<sup>2</sup>, Youichi Matsue<sup>2</sup>, Toshimitsu Maemura<sup>1</sup>, Masahiko Nakata<sup>1</sup>, Yukiko Katagiri<sup>1</sup>, Mineto Morita<sup>1</sup> *Toho University Omori Medical Center<sup>1</sup>, Tokyo Rosai Hospital<sup>2</sup>*

It is difficult to discriminate between pedunculated subserosal leiomyoma and solid ovarian tumor occasionally. Because of pedunculated subserosal leiomyoma frequently grew in the direction of the adnexal lesion. We reported that a case of pedunculated subserosal leiomyoma complicated peritoneal cyst difficult to differentiate from Brenner tumor of the ovary. A 53 year-old woman, G2P2. The menstrual cycle is irregular. The patient was found to have the pelvic mass, but she did not seek medical treatment. Her chief complaint was low back pain. The pain was getting worse and worse as the day went on. She was referred to our hospital for further evaluation by her local physician for a huge pelvic mass by ultrasonography test. Magnetic resonance imaging (MRI) test showed that 22 cm pelvic mass at right adnexal area within complex solid and cystic mass. Her serum tumor markers were within normal limits. These findings suggested that subserosal myoma, ovarian mutinous tumor or Brenner tumor. After GnRH agonist for 2 months, the operation was undergone. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was undergone. Total specimen weight was 2,390 g. The postoperative course was uneventful. Pathological examination revealed that pelvic mass was Leiomyoma. Bilateral adnexa had no structural disorder. Peritoneal cysts might have been adhesive caused by pedunculated subserosal leiomyoma. Leiomyoma caused inflammation. It is difficult to differentiate a mass at the adnexal lesion complicated with solid and cystic tumor. Therefore it is necessary to determine the management of these findings carefully.

### ISP-64-2

**A case of Leiomyomatosis peritonealis disseminata (LPD)** Kana Kasai, Takeshi Kato, Yuri Kadota, Kanako Yoshida, Minoru Irahara *Tokushima University*

Leiomyomatosis peritonealis disseminate (LPD) is a rare disorder characterized by peritoneal dissemination of benign smooth muscle nodule. Most cases occur in individuals of reproductive age and often associated with pregnancy or oral contraceptive use. Treatment is tumorectomy, but there is no consensus on postoperative treatment. This disease is considered to be an estrogen-dependent disease, and there are also papers that recommend GnRH agonist therapy. A 36-year-old woman of gravida 2 para 2 was introduced to our clinic for lower abdominal pain. She had no history of abdominal surgery or hormone therapy. MRI revealed large myoma uteri, and simple total hysterectomy was performed. There were multiple myoma, and many nodular tumors were disseminated on the greater omentum, mesentery and Douglas' pouch. Both ovaries were normal. We suspected a malignant tumor, submitted a tumor of the peritoneum to the rapid examination, but it was the result with leiomyoma. Simple hysterectomy was performed and disseminated lesions were also extracted within a possible range. Since every tissues were leiomyoma in postoperative histopathology, this case was confirmed as LPD. In postoperative CT, disseminated masses of 1 cm in size were found in the peritoneum and Douglas' pouch, but no hematogenous metastasis was observed. Although we recommended GnRH agonist therapy, patients did not wish and follow-up observation, but slightly increase in tumor mass is recognized.

### ISP-64-3

**Effect of uterine artery embolization using by microspheres : review of 129 cases** Gen Ishikawa<sup>1</sup>, Yasunori Taki<sup>2</sup>, Kimisato Asano<sup>3</sup> *Nippon Medical School<sup>1</sup>, Chofu Keijinkai Clinic<sup>2</sup>, Artemis Women's Hospital<sup>3</sup>*

**Introduction** After the year 2014, when use of microspheres for uterine artery embolization (UAE) came to be covered by insurance, number of procedure of UAE has been increased gradu-

ally in Japan. **Methods** Between April and August 2016, the hospital records of our facility who underwent UAE were retrospectively reviewed. **Results** During study period, 129 cases received UAE, and their median age was 44 years (range 35–53). All cases were received UAE in complete. Forty eight cases were undertaken UAE by using only microsphere, in other 81 cases, they were given gelatin sponge additionally. In 48 cases who were undertaken UAE by using only microsphere, their median age was 44.5 years and 75% of them were nulliparous. The median dose of microsphere was 4.5 vials (range 1.6–13.0), fluoroscopy time was 14.3 minutes (range 7.7–27.0) and exposure dose was 483.3 mGy (range 193.0–1384.4). Between preoperative period and 1-year follow-up, uterine volume was evaluated by MRI. The percent reduction in uterine volume was 44.2% (range 13.9–82.4). In those 48 cases, 28 cases were evaluated serum estradiol in 3 points (preoperative, 1-month and 1-year follow-up). As those results, percent change of serum estradiol showed 69.9% at one month after and 77.8% at one year after. **Conclusion** We showed clinical features and outcome of uterine fibroids cases who underwent UAE by using microspheres in the manner of single institutional retrospective study. In all cases, there was no major adverse event, and they received beneficial outcomes.

#### ISP-64-4

**Treatment outcomes of uterine artery embolization with microspheres for symptomatic fibroids : a single-center experience** Kyoso Ishida, Kenjiro Sawada, Aasa Shimizu, Masaki Kobayashi, Eriko Yokoi, Akihiko Yoshimura, Erika Nakatsuka, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Tadashi Kimura *Osaka University*

**Objective** Uterine artery embolization (UAE) with microspheres (Embosphere) for uterine fibroids has been covered by insurance since January 2014 in Japan. We analyzed the efficacies of UAE with microspheres for symptomatic uterine fibroids. **Methods** From January 2014 to August 2017, 34 premenopausal women underwent UAE with microspheres at our hospital. They were routinely followed up at 1, 3, 6, and 12 months after the procedure, checked whether they had any UAE-related complications or not and evaluated the uterine fibroids-related symptoms. Pelvic magnetic resonance imaging (MRI) was performed before and at 3 and 12 months after the UAE and the changes in volume of the uterine fibroids were calculated. **Results** Median age was 45 years (range 38–51 years), and median follow-up period was 12.7 months (range 1–39 months). The volumes of uterine fibroids on MRI decreased by 31.4% at 3 month follow-up and 44.2% at 12 month follow-up compared to baseline volumes. During the follow-up period, only one patient (2.9%) required hysterectomy because of enlarging fibroids after UAE. **Conclusion** Almost all the patients after UAE with microspheres had the symptomatic fibroids decreased and showed improvement in fibroids-related symptoms. UAE is one of the good minimally invasive methods of treating for fibroids.

#### ISP-64-5

**Introduction and Experience to Uterine Artery Embolization** Yousuke Sakai, Hiroe Ito, Michirou Yushima, Naoaki Kuji, Fumitoshi Terauchi, Hirotaka Nishi *Tokyo Medical University Hospital*

The effective treatment options for uterine fibroids are expanding by patient's age and medical history. In 2014, Uterine Artery Embolization (UAE) gained medical insurance and was introduced in our institution. This review will focus on the outcome of treatment and satisfaction from UAE. Seven patients were treated with UAE after acquiring informed consent from July 2016 to August 2017. Inclusion criteria : the average age of 43

years, symptomatic fibroids with no desire for surgery, patients seeking symptomatic relief and no desire for children. The mean fluoroscopic time was 38.8 minutes, mean exposure dose was 815.5 mGy and the mean decrease in fibroid size was 57.6%. Clinical improvement of symptoms in the most patient was noted post-UAE. The degree of satisfaction was analyzed through a set of questionnaire, and all patients gave a fair satisfactory review. The hormone level was within normal range and the effect of UAE on ovaries was avoided. UAE is regarded as a standard treatment in United States and Western Europe, but it is a relatively new in Japan. Publication of UAE as the substitute treatment of surgery to the new 2017 guidelines for Obstetrics and Gynecology, and its adaptation of medical health insurance could expand its usage in future. Most patients were satisfied with the procedure, no complications were noted and most patient's had an adequate reduction in the size of fibroids. UAE is considered as a new treatment option for uterine fibroids regarding complicated surgical cases and preservation of uterus.