Invited Lecture 1

Pre-eclampsia, syncytiotrophoblast stress and a unique form of vascular inflammation

Christopher Redman

University of Oxford, United Kingdom

The syndrome of preeclampsia is associated with a maternal systemic (vascular) inflammatory response which is caused by factors released from the placenta. The stimulus to their release is syncytiotrophoblast stress which includes elements of hypoxic, oxidative and endoplasmic reticulum stress, autophagy, inflammatory stress and in extreme circumstances, necrosis.

The underlying problem is usually placental malperfusion, of which here are two defined causes- poor placentation with maladapted spiral arteries (early onset pre-eclampsia); or congestion, caused by placental growth exceeding utero-placental capacity (late onset pre-eclampsia), to which, in the latter instance, syncytiotrophoblast senescence may contribute. More rarely, placental infection or autoimmune attack can cause syncytiotrophoblast stress associated with atypical presentations of pre-eclampsia.

There are multiple syncytiotrophoblast derived factors that are released in response to stress. In combination they can contribute to a maternal inflammatory response. Most attention has been given to anti-angiogenic factors (soluble Flt1, soluble endoglin) and angiogenic factors (placental growth factor), which are considered to be biomarkers for pre-eclampsia. But there are several other stress markers released into the maternal circulation whose contribution to maternal problems has yet to be defined.

In this presentation five issues will be presented: (1) that pre-eclampsia is not simply a placental disease but a disorder of the placental syncytium; (2) that syncytiotrophoblast stress underlies the clinical problem, which even may have origins other than uteroplacental malperfusion; (3) that the pre-eclampsia biomarkers allow such stress to be diagnosed even when it is not associated with pre-eclampsia, but with other consequences of placental dysfunction (such as fetal growth restriction); (4) that the evidence indicates that at and beyond term, these problems begin to affect all pregnancies and may include a component of placental senescence; (5) that the nature of the maternal vascular inflammation is unique to pregnancy, including a combination of features not encountered in any other clinical situation. This unique inflammatory response is termed "Placentaflammation".

Invited Lecture 2

Developing Academic Proficiency in Clinical Training

Manu Vatish

University of Oxford, United Kingdom

It is essential that clinicians and scientists foster the training of patent-oriented investigators who will continue the current rate of progress and accomplishment in medicine. Developing the medical research community of the future has been made a UK national priority, and there is a clear career pathway for clinical academics.

This talk will focus on the methods that the University of Oxford has implemented to recruit, train and retain physician-scientists in the early part of their professional careers. These clinical academic programmes have been designed to develop academic proficiency in research to continue the rate of current progress in biomedical research.

I will describe the pathways including
Undergraduate opportunities,
Academic Foundation Programme
Academic Clinical Fellowships（Integrated Academic Training Programme）
Clinical DPhils/PhDs
Clinical Lectureships

and how these training schemes allow exposure to high quality research at almost all stages of junior doctor training.

Educational Lecture 1

Management of Cervical Insufficiency

Keun-Young Lee

Hallym University, Korea

Cervical insufficiency is a very important keyword related to preterm birth and is not uncommonly encountered. Despite this, however, there have been many controversies about diagnosis and treatment. A through obstetric history and risk factors for cervical insufficiency should be reviewed and all possible options for treatment discussed. Treatment should be decided based mainly upon the obstetric history and risk factors for cervical insufficiency and monitoring of cervical length and shape (TVU) by ultrasound. After careful review of all obstetric historic risk factors, a therapy plan should be agreed on with the patient involving cerclage and/or other methods. All women having high-risk factors should have CL checked by ultrasound especially during the period from 16 in 24 weeks of gestation. When finding a short cervix of less than 25 mm, we should discuss cerclage and progesterone therapy with uterine monitoring and vaginal examination. Emergency cerclage may be the best hope for rescuing pregnancy in women with advanced cervical changes and prolapsed membranes in the midtrimester. The operative risk is surgically challenging, but recent new devices (Lee's cerclage balloon) may be of great help to the patient. Transabdominal cervicoisthmic cerclage is helpful to patient with extremely short cervix or in case of prior failed transvaginal cervical cerclage procedures.

1）Clinical strategies to reduce unexplained stillbirths at term

Tony Tan[1,2]

Consultant Obstetrician and Gynaecologist, and Clinical Director, Maternal Fetal Medicine, Raffles Hospital, Singapore[1],

Chairman, Maternal Fetal Medicine, Asia Oceanic Federation of Obstetricians and Gynaecologists, Singapore[2]

Stillbirths occur in 1：200 pregnancies, with the majority occurring at term. However unexplained stillbirths still occur despite routine obstetric management. Up to 80% of term stillbirths are due to placental disorders, which could be due to developmental disorders, inflammatory disorders or circulatory disorders like retroplacental clots, diffcuse parenchymal infarction or fetal vascular thrombi. These processes which cause deterioration of placental function remained difficult to detect with routine obstetric management.

In the past, induction of labour has suffered a poor reputation as its outcomes were compared with spontaneous labour. Such comparisons had showed an increased risk of Caesarean section, chiefly from failure of induction. More recently, induction of labour had been compared with expectant management. This is more logical as the 2 management options at any gestational age include induction of labour or expectant management, never induction of labour or spontaneous labour. Of the patients managed expectantly, some would go into labour spontaneously while others may still be induced at a later gestation for various medical or obstetric indications. When compared to expectant management, induction of labour had been associated with decreased perinatal deaths, meconium aspiration syndrome and decreased Caesarean section rates.

As there is now a known intervention for reducing stillbirths at term, clinical strategies are now available to identify the obstetric patients at risk of increased stillbirth to offer induction of labour at term. Historically, risk factors that increase stillbirth risks which are identifiable at booking include advanced maternal age >=35 years old（especially >=40 years old), hypertension, diabetes, smoking, being overweight or obese, and if patients are of low education or socioeconomic status. Implementation of routine monitoring of fetal movement in all pregnant women after 28 weeks has recently been shown to reduce stillbirths when proper protocols are adhered to. This is a low cost policy that can be implemented in most centres easily. In addition, obstetricians need to be better aware of the condition of late intrauterine growth restriction（IUGR）and its diagnosis. This is an ultrasound diagnosis based on the finding of small for gestational age（SGA）i.e. abdominal circumference or estimated fetal weight less than the 10^{th} centile with abnormal Doppler studies of the uterine arteries, umbilical arteries, middle cerebral arteries or cerebroplacental ratio. More recently, it has also been suggested that placental insufficiency as diagnosed by a low cerebroplacental ratio can also be found in appropriate for gestational age fetuses. Hence routine monitoring of cerebroplacental ratio at term for all fetuses may be an additional strategy to detect placental insufficiency, hence allowing induction of labour to reduce the risk of unexplained stillbirths at term. In the future, biochemical markers to detect placental insufficiency may also be utilized to further delineate those who should be offered induction of labour/delivery earlier.

2) Issues with conservative treatments of uterine fibroids related to the problem with leiomyosarcomas

Shin-Wha Lee

University of Ulsan, Asan Medical Center, Korea

Uterine fibroids are the commonest tumor in women and many medical and surgical options exist for their management. Traditionally hysterectomy has been the main modality of treatment of uterine fibroids, modern treatments of these tumors have diversified to include modalities that promote uterine preservation and include medical, conservative or interventional surgical procedures. These treatment modalities, due to the lack of histological specimens can lead to delay in diagnosis of malignancy and treatment and may compromise patient survival. Thus gynecologists evaluating women presenting with fibroids are faced not only with the choice of whether to offer treatment, but also the type of treatment to offer. They have the clinical challenge of deciding which patient, although rare, might have a sarcoma. However, overall preoperative diagnosis of leiomyosarcomas are fraught with inaccuracies even with the best of investigative modalities. The low incidence of the disease also contributes to the inaccuracy in diagnosis.

The risk of leiomyosarcoma arising from uterine fibroids is thought to be extremely rare and not usually considered a reason for surgical management of asymptomatic fibroids. The exact risk of malignant transformation in asymptomatic fibroids is difficult to establish as studies tend to women undergoing surgery for symptomatic fibroids. Current guidance suggests that expectant management of fibroids is a reasonable option. There are currently no data investigating the risk, or effect on diagnosis, of leiomyosarcoma in the medical or hormonal treatments of fibroids such as gonadotrophin-releasing hormone agonists, the levonorgestrel intrauterine system and the recently approved selective progesterone receptor modulators. Focused ultrasound surgery has been widely advocated as a nonexcisional therapy for uterine leiomyomas. The procedure does not produce tissue for diagnosis and can lead to delayed diagnosis and suboptimal treatment of leiomyosarcomas. Accuracy of preoperative diagnosis is essential and case reports have identified MRI screening protocol as valuable in identifying women at high risk for sarcomas. Hysteroscopic resection of fibroids is minimally invasive. The risk of development of uterine sarcomas after resection of endometrium or fibroids is 0.13%, and the risk appears to be greater in the older patient. In women undergoing fertility preserving surgery, disturbance of the tumor mass may lead to dissemination and poor prognosis of an occult malignancy. Thus identification of the patient at high risk of an occult malignancy as well as adequate counseling is essential. The risk of underlying malignancy is 17 in 1,000,000, based on the rate of uterine malignancies in the general population. However, there is no concrete evidence to substantiate this rate in women with symptomatic uterine fibroids. Of additional concern are procedures, which disrupt and disseminate tumor cells as with morcellation.

Over the next several years research needs to be directed at improving the preoperative diagnosis of malignancy, particularly of uterine sarcoma, by identifying risk factors and tumor markers. Further data regarding the incidence of leiomyosarcoma and prognosis following morcellation is required.

3) Progress in pelvic organ prolapse and stress urinary incontinence management–is mesh really so scary?

Christopher Chong

Gleneagles Hospital, Singapore

Stress Urinary Incontinence（SUI）and Pelvic Organ prolapse（POP）are very common female problems. Associated causes include child–birth, menopause, obesity, chronic lifting of heavy loads, chronic cough and constipation. This is a problem with the ageing population and we will expect to manage more and more of such cases.

A national survey on 3,500 females in Singapore by Dr Christopher Chong revealed that 13.5% sufferred from SUI and a shocking 35.6% in the above 50 age group；that is more than 1 out of 3 females above 50 years old suffer from SUI. The lifetime risk of pelvic organ prolapse has been assessed to be 11%, with a recurrence rate of 30% for moderate to severe prolapses. Anterior compartment and apical vaginal prolapses are the most difficult to treat. 50% of patients with POP have SUI and 50% with SUI have POP.

Burch Colposuspension, first started in the 60s', had been the Gold's Standard for the treatment of SUI. It has since been overtaken by the Tension–free Vaginal Tape（TVT）. With the low complication rates and high success rates of the TVT, meshes for POP surgeries were started and over the years, been widely used. Unfortunately, with meshes, come complications associated with them. In the expert Urogynaecologists' eyes, these were due to the lack of proper structured training of the surgeons, doing it for the wrong indications and using the wrong materials. In 2011, FDA from America issued a warning about the use of the mesh. This was followed by the NICE guidelines against the use of meshes. Litigation against companies producing meshes started sprouting. Some companies withdrew meshes from the market. First it was withdrawing meshes for POP；when will sling meshes for SUI be withdrawn?

Any good Urogynaecologist worth his salt will agree that he cannot be entirely satisfied with his results for POP management, especially for severe prolapses, with the high recurrence rates. Most of them still feel the need for additional support for improved surgical results, including the use of meshes. In Asia, results from long term mesh use had yielded good results with low complication rates. This is also seen by the French group with properly assessed and reviewed data.

So is using the mesh really that scary? It is timely for us to take a journey on the progress of SUI and POP surgeries over the years, assessing and recommending the best management options for our patients.

4）Recent Recommendations in Preeclampsia

Walfrido W. Sumpaico

AOFOG Secretary General, Philippines

Prediction

A new concept of inverting the“pyramid of obstetric care” shows the shift of emphasis from the frequent 2nd and/or 3rd trimester visits with mid-trimester screening to newer developments in 1st trimester screening（Nicolaides, 2010）. A new development is the concept of early prediction of preeclampsia. The prediction process is based on a multimodal risk approach at 11-14 weeks AOGusing -

*History risk factors

*Measurement of Mean Arterial Pressure（MAP = DP + 1/3 Pulse Pressure）

*Uterine artery Doppler Indices

*Biomarkers, notably Placental Growth Factor（PlGF）and sFlt1/PlGF ratio.

Recently, however, the ACOG published a Clinical Opinion that one must rely heavily on clinical history alone for the moment.

Prevention

What good is prediction if prevention cannot be accomplished? The lecture reviews the early preventive measures with low-dose aspirin（and high-dose/low-dose calcium）starting before 16 weeks.

Treatment

The mainstay of treatment remains using Magnesium sulfate as the ideal anticonvulsant and acts also for fetal neuroprotection. Recently, Nifedipine in addition to Hydralazine and Labetalol has been added as the 3rdantihypertensive of choice. Delivery decision is individualized based on age of gestation, severity of the disease, maternal status, fetal status and nursery capability. A new treatment modality（dextran sulfate infusion）has been tried.

1）Preimplantation Genetic Screening to Reduce Miscarriage and Improve Live Birth Rates

Min Yu Lim

National University Hospital, Singapore

About 1 in 6 couples have difficulty conceiving. The spontaneous conception rate per cycle is only about 20% in couples without fertility problems. Only 13% of embryos created during IVF result in live birth. At least 65% of spontaneous miscarriages are associated with chromosomal abnormalities, and up to 80% of IVF embryos are chromosomally abnormal, dependent on maternal age.

The goal of reproductive medicine specialists is to achieve healthy live birth with minimal complications. One area of research has been in methods to select the best embryos for transfer.

If we transfer embryos that have a normal number of chromosomes, this should improve the chances of live birth, reduce the chance of miscarriage or birth with chromosomal abnormality.

Preimplantation genetic screening was first performed in 1993, by fluoresence in situ hybridization (FISH). This technique can only screen a maximum of 12 chromosomes. Trials did not show improved outcome, and professional bodies advised against these techniques outside of a reasearch setting. However, newer techniques have become available that allow comprehensive screening of all 24 chromosomes, such as array CGH and next generation sequencing (NGS). Randomised controlled trials using these new technologies have been published, showing an improvement in outcomes compared to selection of embryos for transfer based on their morphological appearance.

An overview will be presented of the background, prior and contemporary techniques, and the evidence base to date.

2) A pilot study on ICG sentinel lymph node biopsy in endometrial cancer performed in KK Women's & Children's Hospital, Singapore

Yong Kuei Lim

KK Women's and Children's Hospital, Singapore

The utilisation of Sentinel lymph node biopsy (SLNB) in gynaecological cancers has been gaining traction in recent years, firstly in vulva cancers and now in endometrial cancers. Recent studies showed that SLNB alone can accurately diagnose lymph node involvement in patients with early endometrial cancer. This procedure is an alternative to a systematic pelvic lymphadenectomy but with the advantage of a reduced risk of lower limb lymphoedema and pelvic lymphocyst formation.

The established technique involves the combined technique of patent blue dye and radioisotope injection. However, recent evidence suggests that fluorescence near-infrared (NIR) imaging of indocyanine green (ICG) for SLNB can also be used as an alternative.

In this presentation, I will review the evidence concerning the various techniques for SLNB in endometrial cancer and present the pilot results of the use of ICG in early endometrial cancer performed in KK Hospital, Singapore.

1）Imput of centralized care on survival in advanced ovarian cancer

Walther Kuhn

University Hospital Bonn / Center for Integrated Oncology Köln Bonn（CIO）, Germany

Introduction Late-stage ovarian cancer patient's survival depends on complete cytoreduction and chemotherapy.

Complete cytoreduction is more often achieved in institutions with a case volume of ＞20 cases per year. The Integrated care program Ovar（IgV Ovar）was founded in 2005 and started recruiting in 2006 with 21 health insurances and six expert centers of ovarian cancer treatment as a quality initiative. Results of the pilot and outcomes of patients of three participating centers will be presented here.

Methods Data of 1,038 patients with ovarian cancer were collected. Adjuvant patients（n=505）stage FIGO IIB-IV（n=307）were analyzed for cytoreduction and survival.

FIGO IIIC patients were analyzed separately. *Results* Median follow-up was 32.7 months. Progression- free survival（PFS）was 23.1 months and overall survival（OS）was 53.6 months for stage IIB-IV. Patients with FIGO IIIC were completely cytoreduced in 48%. PFS was 21, 29 months if completely cytoreduced. OS was 47.4, 64.9 months if completely cytoreduced.

Discussion Although the IgV Ovar Rhineland proved to have some structural problems with recruitment and prospective data collection, cytoreduction rates and outcome of patients prove treatment of patients in expert centers is superior to the national and international mean. Therefore, a new quality initiative will be started to bring more awareness to women and to their gynecologists and general practitioners of just how important a good referral strategy is.

J Cancer Res Clin Oncol（2016）142：481-487

2）Highlights of AGO Gynecological Guidelines for the Treatment of Breast Cancer－a multidisciplinary approach

Wolfgang Janni

University of Ulm, Germany

For the last 15 years, the Breast Committee of the *Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group, AGO)* has been preparing and updating evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer. The AGO Breast Committee consists of gynecological oncologists specialized in breast cancer and interdisciplinary members specialized in pathology, radiological diagnostics, medical oncology, and radiation oncology. The presented update for the 69th Annual Congress of Japan Society of Obstetrics and Gynecology has been performed according to a documented rule-fixed algorithm, by thoroughly reviewing and scoring chapter by chapter the recent publications for their scientific validity（Oxford level of evidence (LoE), *www.cebm.net*）and clinical relevance（AGO grades of recommendation (GR)）. We will present the 2016 update；the full version of the updated slide set is available online as a PDF file in both English and German. Moreover, a version for patients is also available at *www.ago-online.de*.

3）The German System of Medical Check-up in Gynecology in Accordance to the new Guidelines of HPV-Screening

Gernot Beisler

Gynecology and Obstetrics, Gyn. Oncology, Germany

Since 1971 the yearly medical check up in gynecology for all women from the age of 20 is paid by all health insurances in Germany.

The procedure of the purely preventative medical examination is defined in：inspection and palpation of the urogenital organs, colposcopy, cervical smear for cytology；then from the age of 30 the examination of the breasts；and from the age of 50 the mammography and additionally the testing of occult blood in stool（colon cancer prevention program）.

Since the last 40 years the prevalence of invasive cervical cancer has decreased remarkably. In Germany it is No.12 of all cancer types in women, around 4,300 new patients per year.

The cause of the decrease might be multiple and it is still in a permanent discussion among the physicians. Among the experts, however, there is no doubt that the yearly gynecological check up has participated in the reduction of the prevalence of invasive cervical cancer.

Actually the European guide-lines recommend the HPV tests for all women for prevention of cervical cancer. Currently the gynecologists experience-very often in an emotional manner-repeatedly controversial discussions, wether HPV tests should replace the cytology of the cervix for cervical cancer screening. The scientific datas are not definitely clear to decide which method might be better. This discussion is influenced also by economical arguments, scientific self confidence and practical management. Therefore for example the actual American guide-lines do not recommend the sole HPV-tests without cytology in preventive care. As in Germany exists a strong influence of the health insurance companies, the discussion however has not stopped, wether HPV-tests are at least as safe as cytology and simultaneously can reduce the costs for the insurances. Because of this dispute the German Federal Joint Committee（GBA）has decided at September 2016：continuation of the yearly current gynecological check up. But additionally there is one change：beginning from the age of 35 the women should be offered a HPV-test simultaneously with a cytological smear every 3 years. After around 6 years of monitoring the GBA will review, wether a screening change in favour of HPV test can be useful and should be established or not.

4) The clinical role of CTCs in primary and metastatic breast cancer

Tanja Fehm

University of Dusseldorf, Germany

Circulating tumor cells can be detected in 10 to 20% of patients with primary breast cancer. CTC positive patients are at higher risk for relapse and breast cancer death. CTC persistence in patients treated with adjuvant and neoadjuvant systemic treatment also indicates poor clinical outcome. The clinical consequences of CTC persistence after systemic treatment are not yet defined for these patients and currently under investigation. In the metastatic setting, the CTC positivity rate is between 60% and 80%. The prognostic relevance of CTCs has already been shown in a large pooled analysis including more than 1,900 metastatic breast cancer patients. Patients with five or more CTCs per 7.5 ml blood at time of start of first-line treatment had shorter progression-free and overall survival than patients with less than 5 CTCs. Further, a decrease in CTC levels reflected response to treatment whereas tumor cell persistence or increase was associated with therapy resistance and disease progression. These patients may require an alternative treatment. CTCs can also be used as liquid biopsy to reassess therapy relevant markers including HER2 and hormone receptors due to the discordance of hormone receptor and HER2 receptor expression observed between metastases and primary tumors. The DETECT study program is the so far world's largest study concept using CTCs for liquid biopsy in MBC. Treatment decisions are based on the presence and phenotype of CTCs, especially the HER2-receptor expression.

This talk will focus on clinical relevance of CTCs and provides an overview of ongoing and completed trials CTCs in primary and metastatic breast cancer.

1）Cervical cancer in screening in Cambodia：Progress of SCGO–JSOG collaborative project and the future

Koum Kanal

President, Cambodian Society of Gynecology and Obstetrics（SCGO）, Cambodia

After the successful reduction of maternal mortality ratio, uterine cervical cancer is the first cause of death in reproductive age women in Cambodia. According to GLOBOCAN 2012, estimated cancer incidence and mortality in Cambodia are 1512 and 795 per 100,000 persons per year respectively, which is one of the highest in Asian countries. Without a systematic cancer screening program, most women come to hospitals in advanced stage. Treatment options, surgery, radiotherapy, and chemotherapy are available but only in a very limited number of hospitals and not yet standardized. There is also a big challenge in human resources, especially quite limited number of pathologist in country. Cytology is not an option for cancer screening, the same as in other resource limited countries.

SCGO and JSOG started a project since October 2015 for 3 years to develop human resources and prepare cervical cancer screening program with a target group of factory workers. Comprehensive approach is being implemented：1）Health education in factories, 2）Cancer screening（at factory）, and 3）Follow–up（Screen and Treat）at hospital level. Hospital check for Cambodian women is not as easy as for Japanese, because of low level of knowledge on cancer, or high hospital cost and travel cost. Not to miss the opportunity of follow–up, one stop service（screen and treat at hospital using colposcopy and LEEP for pre–cancer）was prepared. Three national hospitals were selected. JSOG doctors provided hands on training to SCGO doctors both in Cambodia and in Japan on colposcopy diagnosis with cytology and pathology, and LEEP treatment. Visual inspection with acetic acid（VIA）was originally considered for cancer screening at factories, but recently HPV test become affordable and now to be implemented instead of VIA. SCGO also encourage Cambodian pathologists to improve communication and start discussion in case conferences to develop the capacity of both pathologists and gynecologists. Under the continuous collaboration between SCGO and JSOG, we hope this project will be a model for the future cervical cancer management system in Cambodia.

2）Cervical cytology and visual inspection with lugol iodine for detection of premalignant condition of cervix

Yin Yin Soe

University of Medicine 1, Myanmar

Objectives：To assess the strength and reliability of Visual Inspection with Lugol's Iodine（VILI）in detection of premalignant condition of cervix.

Methodology：A hospital based cross sectional study carried out in Central Women's Hospital, Yangon from January, 2014 to December, 2014. A total of 108 women between 25–50 years were included in the study. Cytological examination with Ayre's spatula, visual inspection of cervix after application of Lugol's iodine and cervical punch biopsy were performed on each patient.

Results：Data was analyzed by using non parametric tests（Chi square）for all 3 procedures. Agreements between tests（VILI vs histology, cytology vs histological findings）were calculated by using Kappa statistics. The sensitivity of cytology and VILI were 47.1% and 85.2% respectively. The specificity of cytology and VILI were 96.7% and 75.8%. The positive predictive value of cytology and VILI were 72.2% and 40.5% and Negative predictive value were 90.7% and 97.2% respectively. The accuracy of the test for cytology was 88.9% and 77.8% for VILI. The results of VILI were comparable to that of cytology, and the difference between VILI and cytology, was statistically significant.

Conclusion：Cervical cancer is the commonest female genital cancer in Myanmar. Cervical cytology is not available in rural areas due to financial constraints. Alternative screening methods need to be introduced for community screening. This study revealed that high sensitivity of VILI can reduce the false negative results of cytology. It also highlighted that VILI can replace cervical cytology in cervical cancer screening programme in rural areas of low resource countries.

3）Medical Disorders in Pregnancy

Lata Bajracharya

President, Nepal Society of Obstetricians and Gynaecologists（NESOG）, Nepal

A descriptive retrospective study for one year reveals around 3% of medical disorder in pregnant women admitted at Paropakar Maternity and Women's hospital irrespective of gestational age. The commonest disorder was urinary tract infection by 0.75% followed by 0.35% each of thyroid disorder and other infectious conditions. Diabetic complications and chronic infection were 0.35% each with 0.05% heart disease.

4）NESOG（NEPAL SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS）：HISTORY AND ITS ACHIVEMENTS FOR LAST 25 YEARS

Sanu Maiyan Dali

Past President, NESOG, Nepal

Nepal Society of Obstetricians and Gynaecologists（NESOG）is a professional not-for-profit organization of obstetricians and gynaecologists established in 1988 A.D. with forty members and now grown to four hundred members.

The society has to its credit firmly committed and dynamic members who set a fine example of cooperation and coordination in the true spirit of voluntarism to make a grand success of concerted efforts for NESOG. Since its establishment, NESOG has been involved in various activities carrying out numerous services to the community for the betterment of women's health at various stages of life and their newborns, working in harmony and collaboration with the Government of Nepal（GoN）, FHD and numerous other International and regional professional societies like JSOG, AOFOG, FIGO, SAFOG, FOGSI, External Development Partners, International Non Governmental Organizations, Non Governmental Organizations, and other national professional associations and societies.

OBJECTIVES：

- ■To serve the people by rendering fully educational, scientific and public health oriented services of high standard in the field of obstetrics and gynaecology in Nepal.
- ■Upliftment of health of women and newborns
- ■Contribute to quality of education and rendering of best practices in field of Obstetrics and Gynaecology
- ■Recommend standardization of services in the field of Obstetrics and Gynaecology
- ■Assist Government of Nepal（GoN）in formulation of polices, guidelines and research activity in the related fields
- ■Dissemination and sharing of information and skills with medical fraternity, society members and community
- ■Work towards developing NESOG to a fully self-sustainable Institute of excellence in the field of Obstetrics and Gynaecology

It organizes National and International Conference where all members and representatives from various International organizations are invited for scientific deliberations and raise responsiveness towards role of health professionals in maternal and neonatal health care services.

It conducts Continuing Medical Education lectures, Workshops and training programmes.

Nepal Journal of Obstetrics and Gynaecology published biannually is regarded as a scientific journal of high standard and is in the process of indexing in Medline.

NESOG news letter is published providing informations regarding ongoing projects, news and different activities.

Education committee prepares protocol and guidelines in collaboration with GoN and NGO/INGO

NESOG helped in etablishment of functional Comprehensive Emergency Obstetrics and Neonatal Care (CEONC) in Dhankuta district, facilitating existing Human Resource development and strengthening MNH services.

Senior NESOG members and NESOG established various Oration Lectures and Medals.
Honor two senior members during National conferences.
Prof. SOMA award and NESOG Awards are given to young members.
NESOG had hosted AOFOG council meetings and SAFOG Conferences twice.
Purchased land to construct own building with voluntary contributions by NESOG members.
NESOG strategic plan (2012-17) was prepared to formulate annual action plan

VISION :

The society envisions itself as a leader working to provide the highest possible standard of reproductive health, accessible and equally distributed to all Nepalese women which can be achieved by empowering members with education, research and training.

Way ahead

NESOG will continue to work for health of women and neonates in Nepal and establish as a self sustainable Instititute of Excellence in Obstetrics and Gyanecology

International Workshop for Junior Fellows：

1. Current status of gynecologic cancer screening

1）The Current State of Gynecologic Cancer Screening in the United States

Megan Kennedy Burns

TriHealth, USA

ACOG

Screening guidelines in the United States focus primarily on cervical cancer detection and prevention. Although screening tests are available for other primary gynecologic malignancies, research has shown little survival benefit to screening for endometrial or ovarian cancers and current recommendations are to not screen for these malignancies. The most recent evidence–based consensus guidelines for cervical cancer screening in the U.S. were published in 2013 by the American Society for Colposcopy and Cervical Pathology, with the goal of incorporating longer screening intervals and cotesting into the management of women with abnormal screening tests. These revisions reaffirmed most of the prior screening guidelines, but extended screening intervals and started screening tests at a later age：cotesting with cytology and HPV testing is now the preferred screening for women 30 to 64 years of age at 5 year intervals and testing to begin no earlier than age 21.

International Workshop for Junior Fellows：
1. Current status of gynecologic cancer screening

2) Hypermethylation of the Single-minded homolog 1 (SIM1) as a novel biomarker for cervical cancer screening

Eun Ji Choi, Hyun-Jung Kim, Chan Young Kim, Jing Hui Jin, Moon Kyoung Bae, Yun Hee Kim, Woong Ju, Yun Hwan Kim, Seung Cheol Kim

Innovative Research Center for Control and Prevention of Women's Cancer, Ewha Womans University Mokdong Hospital, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ewha Womans University School of Medicine, Seoul, Korea

KSOG

Objective：Although the Papanicolaou smear (Pap smear) and human papillomavirus (HPV) DNA testing have greatly reduced the mortality of invasive cervical cancers, the low sensitivity and specificity of current screening still make a need to develop other biomarkers for cervical cancer screening. Aberrant DNA methylation is a frequent epigenetic event in human cancers including cervical cancer. Here, this study was aimed at investigating the possibility of the *single-minded homolog 1* (*SIM1*) methylation as a biomarker for cervical cancer screening.

Method：Using real-time quantitative methylation-specific polymerase chain reaction (PCR) (qMSP), we analyzed the frequency and relative level of promoter methylation of SIM1 gene in 45 cervical cancer tissues and 10 normal controls. The percentage of methylated references (PMR) was used for analysis of SIM1 methylation using reference gene, ACTB.

Results：We found that *SIM1* gene promoter was highly methylated in a majority of cervical cancer tissues (43/45 (95.6%), median percentage of methylated reference (PMR) 80.9), but in none of normal tissues (0/10 (0%), median PMR 0) ($P<0.0001$). As a result, SIM1 expression level was significantly reduced in cervical cancer tissues compared with normal cervix tissues. We tried to find whether *SIM1* methylation status of cervical scrapes also reflects that of cancer tissues, and found that the median PMR values were 0 (0/17, 0%), 0 (0/20, 0%), 0 (1/19, 5.3%), 0 (14/34, 41.2%), and 27.95 (17/20, 85%) in cervical scrapes of normal, CIN1, CIN2, CIN3, and cancer, respectively (n=120). Moreover, there was significant association between the increase in *SIM1* methylation and disease severity ($P_{trend}<0.0001$) among these samples. We also tried to detect methylated *SIM1* gene in plasma circulating cell-free DNA (ccfDNA) from cervical cancer patients. Methylated *SIM1* genes were detected as high as 15 of 41 (36.6%), and the concordance rate of methylation status between paired ccfDNAs and cancer tissues was 17 of 41 (41.5%).

Discusion：This study showed that *SIM1* hypermethylation is very frequently and specifically oc-

curred in cervical cancer, compared with normal cervix and low-grade CINs in both tissue samples and cervical scrapes, suggesting *SIM1* methylation might be a useful biomarker for cervical cancer screening. Moreover, our study suggested the possibility of plasma ccfDNAs for detecting methylated *SIM1* genes for cervical cancer screening.

3）Current status of gynecologic cancer screening in Taiwan

Lin-Ying Su

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Among all the cancers in Taiwanese women, cancers of the female reproductive tract and breast have a relatively high incidence. According to data of incidence rate in year 2013：Breast cancer has highest rate of 96.5 per 100,000 women per year, uterine cancer ranks 6th with 13.5 per 100,000 women per year and tubal cancer ranks 9th with 11.3 per 100,000 women per year.

Ministry of health and welfare in Taiwan has provided free annual pap smear for cervical cancer screening among women over 30 years of age since 1995. Self-paid HPV vaccination was also available since 2006. According to domestic data, about 2.25 million people over 30 years old has received pap smear in 2014, with 0.64% LSIL, 0.30% HSIL, 0.002% AIS and 0.03% cancer cases detected among them. The screening rate of pap smear in the past 3 years in women aged 30 or over has reached 52.1%. The age-standardized mortality rate of cervical cancer was 22 per 100,000 people in 1995 and 7.8 per 100,000 people in 2014, which is a 62.4% decrease.

The mortality rate of breast cancer ranks 4th among cancers of Taiwanese women. There is more than 50% increase of incidence rate in the past 10 years. Free mammographic exam every two years among women over 45 years of age for breast cancer screen was provided in Taiwan since 2002. More than 1.5 million women over 45 years of age received mammography during 2014~2015（screening rate 39.5%）.

No routine screening test is available for corpus and ovarian cancer yet, but specific screening approaches can be arranged according to symptoms with payment covered by national health insurance in Taiwan：Endometrial sampling or hysteroscopy may be arranged in circumstances of abnormal vaginal bleeding for detection of endometrial hyperplasia or cancer, ultrasonography and CA-125 may be checked when suspicious of adnexal mass. The mortality rate of ovarian cancer ranks 6th among cancers in Taiwanese women, and corpus cancer ranks 11th. Several clinical trials of biomarkers for early screening are still under evaluation.

International Workshop for Junior Fellows：

1. Current status of gynecologic cancer screening

4）Current status of gynecologic cancer screening in Japan

Haruko Kunitomi, Yu Kanzaki, Kaoru Keyama

JSOG

Population-based gynecologic cancer screening in Japan was implemented in 1983, when the Health Law of the Elderly introduced cervical cancer screening. Endometrial cancer screening commenced in 1987, but was suspended in 2006 due to the lack of evidence supporting its mortality-reducing effect. Since 2004, the National Health Promotion Service has recommended a biannual clinical interview, pelvic examination, and cervical cytology, beginning at age 20.

Japanese women have several opportunities to receive cervical cancer screening, including the population-based cancer screening program organized by municipalities（municipal screening）, employee welfare programs, prenatal checkups, private comprehensive medical examinations, or as a part of routine medical care. Nevertheless, according to the Comprehensive Survey of Living Conditions by the Ministry of Health, Labor and Welfare in 2013, only 42.1% of women aged 20 to 69 received cervical cancer screening during the prior two years. Although there was slight improvement compared to the rate of 37.7% in 2010, the figures still remained extremely low in contrast to other developed countries. While municipal screening in 2011 resulted in a recall rate of 1.8% and a cancer detection rate of 0.08%, accurate results for non-municipal screening are difficult to determine due to lack of statistics.

Since 1983, the age-adjusted death rate for cervical cancer declined once in the 1990s, but is now gradually increasing. This trend is notable among the younger generation（20s to 40s）, who tend to have higher recall rates, but often skip screening. For this generation, cervical cytology tests included in the prenatal checkup function as a minimum safety net, but improving the screening rate is a pressing issue. The wide distribution of free coupons initiated in 2009 has resulted in some progress in population-based municipal screening. However, the range of support and educational activity depends mostly on each municipality's financial condition, causing regional disparities in the participation rate.

Although endometrial cancer screening is not a main component of the National Health Promotion Service Program, women who have symptoms can choose to have tests as a part of the municipal screening. In general, endometrial cytology is taken, with or without pelvic ultrasonography, depending on the clinic. Due to insufficient sensitivity of endometrial cytology and the existence of asymptomatic affected individuals, the screening criteria and methods need to be further discussed. As for ovarian cancer screening, there is no consensus to date, and systematic screening has not yet been introduced. In association with lifestyle changes, the incidence rate of endometrial cancer in Japan has increased 1.5-fold from 2001 to 2012, and the incidence rate of ovarian cancer is also rising. Although the usefulness of regular screening for endometrial and ovarian cancer is controversial, health care promotion for women at risk is necessary.

In conclusion, the most important issue in gynecologic cancer screening in Japan is to improve the low participation rate, followed by thorough discussion of appropriate subjects and modalities of screening. Further education on the lifesaving potential of gynecologic cancer screening is required.

International Workshop for Junior Fellows：
2. Adaptation and prospects of Chinese medicine

1）The Role of Acupuncture and Acupressure in Modern Day Obstetrics

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ACOG

Pregnancy and labor can be a time of many sources of discomfort for women including nausea/vomiting of pregnancy, lower back pain, and pain associated with labor. A growing number of women are seeking non-pharmaceutical approaches to these conditions due to concern for safety and side effects of pharmaceutical options. Acupuncture and acupressure are two traditional Chinese medicine therapies that have been used for many centuries to treat a variety of ailments. A fundamental principle of these methods is the concept of chi which is an energy that is believed to flow through the body along meridians. When a patient's chi is either blocked or unbalanced it can lead to pathology. Both acupuncture and acupressure employ manipulation of distinct pressure points across the body with either small needles（acupuncture）or pressure with the hand（acupressure）to restore the body's unbalanced chi.

It is estimated that 50% of women who utilized complementary and alternative medicine（CAM）prior to pregnancy will continue to use these approaches during pregnancy. Many women seek out acupuncture/acupressure as low risk alternatives to standard pharmaceuticals to address a variety of pregnancy related issues. There is little literature around the use of acupuncture and acupressure during pregnancy with most studies being conducted outside of the United States. Of the existing literature, the most commonly studied topics include the use of these methods for pain control in labor, correction of malpresentation of the fetus, and nausea and vomiting of pregnancy. The evidence for the utility of these methods seems to be diverse with different studies from around the globe describing contradictory results. In this session, the body of literature will be examined to determine the role of acupuncture and acupressure in modern day obstetrics as well as current adaptations of these practices.

International Workshop for Junior Fellows：
2. Adaptation and prospects of Chinese medicine

2) Efficacy and safety of Korean red ginseng in postmenopausal women

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KSOG

Background

The WHI findings were first published in 2002, following which the use of HRT rapidly declined due to concern about breast cancer. Istead, alternative medicine such as isoflavone, black cohosh, red clover and Korean red ginseng (RG) has won popularity. However, scientific efficacy and safety data about these alternative therapies are lacking.

Objective

We performed this study to evaluate the efficacy and safety of Korean red ginseng in postmenopausal women.

Methods

We performed a randomized, double-blind, placebo-controlled trial in 72 post-menopausal women aged 45-60 years. Participants were randomized to receive 3g red ginseng daily or placebo for 12weeks. We analyzed changes in menopausal symptoms (the Kupperman index and the menopause rating scale), cardiovascular risk factors (lipid profiles, high-sensitivity C-reactive protein, and carotid intima- media thickness), Antioxidant enzymes activity (superoxide dismutase, glutathione peroxidase) and oxidative stress markers (malondialdehyde, 8-hydroxy-deoxy-guanosine) and serum estradiol levels from baseline to 12 weeks.

To evaluate the safety of Korean red ginseng on breast and endometrium, immature mammary epithelial cells (MCF10), X-ray induced breast cancer cells (MCF-7) and endometrial stromal cells, endometrial epithelial cells (Ishikawa cell line) were used as an *in vitro* model. These cells were treated with ginsenoside Rg3 for 72 hours and proliferation of the cells were evaluated.

Results

Significant improvements in the Kupperman index (P=0.032) and in the menopause rating scale (P=0.035) scores were observed in the RG group compared with the placebo group. Total cholesterol (P=0.009), low-density lipoprotein cholesterol (P=0.015) and carotid intima-media thickness (P=0.049) significantly decreased in the group receiving RG. Serum estradiol levels were not influenced by RG sup-

plementation.

Comparing with control, there was no significant proliferation in cell treated with RG3.

Conclusion

RG could be an safe herbal dietary supplement for relieving menopausal symptoms and conferring favorable effects on markers of cardiovascular disease in postmenopausal women. These effects may result from effect of RG reducing oxidative stress by increasing antioxidant enzyme activity in postmenopausal women.

International Workshop for Junior Fellows：
2. Adaptation and prospects of Chinese medicine

3）CHINESE MEDICINE AND MENOPAUSE：EFFECTS AND SAFETY

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Increasing interest has been drawn in the chinese medicine, one reason is the consideration of the safety of hormone therapy in menopause. Many conventional chinese medicine has been applied in postmenopausal syndrome, such as （JWSYS）, (Six Flavor Rehmanni), Zhi Bo Di Huang Wan, Zuo Gui Yin, You Gui Yin, *Rehmannia glutinosa*, Fructus Corni, *Fallopia multiflora*, *Eucommia ulmoides*, *Semen Cuscutae*, *Psoralea corylifolia*, *Fructus Ligustri Lucidi,* Glossy privet fruit. And different chinese medicine can be used individually according to the various symptoms. A randomized, controlled study comparing the effect of a 16-week treatment with JWSYS or HRT （Premelle） in postmenopausal women. The effects were measured by Greene Climacteric Scale. Both JWSYS and Premelle effectively alleviated most of the menopausal symptoms with no significant differences. JWSYS had a relatively lower adverse effects, in particular the bleeding and breast tenderness. The most effective components of the chinese medicine in menopausal symptom can be attributed to phytoestrogen. Phytoestrogens are known to be present in fruits, vegetables, and whole grains commonly consumed by humans. There are four main classes of phytoestrogens：isoflavones, stilbenes, lignans, and coumestans. Isoflavones are mainly present in legumes such as soybean, kalachanna, mung bean, red lentils, and red clover. Genistein and daidzein are the 2 major isoflavones found in soy beans. Resveratrol is currently recognized as a major stilbene present in grape and red wine and has been intensely studied for its effectiveness. The dietary sources of lignans are flaxseed, seaweed, whole grains, oil seeds, fruits, and vegetables. Coumestans are significantly present in clover, alfalfa, and soybean sprouts.

Phytoestrogens, which are derived from plants, structurally mimic human estrogen 17β-estradiol, enabling them to bind the ER and giving them the ability to cause estrogenic or/and antiestrogenic effects. A recent systematic review （2013） analyzed 127 articles on soy and 4 articles on red clover and undertook a meta-analysis （2013） of eight studies. The effects of soy consumption on the prognosis of breast cancer patients were investigated. The results showed that soy consumption may protect against development of breast cancer and breast cancer recurrence and mortality. Further insight into the relation of phytoestrogen and breast cancer needs to be addressed. Therefore, it is worthwhile investigating the

possible mechanisms of phytoestrogens, especially the anti–breast cancer effects. We focus on the inhibition effects and clarify the underlying molecular mechanisms in our review article. We declare that phytoestrogens exert a plethora of actions beyond weak estrogenic effects and these include regulation of the cell cycle, induction of apoptosis or autophagy, enhancement of antioxidant properties and/or reactive oxidative stress, regulation of estrogen receptors, modulation of cell signaling pathways, and epigenetic alterations.

4) Adaptation and prospects of Chinese medicine

Sayaka Tsuda, Miho Iida, Yukie Kidani, Junko Tsuboki
JSOG

Kampo is a traditional Japanese herbal medicine believed to have been brought from China, c.1800 years ago, via Korea. Since then, Japan has developed it in its own unique way, and the types of herbs and their compositions in prescriptions have changed dramatically from those of classical Chinese and Korean medicine. Kampo is also distinct from Western medicine：while Western medicine focuses on science and evidence and uses a single drug for each condition, Kampo combines multiple herbal extracts into a formula, in order to harmonize the physical constitution of a patient with more than one symptom, largely based on numerous previous experiences.

The Japanese medical system offers a unique medical practice to apply the latest techniques in modern medicine side-by-side with traditional herbal therapeutics. A total of 212 Kampo formulas are covered by the government health insurance and are available in forms of tablets and powders. Constituting 1.4% of all prescription drugs, their sales have rapidly increased by 50% in the last ten years. Japanese obstetricians and gynecologists (ob-gyns) commonly use Kampo products to treat women in various life stages, such as puberty, reproductive age, climacteric period, and in elderly years. Examples include tokishakuyakusan and kamishoyosan for dysmenorrhea, both of which were shown to be effective in randomized controlled trials, hangekobokuto for emesis gravidarum, daikenchuto for postoperative bowel motility and prevention of paralytic ileus, hochuekkito as nutritional supplementation for gynecologic cancer patients, and kamishoyosan for climacteric symptoms. Kampo preparations may represent a safer option, with fewer adverse drug reactions, especially with long-term use and during pregnancy, compared to those used in Western medicine. The existence of over-the-counter drugs also provides women with an easy access to Kampo products.

However, problems still exist in the effective use of Kampo medicine. The methodology for diagnosis and treatment is complex and not theoretically well-structured, and experience and education are necessary to gain skills. Many Kampo products require several weeks to reveal their effectiveness, and doctors tend to rely on it only when they find it difficult to treat patients with Western medication alone.

In recent years, educational programs and research in Kampo medicine have been actively conducted throughout the country. Kampo education had been eliminated from the Japanese medical schools' curricula in 1883, but was re-implemented in 2001 as part of a plan to improve healthcare in the 21st century. Academic societies have been established to promote the use of Kampo medicine, and many ob-gyns participate in these activities. Accumulation of evidence from basic research has revealed effective ingredients and their underlying action mechanisms, opening the "black box" of traditional knowledge. Proteomic and epigenomic analyses are performed to identify biomarkers related to the concepts of "mibyo" (disease-oriented state) and "sho" (Kampo diagnosis). By incorporating scientific evidence into traditional concepts, Kampo medicine is expected to develop and become more integrated into medical practice in Japan.

International Workshop for Junior Fellows：
3. Management of labor, delivery and postpartum with midwife

1）Management of labor, delivery and postpartum with Midwife

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ACOG

Currently in the United States, there are three recognized but separate midwifery credentialing systems including certified nurse midwives（CNMs）, certified midwives（CMs）, and certified professional midwives（CPMs）. Each with various levels of education, training and experience.

The first two, CNMs and CMs, both accredited by the American Midwifery Certification Board（AMCB）, and are held in the highest of standards with the most strenuous regulations. CNMs are registered nurses who have graduated from a midwifery education program accredited by the Accreditation Commission on Midwifery Education（ACME）and have passed a national certification examination administered by AMCB.

Certified midwives also have graduated from a midwifery education program accredited by the ACME, have successfully completed the same requirements, have passed the same AMCB national certification examination as certified nurse–midwives and adhere to the same professional standards as certified nurse–midwives.

Certified professional midwives are boarded by a separate entity known as North American Registry of Midwives（NARM）and are required to complete a course and pass a competency test but are not recognized by the AMCB.

The American College of Obstetrics and Gynecology（ACOG）released a College Statement of Policy regarding Midwifery Education and Certification recently, which has longed endorsed the AMCB（governing body of CNMs and CMs）but now also supports the International Confederation of Midwives（ICM）Global Standards as the common worldwide education, licensure, regulatory and practice standards for midwifery. The AMCB meets and surpasses these baseline standards set forth by the ICM.

In summary,"The College supports women having a choice in determining their providers of care. The College specifically supports the provision of care by midwives who are certified by AMCB（or its predecessor organizations）or whose education and licensure meet the ICM Global Standards. The College does not support provision of care by midwives who do not meet these standards."

Regarding the care provided by Midwifery, ACOG and the Society for Maternal Medicine–Fetal Medi-

cine (SMFM) recently published an Obstetric Care Consensus that attempted to specifically identify and outline the appropriate levels of maternal care required based on objective data starting with a Birthing Center and sequentially increasing with need for increase in potential care：Level 1（Basic Care), Level 2（Specialty), Level 3（Sub-specialty), Level 4（Regional Perinatal Health Care Center).

The Obstetrics Care Consensus outlined Midwifery practices to be best served in Birthing Centers which were defined as peripartum care of low-risk women with uncomplicated singleton term pregnancies with a vertex presentation who are expected to have an uncomplicated birth. The role of Midwifery during Labor and Delivery is limited in the subsequent Levels as denoted by the consensus.

In addition to Birthing Centers, midwifes also play an incremental part in home births. Currently, in the United States, there are approximately 35,000 home births per year which is roughly 0.9% of all births. A quarter of these are unplanned with midwives playing an integral part in the majority of the remaining. Proportionately more home births are attended by midwives than planned hospital births, and randomized trials show that midwife-led care is associated with fewer intrapartum interventions.

Currently at my Home Institution we are responsible for two large Labor and Delivery Centers which would fit into a Level 3 & Level 4 Center respectiavely. At both of these facilities midwives play a critical role in the antepartum and postpartum care of low-risk women however do not currently actively participate in intrapartum care.

Midwifery practices with adequate standardized training and the appropriate patient population can serve as highly valuable providers in the obstetrical care of women.

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International Workshop for Junior Fellows：
3. Management of labor, delivery and postpartum with midwife

2）Midwives in Korea；in terms of doctor's role

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Introduction

In 1990s, the national health insurance system was started and this system offered high-quality obstetric doctor's medical service at a relatively lower cost than before. This lowered entry barrier to obstetric doctor's medical service resulted in the abrupt decline in the number of midwives. After that time, most deliveries（99.4%）and prenatal care have been performed by obstetric doctor in hospitals. In addition, the lack in the proper protocols and guidelines for the roles of midwives prohibit doctors from cooperating intimately with the midwives. The aim of this study was to demonstrate the current roles of midwives in the Korean society and to suggest proper roles in midwives, as a cooperator of obstetric doctors.

Methods and Findings

For national statistics, data from a ministry of health and welfare statistical year book of 2015 and legislative assembly records in 2007 were retrieved.

The midwives can be divided into 3 categories, according to their working place：1）midwife office in which the midwives are conducting the delivery by themselves（2.3%）；2）hospital in which the midwives are assisting the obstetric doctor during labor and delivery（63%）；and 3）postpartum care unit in which the midwives are involved only in the postpartum care and neonatal care（1.5%）. Based on the national report, the deliveries in midwife offices accounted for only 0.3% of the total birth in 2014（1,330 babies）, and most midwives are acting as assistant for doctor during delivery or involving in the postpartum care.

To explore the proper model, we interviewed 2 midwives who are working in the "natural birth centers" on their current roles during labor and delivery. In these hospitals, midwives take the role of a partner with doctors in deliveries. Private midwives give several programs to help mothers being ready before birth such as nutritional consultation, exercise lessons and delivery rehearsals. When the labor pain begins, midwives decide the time of administration and calling for help of doctors in emergency situation. After administration, private midwives stay by mothers' sides encouraging them, providing massages, and also performing adequate breathing practices.

Conclusion

Although midwives have taken various roles in different institutions, there were no definite guidelines that define their jobs thoroughly. Here are a few suggestions to establish proper roles of midwives. First, the roles of doctors and midwives should be reestablished for efficient cooperation. Second, to overcome the issue with the lack of proper training institutions for midwives, obstetricians should provide education and practical training for midwives. Third, in case of emergency during birth of midwives, well-established cooperation is required with the nearby hospitals for high risk mothers. Finally, mothers with high risks in birth should be evaluated by obstetricians. With these above-mentioned methods, healthier and safer medical environment will be guaranteed to mothers.

3) Management of labor, delivery and postpartum with midwife

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The definition of midwife is a person, who is trained to assist woman in childbirth. The occupation was set up for women`s demand. Midwives believe that to safe satisfying health care with respect for human dignity and cultural determination, and to active participation in all aspects of care. Taiwan government makes a midwife law in 2005. The business of midwife includes delivery, prenatal care, and postpartum care. Licensed as certified nurse-midwife by the examination Yuan of R.O.C. Total 183 midwife clinics are registered in Taiwan. Once pregnant woman wants to have prenatal care in midwife clinic, the midwife can help to arrange all the prenatal examination, like blood survey and ultrasound. Although the patient still need to have these examinations at hospital. The government branch, centers for disease control (CDC, Taiwan), will pay consult fees up to 50～100NT to midwife each prenatal consultation. The midwife can provide more detail health counseling and prenatal class education. Our government also encourage people, living in remote districts, to have prenatal care and delivery at midwife clinics by means of medical fee remission. Midwives can perform vaginal delivery, fleet enema, ICP, perineorrhaphy, and giving oxytocin independently. In the respect of postpartum business, midwives also provide Pap smear and infant health care.

However, the mechanism of midwife clinics is still far from perfect. We need more clear clinical practice guidelines and medical referral system. Why is the midwife policy so important? First, the obstetricians decrease year by year. Second, we can cut down the medical cost. Third, diversified services can be offered.

International Workshop for Junior Fellows：
3. Management of labor, delivery and postpartum with midwife

4) Management of labor, delivery and postpartum with midwife in Japan

Ayaka Nakashima, Takashi Nakasuji, Yoshinori Moriyama
JSOG

In the 1950s, 95% of babies in Japan were born at midwifery centers or at home, assisted by midwives without obstetricians. However, in the 1960s, this proportion was exceeded by that of deliveries at hospitals that were assisted by obstetricians and midwives. Today, about 30,000 midwives and 10,000 obstetricians assist 1 million deliveries per year, and ＞99% of babies are born at hospitals. Owing to the high medical quality of perinatal and maternal management, perinatal and maternal mortality rates have reached as low as 2.6 per 1,000 live births and 3.5 per 100,000 live births, respectively.

In outpatient departments, obstetricians perform ultrasonography and blood tests, and prescribe medication if needed. On the other hand, midwives give health guidance about nutrition, exercise, and breastfeeding to pregnant woman. They are not permitted to make a diagnosis or prescribe medication. In inpatient departments, midwives observe the process of labor through internal examination and cardiotocography. They assist normal vaginal delivery in the presence of obstetricians, and obstetricians perform episiotomy and suture perineal laceration. If the delivery deviates from the normal process, such as in a non-reassuring fetal status according to the 5-tier system or prolonged labor, midwives consult obstetricians. Obstetricians assess the necessity of intervention and perform vacuum extraction, forceps delivery, or cesarean delivery, if needed. As many facilities lack pediatricians, the cooperation of obstetricians with midwives in case of neonatal resuscitation is highly important. Most obstetricians and midwives are qualified to perform neonatal cardiopulmonary resuscitation. Women in puerperium, along with their babies, usually stay at hospitals for a few days and receive guidance on breastfeeding and bathing their babies from midwives. Women in puerperium undergo examination by obstetricians at least once before discharge. Both women in puerperium and their babies are followed up for 1 month. Obstetricians conduct physical examinations to women in puerperium, and midwives provide advice about the puerperal period and child care. Pediatricians assess babies' growth.

To compliment the shortage of obstetricians and satisfy various needs in pregnancies, deliveries, and baby care, systems have been established where midwives can handle deliveries on their own initiative, that is, in-hospital midwifery centers, where midwives take care of normal pregnant women and handle deliveries in facilities where emergency treatment can be performed, and maternity outpatient department, where midwives perform prenatal checkup and health guidance for normal pregnant women in hospitals.

As all deliveries could not be handled by obstetricians or midwives alone because of the shortage of obstetricians and the expanding demand for high-level medicine, obstetricians and midwives share roles and cooperate with each other in effective ways for better management of pregnancies in Japan.

1）Sound development of gynecologic laparoscopic surgery in Japan

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Endoscopic surgery has many advantages compared to open surgery and is well accepted and performed in daily practice in Japan. Experience of conducting laparoscopic surgeries is mandatory to obtain a board certification of Japanese Society of Obstetrics and Gynecology. Most of laparoscopic and hysteroscopic surgeries for benign gynecologic diseases are covered by health care insurance. In malignant conditions, only laparoscopic hysterectomy and pelvic lymphadenectomy are covered by the insurance now, but radical hysterectomy and paraaortic lymphadenectomy are highly expected to be covered soon. On the other hand, laparoscopic surgeries have disadvantages compared to open surgeries in some points. It demands a high skill to manipulate tissues and organs in a limited space with a limited movement of forceps. Recently, poor performances of a general laparoscopic surgeon have been highly publicized and attracted huge attention in Japan. Japanese Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy (JSGOE) regards safety of endoscopic surgery as utmost important and organizes various activities. The society has its original board certification system. Applicants for the certification have to have completed at least 100 laparoscopic surgeries and submit a non-edited video of his/her operation, which will be reviewed by the referees. Usually, around a half of the applicants are admitted to fulfill the criteria. In addition, the board-certified members are obliged to report the number and the types of operations including complications. By this surveillance system, JSGOE garners the data of laparoscopic surgeries in Japan and uses it for education and training of the members. JSGOE publishes its own journal and guidelines and hold the annual congress, which collected around 800 abstracts in 2016. JSGOE is also committed to internationalization by partnership with global societies and is pleased to communicate and cooperate with foreign organizations.

2) The World of Advanced Laparoscopy

Sven Becker

Frankfurt University, Germany

Laparoscopy has changed gynecologic surgery more than any other technology since the beginning of academic surgery in the late 1900s. Today, all major areas of gynecologic surgery are dominated or heavily influenced by minimally invasive surgery：hysterectomy, myomectomy, endometriosis–surgery, oncologic surgery and surgery for infertility. Often, the way we practice gynecology has changed because of laparoscopy, as is especially evident in our treatment of endometriosis and of endometrial cancer. This presentation will look at different aspects of specific surgeries as well as surgical challenges such as hysterectomy, endometriosis surgery and laparoscopy for gynecologic oncology and review available data. The second focus will be on practical advice with regard to setup, surgical strategy as well as tips and tricks for actual surgery. This will be a surgeon's presentation both for experiences colleagues as well as for those interested in expanding their clinical horizons in the world of laparoscopy.

Hysterectomy. Laparoscopic hysterectomy will be used to explain basics of advanced laparoscopy：setup, anesthesia, team support. One technical approach will be described. The data regarding different forms of hysterectomy sill be reviewed.

Endometriosis. Overall treatment strategies for endometriosis incorporating laparoscopy will be reviewed. The data regarding radicality and management of deep infiltrating endometriosis will be analysed. Tips and tricks regarding Grade III and IV endometriosis will be discussed.

Oncologic Surgery. The available data concerning laparoscopy for endometrial, cervical and ovarian cancer will be reviewed. The technical approach to the pelvic sidewall, to the radical ureteral dissection as well as to the abdominal retroperitoneum will be discussed.

Finally, the importance of new technologies such as 3D–Vision, haptic feedback and new energy sources（harmonic scalpel）will be reviewed in light of recent advances.

IS-AC-1-1

Optimal functional maturation of the premature ovine lung is independent of peak fetal steroid exposure Matthew Kemp[1], Haruo Usuda[1], Judith Rittenschober-Bohm[2], Peter Eddershaw[3], Alan Jobe[4] *The University of Western Australia, Australia[1], University of Vienna, Vienna, Austria[2], GlaxoSmithKline, Stevenage, UK[3], Cincinnati Children's Hospital Medical Centre, USA[4]*

Objectives Antenatal steroid therapy to improve neonatal outcomes has undergone limited optimisation. We used a pregnant sheep model to investigate the relationship between the magnitude of fetal steroid exposure and lung maturation. **Methods** Ewes with single fetuses (120d gestation) received 12h betamethasone phosphate (BP) infusions giving constant fetal plasma betamethasone levels of either ; i) 10ng/mL ; ii) 2ng/mL (n=9/group) ; or iii) two intramuscular injections of 0.25 mg/kg Celestone Chronodose (CC) separated by 24h (n=10/group). Saline-treated animals served as controls (n=19). At 122 d gestation, fetuses were delivered, ventilated to assess gas exchange, and euthanised. Group differences were tested with ANOVA. Betamethasone levels were confirmed by LCMS analysis of serial samples from additional, identically-dosed catheterised fetuses (n=4/group). **Results** LCMS analysis confirmed BP infusions maintained fetal plasma targets of 10ng/mL and 2ng/mL betamethasone for 12h. Fetal betamethasone concentrations in the 2ng/mL BP and 0.25mg/kg CC groups were similar, and 2-3 times lower than the 10ng/mL BP group. After 30 minutes of ventilation, arterial cord blood pH ($p=0.43$), paCO2 ($p<0.01$), tidal volume ($p<0.01$) and compliance ($p=0.005$) in the 10ng/mL BP group and paCO2 alone ($p=0.019$) in the 2ng/mL BP group were improved vs. control. Arterial cord blood pH, paO2, paCO2, tidal volume, compliance, peak inspiratory pressure and lung gas volume in the 0.25mg/kg CC group were all significantly improved vs. control ($p<0.01$). **Conclusions** Higher fetal betamethasone exposures did not yield improved preterm pulmonary function. In preterm sheep, lung maturation can be achieved at fetal betamethasone levels substantially lower than those achieved with current clinical dosing.

IS-AC-1-2

Fetal therapy model of myelomeningocele with three-dimensional skin using amniotic fluid-derived iPS cells Kazuhiro Kajiwara[1], Seiji Wada[2], Norimasa Ihara[3], Hidenori Akutsu[3], Haruhiko Sago[2], Aikou Okamoto[1] *The Jikei University School of Medicine[1], National Center for Child Health and Development[2], National Center for Child Health and Development[3]*

Objective Current operative approach of myelomeningocele shows improved neurological prognosis, but requires large uterine incision that results in serious pregnancy complications. We presumed that a less invasive fetal therapy such as a skin patch is effective for myelomeningocele, and attempted to generate human induced pluripotent stem cells (iPSCs) from amniotic fluid cells (AFCs) and induced differentiation into a epithelial lineage to create transplantable biomaterials. **Methods** We performed primary culture of AFCs obtained from patients with twin-to-twin transfusion syndrome. To generate iPSCs, reprogramming genes using an episomal vector were introduced. iPSC-derived keratinocytes were reconstructed using *in vitro* three-dimensional cultures. To investigate the efficacy of "Artificial Skin" *in vivo*, we have developed a myelomeningocele rat model and performed transplantation assays of "Artificial Skin" into rat fetuses. Tissue and cytogenetics assays of transplanted tissue were performed after birth. **Results** Multiple cell lines of iPSCs were effectively generated from AFCs. These iPSCs expressed undifferentiated markers such as OCT3/4 and NANOG, and displayed ability of pluripotent differentiation into all three germ layers both *in vitro* and *in vivo*. Our iPSCs successfully differentiated into keratinocytes with high expression level of epithelial markers such as keratin 14 and P63. Furthermore, these iPS-derived keratinocytes were successfully reconstructed into multilayered epidermis. Through transplantation of "Artificial Skin", the defects of the myelomeningocele model in rat fetuses were successfully treated. **Conclusion** Our fetal cell therapy is minimally invasive and may become a novel treatment for myelomeningocele.

IS-AC-1-3

Healthy, infection-free growth of preterm lambs maintained with ex-vivo uterine environment (EVE) therapy for one week Haruo Usuda[1], Gabrielle C. Musk[2], John P. Newnham[1], Matthew W. Kemp[1] *School of Women's and Infants' Health, The University of Western Australia, Australia[1], Animal Care Services, The University of Western Australia, Crawley, WA 6009, Australia[2]*

Objectives Extremely preterm infants are at significant risk of morbidity and mortality, suggesting a need for alternative life-support strategies. *Ex-vivo* uterine environment (EVE) therapy is an experimental neonatal intensive care strategy. Gas exchange is provided by parallel membranous oxygenators connected to the umbilical vessels, and the infant submerged in protective artificial amniotic fluid. Herein, we aimed to achieve one week of healthy, infection-free growth in preterm lambs using our EVE therapy platform. **Methods** Six ewes with singleton pregnancies underwent surgical delivery at 114d gestation (term is 150d). Fetuses were adapted to EVE therapy and maintained for one week with constant monitoring of key physiological parameters. Antibiotics and nutrients were provided by continuous infusion. Humerus and femur lengths were measured daily with ultrasound ; Blood cultures were performed daily to exclude infection. Six pregnant control animals were euthanized at 121d gestation to allow comparative post-mortem analyses. Data were tested for group differences with ANOVA. **Results** Five of six fetuses completed one week of EVE therapy with stable vital signs and no significant differences ($p>0.05$) in arterial spO2, lactate or weight at euthanasia vs. control. Blood cultures were negative for infection. Humerus ($p<0.05$) and femur ($p<0.001$) lengths were significantly increased at euthanasia, relative to length at EVE therapy day one. **Conclusions** Preterm lambs were maintained in a stable condition for one week using EVE therapy. Significant growth was obtained without clinically significant bacteremia. A refined *ex-vivo* uterine environment therapy platform may thus provide an avenue to improve outcomes for extremely preterm infants.

IS-AC-1-4

Urinalysis in Obstetrical Triage Visits Amy Addante, Bruce Morris *Mercy Hospital St. Louis, USA*

Introduction Urinalysis is commonly used in obstetrical triage visits for evaluation of a myriad of symptoms. Symptomatic and asymptomatic bacteriuria is commonly associated with pregnancy due to physiologic changes of the urinary tract in pregnancy. Treatment of both symptomatic and asymptomatic bacteriuria in pregnancy has been shown to decrease the incidence of pyelonephritis and preterm deliveries. The goal of this study was to determine if a urinalysis positive for reflex for culture was predictive of positive urine culture. Lab criteria for reflex culture included presence of leukocyte esterase, presence of nitrites, or pyuria of>6 WBCs on microscopy. **Methods** A retrospective chart review was performed which analyzed urinalysis tests from all obstetrical triage visits at a single hospital, at any gestational age, for all indications. Data collected included gestational age, indication for urinalysis, urinalysis result, and urine culture result if indicated. Patients were excluded if they had

received antibiotic therapy in the last 7 days. **Results** A total of 657 urinalyses were identified. 10 patients were excluded due to recent antibiotic therapy. 299 urine cultures were performed. There were 24 positive cultures of which only 11 had significant colony count of greater than 100,000. **Conclusion** The most common indications for urinalysis in triage visits are preterm labor symptoms and pre-eclampsia work up. Urinalysis that is positive for reflex culture has a low predictive value for UTI.

IS-AC-2-1

The Effect of Chemical inhibition of Lysyl-tRNA Synthase-Laminin Receptor in Ovarian Cancer E Sun Paik, Ju Young Park, Myeongseon Kim, Sooyoung Jeong, Ji Hye Kim, Chel-Hun Choi, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Purpose Lysyl-tRNA synthase (KRS), protein synthase enzyme in the cytosol, relocates to the plasma membrane after a laminin signal and stabilizes a 67-kDA laminin receptor (67LR) that is implicated in cancer metastasis. In this study, we sought to evaluate the significance YH16899, small compound which binds to KRS to impinge on the interaction of KRS with 67LR, as a tumor suppressor of epithelial ovarian cancer (EOC). **Method** KRA and 67LR expression was examined in 52 formalin-fixed, paraffin-embedded ovarian cancer tissues using immunohistochemistry, and survival comparison with prognostic significance were analyzed. Ovarian cancer cell lines including HeyA8 and SKOV3ip1 were treated with the YH16899, and effects on cell survival, apoptosis, migration, and invasion were examined. Moreover, the effects of YH16899 on tumor growth were evaluated using ovarian cancer cell line xenograft models. **Result** Patients with high KRS and 67LR expression had lower overall survival and recurrence-free survival rates than those with low expression. Treatment with YH16899 significantly reduced viability, migration, invasion and increased apoptosis in ovarian cancer cells. Furthermore, YH16899 significantly decreased in vivo tumor weight in the xenograft models of ovarian cancer. **Conclusion** We provide the evidence that KRS and 67LR are involved in progression of EOC. Our data suggest that specific modulation of a cancer related KRS-67LR interaction by YH 16899 may offer way to suppress metastasis in treatment of EOC.

IS-AC-2-2

Anti-cancer Effect of Ulipristal Acetate in Uterine Leiomyosarcoma Ji Hye Kim, Jeong-Won Lee, Wonkyo Shin, Minjung Kwon, Ju Young Park, E Sun Paik, Hyeyeon Yi, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Objectives Ulipristal acetate (UPA, selective progesterone receptor modulator) is used for pre-operative treatment of uterine fibroids. However, anti-cancer effect of leiomyosarcoma (LMS) has not yet been reported. This study was designed to investigate preclinical efficacy of UPA as anti-cancer agent in LMS cells. **Methods** We treated UPA in human LMS cells (SK-UT-1, MESSA) to evaluate the effect on cell proliferation using MTT assay. To check the apoptosis according to UPA treatment, we performed ELISA in LMS cells. In addition, in vivo therapy experiments of UPA were done using xenografts using SK-UT-1 and MESSA in nude mice. SK-UT-1 or MESSA cells were injected into mice (n=10 per group) and these were randomly assigned to two groups : PBS (control), oral UPA 2mg/kg once daily. All specimens were fixed in 4% paraformaldehyde and paraffin-enclosed for examination. **Result** UPA significantly inhibited the cell survival the growth and increased the apoptosis in SK-UT-1 and MESSA cells. In in vivo experiments, UPA significantly decreased the tumor growth in both mice with SK-UT-1 and MESSA cells compared with control (both $p<0.001$). Moreover, the immunohistochemical analysis using in vivo tumor samples showed that UPA treated group decreased Ki-67 expression and increased apoptosis revealed by TUNEL assay compared with control. **Conclusions** We found that UPA have anti-cancer-effects in LMS cells via the action to cell proliferation and apoptosis through in vivo and in vivo tests. Further studies using patient-derived tumor xenograft model and detailed mechanisms of anti-cancer effects for UPA will be needed.

IS-AC-2-3

Prognostic impact of *PIK3CA* mutation in stage IIIB or IVA cervical cancers treated by concurrent chemoradiotherapy with weekly cisplatin Bouchra Lachkar, Takeo Minaguchi, Shuling Liu, Ayumi Shikama, Nobutaka Tasaka, Azusa Akiyama, Manabu Sakurai, Sari Nakao, Hiroyuki Ochi, Toyomi Satoh *Tsukuba University*

Objective The standard treatment for locally advanced cervical cancer is cisplatin-based concurrent chemoradiotherapy (CCRT). Although activated PI3-kinase/Akt pathway is known to be involved in both cisplatin-resistance and reduced radiosensitivity, to date only a few studies have reported significant associations between *PIK3CA* gene mutational status and outcome by CCRT in the disease. The aim of this study was to clarify the prognostic significance of *PIK3CA* mutational status in locally advanced cervical cancers treated by CCRT. **Methods** We analyzed *PIK3CA* mutation in 50 patients with stage IIIB or IVA cervical carcinomas treated by CCRT with weekly cisplatin. Study protocol was approved by the ethical committee of our institution. All patients provided informed consent. Median follow-up duration was 77 months. **Results** *PIK3CA* mutation was found in 7 patients (14%), and all of the mutations were mapped inside the helical or kinase domains of p110α protein. Patients with wild-type *PIK3CA* showed significantly improved overall survival as compared with mutated pateints ($p=0.016$). Among prognostic factors including age, histological type, and pelvic/para-aortic lymphnode metastases diagnosed by computed tomography, the univariate analysis showed that *PIK3CA* mutation, pelvic node metastasis, and advanced FIGO stage were significant for poor overall survival ($p=0.024$, 0.047, and 0.033, respectively). The subsequent multivariate analysis demonstrated that *PIK3CA* mutation and advanced stage were significant and independent factors for poor overall survival ($p=0.0085$ and 0.034, respectively). **Conclusion** The current findings suggest that molecular inhibitors targeting the PI3-kinase/Akt pathway may improve the outcome by CCRT in locally advanced cervical cancers harboring *PIK3CA* mutation.

IS-AC-2-4

The impact of anti-PD-1 antibody Nivolumab on chemo-sensitivity of platinum-resistant recurrent ovarian cancer Yoshihide Inayama[1], Junzo Hamanishi[1], Masaki Mandai[2], Noriomi Matsumura[1], Kaoru Abiko[1], Ryusuke Murakami[1], Ken Yamaguchi[1], Tsukasa Baba[1], Ikuo Konishi[3] *Kyoto University Hospital[1], Kinki University Hospital[2], Kyoto Medical Center[3]*

Objective Platinum-resistant recurrent ovarian cancer is generally refractory to chemotherapy. Anti-PD-1 antibody Nivolumab showed 10% durable complete response in our phase II clinical trial. However how Nivolumab affects sensitivity to subsequent chemotherapy in ovarian cancer patients remains unclear. We investigated the effect of Nivolumab on subsequent chemotherapy in ovarian cancer. **Methods** We retrospectively analyzed the follow-up data from 20 patients with platinum-resistant ovarian cancer who had received Nivolumab in phase II

clinical trial at our hospital. The cut-off date was 1st Sep 2016. **Results** Among 20 patients (pts), 2 pts showed complete response to Nivolumab and have no recurrence of disease without any additional treatment, while the remaining 18 pts showed progressive disease (PD). 13 of 18 pts received chemotherapy (pegylated liposomal doxorubicin [PLD, n=3], gemcitabine [GEM, n=5], nedaplatin [NED, n=2], and others, including duplicates), and 2 pts showed partial response (PR), 1 stable disease (SD), 9 PD and 1 not-evaluated. The best response rates/the disease control rates of these agents (PLD, GEM or NED) were 67%/67%, 0%/20% or 50%/100%, respectively. **Conclusion** Nivolumab may improve sensitivity to chemotherapy following Nivolumab treatment and hence prolong overall survival in progressive cases of platinum-resistant recurrent ovarian cancer.

IS-AC-3-1

A model system for syncytiotrophoblast generation from human pluripotent stem cells Shinichiro Yabe[1], Danny J. Schust[2], R. Michael Roberts[2] *Aiiku Hospital[1], University of Missouri, Columbia, USA[2]*

Objective Syncytiotrophoblast (STB) releases placental hormones and plays a primary role in exchange of gases and nutrients. In addition, STB forms the interface with maternal blood and is important for maternal-fetal transmission. Here we generated STB in vitro from human embryonic stem cell (ESC) and compared the STB with that generated from cultured cytotrophoblast isolated from term placentas. **Methods** We conducted STB by treating with BMP4, ALK4/5/7, and FGF2 inhibitor from ESC and made morphological assessment by immunofluorescence. And we compared the transcriptome profiles between STB generated from ESC (STB-ESC) and STB generated from term placentas (STB-TP) by RNA-seq. This study was approved by the National Institutes of Health and the local research ethics committee. **Results** Immunostaining analysis indicated STB-ESC was positive for STB markers CGA, CGB, and ERVW-1. The transcriptome analysis provided evidence that the STB marker genes, enzymes involved in progesterone/estrogen biosynthesis e.g., *HSD3B1*, *CYP11A1*, and *CYP19A1*, and various transporters such as solute-carriers and ATP-binding-cassette, were expressed in STB-ESC same as in STB-TP. However, there were major discrepancies in expression of several other genes. *GABRP*, *NTRK2*, *WFDC2*, and *VTCN1*, appear to be features of the early placental samples, were up-regulated in STB-ESC but barely in STB-TP. Conversely, *PSG4*, *CSH1*, and *ALPP*, which are associated with term placentas, were the opposite result. Moreover, the expression of Zika virus entry cofactors *AXL* and *TYRO3* was much higher in STB-ESC than in STB-TP. These results suggest that STB-ESC represents STB from early stage pregnancies. **Conclusion** ESC-derived STBs may provide the first in vitro model of initial STB formation in early placenta, which cannot be studied in vivo.

IS-AC-3-2

Pregnancy outcomes in patients with pulmonary arterial hypertension associated with congenital heart disease Jacky Nizard[1], Magalie Ladouceur[1,2,3], Marielle Gouton[1], Louise Benoit[1], Jelena Radojevic[4], Adeline Basquin[5], Claire Dauphin[6], Sebastien Hascoet[7], Pamela Moeri[8], Charlene Breda[9] *Hospitalier Pitie Salpetriere Paris APHP, France[1], Centre de reference des Malformations Cardiaques Congenitales Complexes, M3C, France[2], Adult Congenital Heart Disease Unit, Department of Cardiology, Hopital Europeen Georges Pompidou and Necker Hospital, APHP, Paris Descartes University, Paris, France[3], Cardiologie congenitale, Strasbourg, France[4], Cardiologie Pediatrique et Congenitale, Service de cardiologie, CHU Rennes, France[5], Cardiology Department, CHU Clermont-Ferrand, France[6], Congenital Heart Diseases Department, Marie Lannelongue Hospital, Plessis Robinson, France Inserm UMR 1048, equipe 8 I2MC institut des maladies metaboliques et cardiovasculaires, Paul Sabatier University, Toulouse, France[7], Cardiology Department, Hopital Pasteur, University de Nice Sophia-Antipolis, Nice, France[8], Pediatric and Congenital Cardiology Unit, M3C Regional Reference Center, Montpellier University Hospital, Montpellier, France[9]*

Maternal mortality in pregnant women with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is probably lower than that in available data. To evaluate this hypothesis, we collected data of pregnancies in women with PAH-CHD. **Methods** Women with PAH-CHD followed in seven French referral centres were retrospectively included from 1997 to 2015. All pregnancies were recorded. We collected data on maternal, obstetrical and neonatal outcomes. **Results** 28 pregnancies in 20 women (26 ± 6 years old) with PAH-CHD were managed during this period. There were 18 complete pregnancies (≥20 weeks gestation (WG)), 8 abortions and 2 miscarriages. Six (33%, 95% CI (11.9 to 54.3)) patients experienced severe cardiac events. The concerned women had lower resting oxygen saturation (79.6 ± 4.1% vs 89.3 ± 3.8%, $p < 0.01$). The most common cardiac complications during complete pregnancies were heart failure (n=4) and severe hypoxaemia (n=5). Heart failure was overall severe, requiring inotropic treatment in three patients, mechanical circulatory support in one and led to one maternal death (mortality=5.0% 95% CI (0.1 to 24.9)). Obstetrical complications occurred in 25% of pregnancies. Small for gestational age was diagnosed in 39% (7/18) of fetuses. Prematurity was frequent (78%), but no neonatal death occurred. **Conclusions** Outcome of pregnancy in women with PAH-CHD is better than previously reported, with only 5% maternal mortality in our cohort. However, because of the severity of heart failure and the high rate of neonatal complications, patients should still be advised against pregnancy.

IS-AC-3-3

Mean Sac Diameter is an Important Indicator for Choosing the Better Method to Managing Cesarean Scar Pregnancy：a Retrospective Cohort Study Ying-Cheng Chiang, Yi-An Tu, Jehn-Hsiahn Yang, Shin-Yu Lin, Chien-Nan Lee, Jin-Chung Shih *National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

Objective To identify the risk factors associated with treatment failure in women with Cesarean scar pregnancy. **Methods** In a retrospective study, medical records were reviewed for 90 patients with CSP treated at National Taiwan University Hospital from 1994 to 2015. They were managed primarily with either hysterotomy, evacuation or methotrexate. Receiver operating characteristic curve analysis and logistic regression analysis were used to evaluate the factors associated with treatment failure. **Results** The success rates were 100% for 44 women with hysterotomy, 83.3% for 18 women with evacuation and 57.1% for 28 women with methotrexate. ROC curve analysis showed 8 week gestational age (GA) and 4 cm mean sac diameter (MSD) were both good for predicting treatment failure of primary evacuation and methotrexate. The area under curve of MSD 4 cm was better than GA 8 weeks (0.868 versus 0.689). The multivariate logistic regression analysis confirmed the MSD more than 4 cm (OR：68.99, 95% CI：6.27-759.60, p=0.001) was the only independent risk factor for treatment failure. **Conclusion** Primary hysterotomy was suitable for any size of CSP. Treatment failure of primary evacuation or methotrexate was usually encountered when MSD more than 4 cm.

IS-AC-3-4

THYROID DISORDERS AND PREGNANCY OUTCOME—AN AMBISPECTIVE COHORT STUDY AT A SECONDARY CARE CENTRE IN SOUTH INDIA Shashikala Bhat, Ashwini Ap, Shashikiran Umakanth *Melaka Manipal Medical College, Manipal University, India*

Background Thyroid disorders and autoimmunity are associated with adverse pregnancy outcomes. Pregnancy may modify the course of these conditions. **Objective** To study pregnancy outcome in thyroid disorders. **Materials and Methods** This ambispective cohort study was done from December 2014 to November 2015 at Dr. TMA Pai Hospital, Udupi. All singleton pregnant women willing for study were included. Multiple pregnancy, known hypertensive or diabetic were excluded. Based on TSH during booking visit, women were divided into 2 groups. Group A (n=81) included those with abnormal TSH (new and overt). Group B (n=1167) included those with normal TSH. Free T3, free T4, anti-thyroid peroxidase (anti-TPO) antibody and thyroid receptor antibody levels were done if TSH levels were abnormal. Depending on underlying disorder, treatment was given. TSH was repeated every 4-6weeks and treatment optimized. Both groups were followed and pregnancy outcomes compared. **Results** Groups were similar in age, parity and demographic characteristics. Prevalence of hypothyroidism was 5.7% (subclinical 3.5%, overt 2.2%) and hyperthyroidism 1.1% (gestational 0.9%, overt 0.2%). Anti-TPO positive women needed 37% more levothyroxine than negative women (p=0.05). Abortion, gestational hypertension and low birth weight were higher in anti-TPO women (13% vs 2%, 13% vs 4.65% and 21.7% vs 9.3%). Women with pre-existing hypothyroidism needed 28% more levothyroxine than their pre-pregnancy dose ($p<0.05$). Pregnancy outcomes were similar in both groups. **Conclusion** With optimized treatment, adverse outcomes in pregnancy with thyroid disorders were similar to general pregnant population. Mandatory TSH screening in first trimester helped identify subclinical cases and prevent adverse outcomes.

IS-AC-3-5

Uterine flexion suture : Modified B-Lynch uterine compression Suture for treatment of uterine atony during cesarean section Srisuda Songthamwat, Metha Songthamwat *Udonthani Medical Education Center, Thailand*

Background To report our clinical experience of applying a uterine flexion suture which was modified from the B-Lynch uterine compression suture for treatment of atonic uterus during cesarean section. **Method** A retrospective descriptive study describing the use of a new technique, uterine flexion suture operation, for treatment of uterine atony during cesarean section. The study period was from January 2009 to February 2016 at Udonthani Hospital, Thailand. The atonic uterus during caesarian section were treated by manual compression, intravenous oxytocin, ergometrine and prostaglandins then observed for 10-15 minutes before applying a uterine flexion suture in cases of non-response to medical treatment. The patients were observed for vaginal bleeding, hematometra and infection after operation. Results of ultrasound scan of the uterus on days 1, 7 and 30 post-operation were also reviewed. **Results** Fifty three patients with uterine atony during cesarean delivery received the operation by this technique. Mean age of patients was 27.1 (15-44 years). Twenty patients were primipara. The indications for cesarean section were twenty six cases (49.1%) of cephalopelvic disproportion, ten cases (18.9%) of previous cesarean section. Ten patients needed blood transfusion after surgery. Neither post-operative excessive bleeding nor hysterectomy was observed. There was no hematometra or serious complication after surgery. The estimated time for uterine flexion suture is only two to three minutes and was very easy to perform. **Conclusions** Uterine flexion suture technique which was modified from the B-Lynch operation was cheap, quick and effective in treatment of atonic postpartum uterus in women undergoing cesarean section.

IS-AC-4-1

Comprehensive analysis of methylation of blastocysts cultured by four different constituents derived from In Vitro Fertilization in mice Yu Horibe, Hideo Matsui, Kazunori Hashimoto *Tokyo Women's Medical University Hospital*

Objective Since Assisted Reproductive Technology (ART) established, various methods were examined to improve the rate of implantation and further subsequence, whereas imprinted diseases attributed to ART have been pointed out. However, does manipulation of ART actually perturb methylation? We cultured mice zygotes under the different condition, then investigated condition of methylation comprehensively by Reduced Representation Bisulfite Sequence method. **Methods** 8 weeks ICR female and 10 weeks ICR male mice were used. 7.5 IU PMSG and 7.5 IU HCG were injected as ovarian stimulation. The embryos were cultured and evaluated 84 hours (E=3.5), which they reached to blastocyst stage, into 4 different media (1. NoAA =KSOM media only, 2. EAA=NoAA+Essential Amino Acid, 3. NEAA=NoAA+Non-Essential Amino Acid, 4. AllAA=NoAA+ Essential Amino Acid+Non-Essential Amino Acid). Obtained blastocysts were sequenced by Next Generation Sequencer and analyzed by R software. **Results** There is no difference in rate of reaching to blastocyst between 4 media. As methylation analysis, highly methylated regions are confirmed at NEAA, which is anticipated as resistance towards reprogramming. Under the regional methylation analysis, there is less methylation change at 5'UTR and promoter compared to other region. Focused on imprinted gene, aberrant methylation change was confirmed at several imprinted gene such as Mest, H19 and Nespas. **Conclusion** In conclusion, Amino acid may protective role towards methylation by stimulation of external environment. Lack of amino acid may disturb methylation at specific imprinted gene. Further study of relationship between aberrant methylation and gene expression is needed.

IS-AC-4-2

Characteristic in the placental differentiation process, using human induced pluripotent stem cells Junya Kojima[1], Hidenori Akutsu[2], Hiroe Ito[1], Naoaki Kuji[1], Keiichi Isaka[1] *Tokyo Medical University[1], National Center for Child Health and Development[2]*

Objective It was reported the hiPS cells can differentiate into extra-embryonic cells in the presence of BMP4. However, parental cells and culture conditions might affect differentiation potential. In this study, the effect of parental cells and culture condition were examined in our hiPS cell culture system. **Methods** Three iPS cell lines (menstrual blood, uterine endometrium and placental artery) established in our laboratory were used in this study. The iPS cells were subcultured to the animal and human-drived substitues free medium, supplemented with Bone morphogenetic protein 4 (BMP4 0-100 ng/mL) up to 9 days. Morphologic change, hormone level in supernatant and 20 genes expression levels about trophoblast related genes were examined. **Results** The morphologic changes occurred after about 5 days. The concentration of HCG, P4 and the expression levels of various trophoblast marker genes are upregulated by BMP4 in dose-dependent manner in all types of hiPS cells. Furthermore, HCG and HLA-G positive cells were recognized by immunohistochemistry. Furthermore, high dose BMP4 differentiation formed cluster in array card analysis. However, not trophoblast-related miRNA expressions but other markers of miRNA were

upregulated by BMP4. **Conclusion** It was demonstrated that hiPS cells could differnttiate to trophoblast lineages in animal and human-drived gradient free conditions, since the expression states of trophoblast-related genes and proteins were detected on BMP4 supplementation. However, non-coding RNA expression states were affected by donor cell types rather than dose effect of BMP4. It might indicate the non-coding RNA is important for optimal conditions for trophoblast differentiation.

IS-AC-4-3

Involvement of NADPH oxidase and NF-κB activation in CXCL1 induction by vascular endothelial growth factor in human endometrial epithelial cells of patients with adenomyosis
Tsung-Hsuan Lai[1,2,3], Pi-Hui Wu[2], Wen-Bin Wu[2] *Cathay General Hospital, Taipei, Taiwan[1], School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan[2], Institute of Systems Biology and Bioinformatics, National Central University, Taoyuan City, Taiwan[3]*

Chemokines were known to participate in inflammation and angiogenesis but have been recently recognized to be involved in embryonic implantation and endometrial-related pathologies. Among these kimokines, the CXC kimokine, such as CxCL1, have potential roles to work as biomarkers to identify patients with uterine adenomyosis. In this study, human endometrial epithelial cells (HEECs) were derived from patients' endometrium with adenomyosis. The inductive effects of CXCL1 production by various mediators/growth factors were investigated in the HEECs. Of the tested mediators, VEGF was found to be the most effective. The immunohistochemistry and RT-PCR analysis revealed a positive staining for VEGF and CXCL1 at the epithelium and the presence of CXCL1 in the human endometrium specimens, respectively. The CXCL1 induction by VEGF could be reduced by the antagonist for VEGF receptor (VEGFR), and by the inhibitors of NADPH oxidase and NF-κB signaling pathway. However, it was not affected by sex hormones and the inhibitors for MAPKs, PI-3K, protein kinase A and C. In parallel, VEGF induced P47 phox NADPH oxidase activation. IκBα phosphorylation. NF-κB translocation and NF-κB DNA complex formation in the HEECs. Moreover, the CXCL1 released by the HEECs with VEGF stimulation attracted vascular endothelial cell migration. Taken together, we show that VEGF and CXCL1 are expressed in epithelium of the endometrium with adenomyosis and demostrate here for the first time that VEGF is capable of inducing CXCL1 expression in HEECs through VEGFR, P47 phox NADPH oxidase and NF-κB signaling pathway, which is functionally required for attracting vascular endothelial cell migration.

IS-AC-4-4

Anatomical and functional assessment of the pelvic autonomic nerves using a female swine model
Hee Seung Kim, Maria Lee, Jae Weon Kim *Seoul National University College of Medicine, Korea*

Objective To develop a female swine model for anatomical and functional assessment of the pelvic autonomic nerves, and then validate the assessment in women. **Methods** We used 11 female domestic swine, weighing 30 to 40 kg. Among them, we sacrificed three swine for the anatomical assessment, and eight swine for the functional assessment of the pelvic autonomic nerves. We developed a new stimulation & monitoring system for evaluating the function of the pelvic autonomic nerves of female swine. Moreover, the result from swine were compared with those of women with cervical cancer during surgery. **Results** For the anatomical assessment, we found bilateral sympathetic trunk and ganglions run beside aorta and inferior vena cava, and thin fibers from sympathetic ganglions joined together to become the superior hypogastric nerve, which runs bilaterally as the inferior hypogastric nerves. The parasympathetic nerves joined together with inferior hypogastric nerves and formed the pelvic plexus, and we found the rectal, vesical and uterine branches of the pelvic plexus. For the functional assessment, we found regular contraction in bladder, vagina and rectum by stimulating the parasympathetic nerves. After resection of the sympathetic nerves, interval from stimulation to contraction, duration of contraction were decreased, whereas maximal pressure and frequency of contraction were increased. These results were similar to those from twelve patients with cervical cancer whose functions of the pelvic autonomic nerves were evaluated during surgery. **Conclusions** A female swine model may be adequate for the anatomical and functional assessment of the pelvic autonomic nerves in women.

IS-AC-4-5

Modulation of gene expression and physiological activity of skeletal muscles by estrogen in female mice
Saki Nagai, Saya Nagasawa, Satoru Takeda *Juntendo University*

Objective Estrogen deficiency relates to musculoskeletal diseases among postmenopausal women as well as women with amenorrhea. We thus studied how estrogen modulates exercise performance and skeletal muscle regulation in female mice. **Methods** Ovariectomized C57BL/6 mice were administered with estradiol benzoate (OVX + E) or vehicle (OVX + V). As a control group, sham-operated mice were administered with vehicle (Sham + V). Mice were exercised on a treadmill and gene expression in muscles was analyzed by microarrays. Estrogen-dependent gene expression was also analyzed during myoblast differentiation in mouse C2C12 cells expressing constitutively active estrogen receptor α (caERα). **Results** In treadmill test, OVX + V group exhibited a shorter running duration compared with control Sham + V group. Estrogen administration recovered exercise endurance of ovariectomized mice (OVX + E) to a similar level compared with control group. Microarray analysis of soleus muscle showed that genes involved in mitochondrial and muscle functions were differentially expressed among groups. Notably, expression of a gene encoding a mitochondrial protein was significantly enhanced in OVX + V group compared with controls whereas its expression was repressed in estrogen-supplemented ovariectomized group. Downregulation of the gene was also shown in myoblastic C2C12 cells expressing caERα. **Conclusion** Estrogen could play a critical role in muscle activity and exercise endurance in female.

IS-WS-1-1

The association between pregnancy-induced hypertension and hypertension in later life by age group : A cross-sectional analysis Maiko Wagata[1], Yasuhiro Kurosawa[2], Hirotaka Hamada[2], Michiyo Kurakata[2], Tetsuro Hoshiai[2], Hidekazu Nishigori[2], Masatoshi Saito[2], Akimune Fukushima[3], Nobuo Yaegashi[2], Junichi Sugawara[1] *Division of Feto-Maternal Medical Science, Tohoku Medical Megabank Organization, Tohoku University[1], Tohoku University Graduate School of Medicine[2], Division of Innovation & Education, Iwate Tohoku Medical Megabank Organization, Iwate Medical University[3]*

Objective To clarify the association between pregnancy-induced hypertension (PIH) and hypertension in later life by age group. **Methods** A cross-sectional population based cohort study was conducted from May 2013 to March 2016. Of the 39,379 women between the ages of 20 and 75 (mean 59.7 ± 11.3), 33,303 parous women were included in this analysis. A history of PIH was determined by questionnaires, and hypertension was defined as systolic blood pressure>=140mmHg or diastolic blood pressure >=90mmHg or current medication for hypertension. We analyzed the association between history of PIH and hypertension using chi-square test. Multivariable logistic regression analysis was also performed to adjust for age, body mass index and drinking status in each age group. **Results** In total, 1,575 (4.7%) women had a history of PIH. The prevalence of hypertension in women with and without a history of PIH was 51.8% and 36.8% respectively ($p<0.0001$). Women with a history of PIH had higher prevalence of hypertension in all age group. The adjusted odds ratio for hypertension in women with a history of PIH and 95% confidence interval in 30s, 40s, 50s, 60s, and 70s were 3.88 (2.08-7.23), 2.30 (1.58-3.36), 2.34 (1.85-2.97), 1.64 (1.40-1.92) and 2.04 (1.52-2.73), respectively. **Conclusion** Women with a history of PIH had a higher risk of hypertension in later life and the impact was greater in younger age group. We should recommend health examination and home blood pressure monitoring for women with a history of PIH even after puerperal period.

IS-WS-1-2

A study of neuroimaging in cases of eclampsia Priyadarshini Tiwari[1], Gajendra Kushwaha[1], Tanu Soni[1], Pushparaj Bhatele[2], Avadhesh Kushwaha[1] *NSCB Medical College Jabalpur, India[1], MP MRI and CT Scan Centre, India[2]*

Aim The aim of our study was to determine the findings on neuroimaging in cases of eclampsia. **Methodology** out of the cases of eclampsia coming to our teaching hospital in the period of one year, those patients who were either willing to pay for imaging studies or had access to a concessional card were subjected to MRI imaging of the brain and the findings were studied. **Results** out of the twenty five patients thus studied, seven (28%) showed normal findings. Nine (36%) showed posterior reversible encephalopathy syndrome. Six (24%) had ischemic infarcts. Three (12%) had hemorrhagic infarcts. The patients with hemorrhagic infarcts had the worst prognosis with 100% mortality. Infarcts were seen in the frontal lobes also apart from those in the parietal or occipital region though the occipital region is the most common area of the brain affected in eclampsia. **Conclusion** Our study showed a high number of hypertensive strokes in cases of eclampsia apart from PRES. This can only be improved by improving the antenatal care in our region and also improving referral services to the tertiary centre.

IS-WS-1-3

Uterine artery and umbilical artery doppler in prediction of fetal outcomes in severe pre-eclampsia Khin Lay Kywe, Bawi Cin Tial *Central Women's Hospital, Myanmar*

Objective To evaluate the clinical utility of uterine and umbilical artery Doppler waveforms analysis as apredictive marker of perinatal outcomes in pregnant women with severe pre-eclampsia. **Methodology** The present study is a hospital-based cross sectional diagnostic study conducted in Central Women's Hospital, Yangon, Myanmar. During the study period of one year (from January 2014 to December 2014), 58 severe pre-eclamptic patients admitted to Central Women's Hospital were investigated for the patterns of end-diastolic flow in umbilical artery and presence or absence of diastolic notch in uterine artery by Doppler ultrasonography. **Results** Out of 58 cases, abnormal umbilical artery Doppler waveform was recorded in 9 patients and abnormal uterine artery Doppler waveform was recorded in 29 patients and the remaining patients had normal Doppler scan. There were 4 perinatal deaths (2 still births and 2 early neonatal deaths) occurred and all the cases of perinatal mortality were encountered in the group presenting with abnormal Doppler scan. Also, other parameters of poor perinatal outcomes (preterm birth, low birth weight, poor Apgar scores and intrauterine growth restriction) showed statistically significant difference between the two groups. **Conclusion** It is apparent from the present study that the Doppler flow waveforms analysis of uterine and umbilical artery in severe pre-eclamptic patients is of crucial importance for fetal outcome as the occurrence of the abnormal Doppler waveforms is invariably associated with high perinatal mortality and morbidity.

IS-WS-1-4

Squamous cell carcinoma (SCC) antigen as a novel candidate marker for amniotic fluid embolism Natsuki Koike[1], Hidekazu Ooi[2], Katsuhiko Naruse[1], Toshiyuki Sado[1], Kazutoshi Nakano[3], Naohiro Kanayama[4], Hiroshi Kobayashi[1] *Nara Medical University[1], Kindai University Nara Hospital[2], Yao Municipal Hospital[3], Hamamatsu University School of Medicine[4]*

Objective This report aimed to explore the diagnostic value of serum squamous cell carcinoma (SCC) as a marker in amniotic fluid embolism (AFE) in 4 cases of autopsy-proven AFE and in 16 cases of clinical AFE. **Methods** Sera and information from these 20 cases of AFE were obtained from the Japan amniotic fluid embolism registration center in Hamamatsu University School of Medicine. As controls, seventy-four healthy women who gave birth to healthy newborns during the period from December 2011 to January 2014 were included in the study. The sensitivity and usefulness in diagnosis of AFE using the serum SCC concentration was compared with controls. **Results** We found significantly elevated serum levels of SCC in 4 cases of autopsy-proven AFE and 16 cases of clinical AFE relative to controls with a normal delivery (autopsy-proven AFE : 112.0 ± 169.4 ng/ml vs. 4.4 ± 2.2 ng/ml, p=0.0009, clinical AFE : 9.5 ± 10.3 ng/ml vs. 4.4 ± 2.2 ng/ml, p=0.004, respectively). The sensitivity and specificity of the SCC threshold level (8.8 ng/ml) for differentiating patients with autopsy-proven AFE and clinical AFE from controls were 100% and 97%, 31% and 97%, respectively. **Conclusion** These results suggest that serum SCC might be a promising predictor of the entry of amniotic fluid into the maternal circulation after delivery or might function as a candidate marker for noninvasive diagnosis of AFE.

IS-WS-1-5

Use of Extracorporeal Membrane Oxygenation in Critically Ill Obstetric Patients Huang Kuan-Ying, Li Yi-Ping, Lin Shin-Yu, Shih Jin-Chung, Chen Yih-Sharng, Lee Chien-Nan *National Taiwan University Hospital, Taiwan*

Objectives Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support is commonly employed in patients with circulatory arrest or significant cardiac dysfunction and

associated with an improvement in clinical outcomes. We describedour institutional experience with ECMO usage in critically ill obstetric women in this study. **Methods** We conducted a retrospective observational study on the application of ECMO in critically ill obstetric patients at a single tertiary center, National Taiwan University Hospital in the past five years. **Results** Five critically ill postpartum women were treated with ECMO in 2012–2016. The mean age was 36.8 ± 3.9 year-old and the mean gestational age was 36.8 ± 2.6 weeks. Three patients (60%) were diagnosed with postpartum hemorrhage and one (20%) with suspected amniotic fluid embolism plus postpartum hemorrhage and another (20%) with pulmonary embolism. All patients were treated with veno-arterial (VA) ECMO and the mean ECMO usage duration was 30 ± 19.7 (range：10–54) hours. Four (80%) patients survived to discharge but one survivor became left hemiplegia；all neonates (100%) survived in 6-month follow-up. **Conclusions** Pre-ECMO postpartum hemorrhage may not be contraindications of ECMO application in critically ill obstetric patients. The use of ECMO in this population is associated with high maternal survival rate.

IS-WS-2-1

The sirtuin 1 activator resveratrol regulates the retinoic acid signaling pathway and suppresses decidualization of human endometrial stromal cells Asako Ochiai, Keiji Kuroda, Keisuke Murakami, Rie Ozaki, Yuko Ikemoto, Yuki Ujihira, Makoto Jinushi, Jun Kumakiri, Mari Kitade, Satoru Takeda *Juntendo University*

Objective Our previous study has shown that retinoic acid (RA) signaling pathway plays a significant role in balancing differentiation and apoptosis upon decidualization of the peri-implantation endometrium. Resveratrol is a natural activator of sirtuin1 (SIRT1) and protects against oxidative stress and cellular senescence via various signaling cascades, including the RA signaling pathway. Clinically, resveratrol may potentially be useful to protect against ovarian aging, although its effect on endometrial decidualization is not known. In this study we investigated the impact of resveratrol on decidualization and the RA signaling pathway of human endometrial stromal cells (HESCs) in vitro. **Methods** Primary HESCs were decidualized with 8-bromo-cAMP, progesterone in the presence or absence of resveratrol (100μM). Various molecular techniques, including immunostaining, RTQ-PCR, and Western blot analysis, were employed to define the role of resveratrol treatment. **Results** Treatment of HESCs with resveratrol increased the expression of SIRT1. Decidualization of HESCs in the presence of resveratrol selectively inhibited the expression of the RA-binding protein, CRABP2, and RA receptor, RARalpha (associated with apoptosis induction) but induced the expression of the alternative RA receptors, PPARbeta/delta and PPARgamma (associated with cell differentiation). However, resveratrol also inhibited the induction of classical decidual markers, such as PRL and IGFBP1. **Conclusion** Resveratrol treatment may potentially be useful to improve oocyte quality but our findings suggest that it may also adversely impact on implantation by interfering with the decidual transformation of the endometrium. Furthermore, optimal decidual transformation of primary cultures may involve apoptosis or senescence of specific subpopulations.

IS-WS-2-2

Intentional endometrial injury enhances endometrial angiogenesis in a mouse model：a possible mechanism accounting for the increased embryo implantation potential Jehn-Hsiahn Yang, Chia-Hung Chou, Mei-Jou Chen, Hong-Nerng Ho, Yu-Shih Yang *National Taiwan University Hospital, Taiwan*

Intentional endometrial injury before in vitro fertilization (IVF) has been reported to increase embryo implantation rates, but its underlying mechanism remains unclear. In this study, 8-week-old female ICR mice were used, in which they did (Group 2) or did not (Group 1) undergo endometrial injury with a 7-mm-diameter brush inserted into their left uterine horns. Intraperitoneal equine chorionic gonadotropin 5 IU was injected for 2 consecutive days, followed by human chorionic gonadotropin 10 IU injection, and endometrial tissue was obtained 3.5 days later, roughly at the peri-implantation period.Mouse angiogenesis array was done using endometrial tissue lysate, and showed that matrix metalloproteinase-3 (MMP-3), plasminogen activator inhibitor-1 (PAI-1), insulin-like growth factor binding protein 1 (IGFBP-1), and IL-1α were more strongly expressed in Group 2 than in Group 1. Mouse endometrial endothelial cells were purified, and were tested for permeability, proliferation, tube formation, and migration abilities. All these assays were much more conspicuous in Group 2 than in Group 1. Immunohistochemistry also demonstrated prominent CD34 staining, a marker of endometrial microvessel density, on the endometrium in Group 2 but not in Group 1. After transfer of donated embryos obtained from aged female mice (>8-month-old), the embryo implantation rate in recipient mice was much higher in Group 2 that that in Group 1 (63% vs. 7%, P<0.001). Our results suggest that enhanced endometrial angiogenesis may be a possible underlying mechanism accounting for the increased embryo implantation potential after intentional endometrial injury.

IS-WS-2-3

MOTHERHOOD AFTER AGE 50：LONG-TERM FOLLOW UP OF PHYSICAL AND MENTAL WELL-BEING OF WOMEN WHO BECAME MOTHERS THROUGH OOCYTE DONATION Erica Davenport[1], Heather Burks[1,2], Richard Paulson[1,2] *University of Southern California, USA[1], USC Division of Reproductive Endocrinology and Infertility, USA[2]*

Background A greater proportion of infertility patients who are "advanced reproductive age" utilize oocyte donation, because of diminished ovarian reserve. Children conceived using donor gametes are a new population and we are still struggling to understand this population. **Objective** To compare long-term mental and physical health outcomes of women who became mothers in their 50s to outcomes of younger women who also became mothers through oocyte donation. **Design** A prospective cohort study. **Materials & Methods** Participants were former infertility patients at an academic IVF center who became pregnant at any age through oocyte donation, and who had a live birth. Participants completed a demographic survey and the SF-36-v2 Health Survey. The SF-36-v2 scores for physical and mental well-being were calculated for each age group：<40 years, 40–44 years, 45–49 years, and ≤50 years of age at the time of live birth. SF-36-v2 scores were compared between age groups using a Kruskal-Wallace test. **Results** Of 201 eligible patients, 33 were reached by telephone and 27 agreed to participate. 74% were White, 21% were Asian, and the remainder were Latina. 18 of 19 (95%) were satisfied with their decision to become a parent at the age they did. All parents in their 50s were satisfied or extremely satisfied with their decision. There were no significant differences among age groups in physical (p=0.14) or mental (p=0.06) health scores. **Conclusion** Women who became mothers in their 50s have similar health-related quality of life to their younger counterparts who became mothers through oocyte donation.

IS-WS-2-4

Suggested indications of preimplantation genetic screening (PGS) for in vitro fertilization-embryo transfer (IVF-ET) for successful pregnancy outcomes Seung Joo Chon, Jin Woo Shin,

Yoo Jung Lee, Ryun Sun Lee *Gachon Medical University, Gil Hospital, Korea*

Although there have been improvements in a process of in vitro fertilization–embryo transfer, implantation rates are not high. Approximately 50 to 75 percent of spontaneous miscarriages are due to numeric chromosomal abnormalities of embryos. Recently, preimplantation genetic screening seems to be one of the methods in screening chromosomally abnormal embryos. Therefore, we are to study on indications of women and embryos undergoing PGS for successful pregnancy outcomes. Total 51 cases of infertile couples who visited, underwent IVF and agreed to do PGS at Gil hospital in between August 2014 and January 2016 were included in this study. Data were collected by reviewing charts retrospectively. PGS was recommended to couples under certain 4 indications. Total 234 embryos were sent for PGS and 188 embryos were aneuploidy. Thirteen point six percents of women aged more than 38 years were euploidy and it had statistically significant impact on euploidy status. Secondly, a percentage of euploidy status among couples who at least have abnormal serum karyotyping was 11.7 percent which was significant on euploidy status. However, history of spontaneous miscarriages equal to more than 2 times did not have significant impact on euploidy status. Lastly, a percentage of euploidy status among couples having history of repeated implantation failure equal to more than 2 times was 10.6 percent and it had significant impact on euploidy status. Although embryos are graded as good qualities morphologically, couples having certain risk factors should undergo PGS for better pregnancy outcomes.

IS-WS-2-5

Organ perfusion for uterus transplantation in non–human primates with assumed procurement of a uterus from a brain–dead donor Yusuke Matoba, Iori Kisu, Takashi Takeda, Kanako Nakamura, Masataka Adachi, Kiyoko Umene, Yuya Nogami, Yusuke Kobayashi, Eiichiro Tominaga, Kouji Banno, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective Clinical studies of uterus transplantation have been performed to treat uterine factor infertility overseas. Since the uterus is a visceral pelvic organ, it is impossible to perfuse the uterus sufficiently using the established method of perfusion for procurement of vital organs from a brain–dead donor. This study was performed to investigate a new perfusion method for uterus transplantation using cynomolgus monkeys, based on assumed procurement of a uterus from a brain–dead donor. **Methods** Four female cynomolgus monkeys with an average body weight of 3.33 ± 0.45 kg were used in the study with approval of the Animal Care and Use Committee of our Research Center. Thoracolaparotomy was performed and a perfusion catheter was placed. Cross–clamping for the aorta under the diaphragm and exsanguination from the inferior vena cava were performed. The perfusion solution was administered via the catheter to perfuse all organs in the abdominal cavity, including those in the pelvic cavity. The femoral artery and/or external iliac artery were used in the new perfusion method and the status of perfusion of organs was evaluated grossly and pathologically. **Results** The perfusion method from a catheter inserted into the unilateral femoral artery and/or external iliac artery was feasible in all cases. After perfusion, gross findings showed that the uterus and all other abdominal organs were blanched simultaneously. Pathological findings showed that almost no hemocytes were present in the vessels of each organ. **Conclusion** This new method permits perfusion of the uterus and could be useful for uterus transplantation from a brain–dead donor.

IS-WS-2-6

Attitudes towards uterus transplantation compared to surrogacy and adoption : A survey among university students in Japan Sayoko Kotani[1], Mikiya Nakatsuka[2], Chiaki Kashino[1], Hirofumi Matsuoka[1], Toru Hasegawa[1], Ai Sakamoto[1], Yasuhiko Kamada[1], Yuji Hiramatsu[1] *Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences[1], Okayama University Graduate School of Health Sciences[2]*

Objective Although the first delivery of women with uterus transplantion (UTx) in Sweden was reported, it is still in debate whether or not UTx outweighs the other treatments, such as surrogacy and adoption. We conducted self–administered questionnaire survey on attitudes to having children by UTx, surrogacy, and adoption among Japanese university students. **Methods** From May to August, 2015, 415 University students who are in a reproductive age were recruited in this study after informed consent. Responses were obtained from 368 subjects (response rate : 88.7%). **Results** 81.5% of the respondents supported that UTx would be conducted in Japan. Women with congenital uterine deficiency (94.3%) and women treated by hysterectomy (91.3%) were considered to be valid recipients. Women with brain death (39.7%), cadavers (25.2%), or living women (35.0%) were considered as uterine donors. Mother (72.8%), sister (68.6%), non–relatives (47.8%), mother in low (45.9%), transsexuals (42.9%) were considered as candidates of living donors of uterus. 21.2% of respondents were affirmative to pay financial reward to the uterine donor. Opponents of UTx indicated superiority of surrogacy or adoption (23.1%) or indicated problems such as possible organ trade (20.0%), risk of fetal death (16.9%), and significant physical and mental burdens of donors (12.3%). **Conclusion** Majority of female University students supprted UTx in Japan ; however, underlying medical and ethical issues are also revealed. Guideline is necessary to balance against surrogacy and adoption.

IS-WS-3-1

Redox balance and heme oxygenase 1 state in iron–induced carcinogenesis in ovarian endometrioma Fuminori Ito, Yuki Yamada, Chiharu Yoshimoto, Hiroshi Shigetomi, Ryuji Kawaguchi, Eriko Fujii, Toshiyuki Sado, Hiroshi Kobayashi *Nara Medical University*

Objective Malignant transformation of ovarian endometrioma (OE) is thought to involve iron–induced carcinogenesis. Iron concentrations are known to be higher in OE than in endometriosis–associated ovarian cancer (EAOC). In this study, we further investigated factors related to redox caused by iron. **Methods** We examined the cyst fluid of 44 OE and 14 EAOC samples. The met–heme to oxy–heme ratio was calculated by electron absorption spectrum measurement. Antioxidant capacity was examined by the TAC assay. Levels of 8–OHdG, a DNA damage marker, and heme oxygenase 1 (HO–1), an antioxidative enzyme, were analyzed by ELISA. Immunohistochemical (IHC) analysis was performed for 15 OE and 10 EAOC paraffin–embedded tissues. **Results** In OE, the met–heme to oxy–heme ratio was higher, reflecting the presence of a greater amount of met–heme and a lesser amount of oxy–heme, than that in EAOC. Antioxidant capacity was higher in EAOC, and 8–OHdG and HO–1 levels were higher in OE. IHC analysis showed that HO–1 expression levels were higher in OE than in EAOC and that expression mostly occurred in histiocytes that were CD68/CD163 positive, indicating that they were M2 macrophages. **Conclusion** In EC, autoxidation, through which oxy–heme is transformed into met–heme, may lead to increased met–heme content, resulting in decreased antioxidant capacity and increased 8–OHdG and HO–1 levels. In carcinogenesis, met–heme is resolved, which could be due to increased antioxidant capacity, for example, because of HO–1 from M2 macrophages during benign OE, resulting in decreased oxidative stress, which is favorable for carcinogenesis and cancer cells.

IS-WS-3-2

DNA methylation-based biomarkers for uterine leiomyomas and their clinical application Ryo Maekawa, Isao Tamura, Yumiko Mihara, Masahiro Shinagawa, Maki Okada, Toshiaki Taketani, Hiromi Asada, Hiroshi Tamura, Norihiro Sugino *Yamaguchi University*

Objective Differential diagnosis of uterine leiomyomas and leiomyosarcomas is needed to determine whether the uterus can be retained. Because uterine leiomyosarcomas are diagnosed based on three pathological findings using light microscopy at present, reliable and objective diagnostic methods have been desired. Therefore, we attempted to establish the biomarkers for uterine leiomyomas based on DNA methylation levels, and examined their clinical application for diagnosis of uterine leiomyosarcomas. **Methods** We first selected 33 aberrantly DNA-methylated genes specific to uterine leiomyomas by using genome wide DNA methylation data of 3 paired samples of the leiomyoma and adjacent normal myometrium. Next, we confirmed their DNA methylation levels with 10 paired samples of the leiomyoma and adjacent normal myometrium by the combined bisulfite restriction analysis. The genes that showed hypermethylation or hypomethylation in at least 70% of the leiomyoma specimens were defined as leiomyoma-specific marker genes. **Results** We identified 12 leiomyoma-specific marker genes based on DNA methylation. Using these marker genes specific to uterine leiomyomas, we established a hierarchical clustering system based on the DNA methylation level of the marker genes, which could completely differentiate between uterine leiomyomas and normal myometrium. Furthermore, our hierarchical clustering system completely discriminated uterine cancers and differentiated between uterine leiomyosarcomas and leiomyomas with more than 70% accuracy. **Conclusion** This study identified DNA methylation-based biomarker genes specific to uterine leiomyomas, and our hierarchical clustering system using these biomarker genes was useful for differential diagnosis of uterine leiomyomas and leiomyosarcomas.

IS-WS-3-3

Decreased expression of ESR1 in endometriosis is caused by aberrant DNA methylation of T-DMRs (Tissue-dependent and differentially methylated regions) Yumiko Mihara, Ryo Maekawa, Yuichiro Shirafuta, Masahiro Shinagawa, Maki Okada, Isao Tamura, Hiromi Asada, Toshiaki Taketani, Hiroshi Tamura, Norihiro Sugino *Yamaguchi University*

Objective The expression of estrogen receptor 1 (ESR1), which codes estrogen receptor alpha, is decreased in endometriosis compared with normal endometrium, but the mechanism is unclear. Aberrant DNA methylation is involved in the pathogenesis of endometriosis. ESR1 shows tissue-specific expression and has several upstream exons (uExons) from which ESR1 variants are transcribed. Recently, we revealed that ESR1 has tissue-dependent and differentially methylated regions (T-DMRs) at the upper regions of the promoters of uExons. Here, we investigated whether the decreased expression of ESR1 in endometriosisis is attributable to the DNA methylation of the T-DMRs. **Methods** This study was approved by the Institutional Review Board of our hospital. Written informed consent was obtained from the participants. We first examined mRNA expression statuses of uExons in chocolate cyst and normal endometrium. Then we examined the DNA methylation statuses of the promoter regions and the T-DMRs in uExons by Illumina HumanMethylation450 K and bisulfite sequencing. **Results** ESR1 mRNA expression from uExsons were remarkably lower in the chocolate cyst than in the normal endometrium. The promoter regions of uExons showed DNA hypomethylation statuses in both chocolate cysts and normal endometrium. Interestingly, the T-DMRs of the chocolate cyst showed DNA hypermethylation statuses while they were hypomethylated in the normal endometrium. Furthermore, we confirmed that DNA methylation of the T-DMRs decreased the transcriptional activity of ESR1 by reporter assay. **Conclusion** Decreased expression of ESR1 in endometriosis is caused by the aberrant DNA hypermethylation of the T-DMRs.

IS-WS-3-4

Resveratrol suppresses inflammatory responses of peritoneal macrophages in endometriosis Erina Satake[1], Kaori Koga[1], Arisa Takeuchi[1], Tomoko Makabe[1], Ayumi Taguchi[2], Miyuki Harada[2], Tetsuya Hirata[2], Yasushi Hirota[2], Tomoyuki Fujii[1], Yutaka Osuga[1] *Graduate School of Medicine, The University of Tokyo[1], Faculty of Medicine, The University of Tokyo[2]*

Objective Resveratrol is shown to control endometriosis in a mouse model but the mechanism is undetermined. Our group previously showed that resveratrol suppresses inflammatory responses in endometriotic stromal cells. This study was aimed at investigating whether resveratrol suppresses inflammatory responses of peritoneal macrophages in endometriosis patients. **Methods** Under IRB approval and informed consents, peritoneal fluid was collected from patients with endometriosis. Macrophages were isolated using CD14 MicroBeads, cultured at a density of 5.0×10^5 cells/ml, and exposed to resveratrol at doses of 25, 50, and 100 μM one hour before the stimulation. Stimulation was done by treatment with IL-1β (5 ng/ml) or LPS (100 ng/ml) to mimic local inflammation. After 24 hours, supernatants were collected and concentrations of IL-6 and IL-8 were measured by ELISA. **Results** Resveratrol significantly reduced IL-1β-induced IL-6 and IL-8 secretions to 96.7 ± 46.0% and 81.0 ± 4.3% (25 μM), 89.0 ± 13.2% and 67.3 ± 10.8% (50 μM), and 62.0 ± 22.3% and 55.8 ± 14.1% (100 μM), of that without any stimulation or treatment, respectively. Similarly, resveratrol significantly decreased LPS-induced IL-6 and IL-8 secretions to 48.9 ± 3.8% and 60.2 ± 8.7% (25 μM), 8.1 ± 1.8% and 46.0 ± 13.2% (50 μM), and 5.7 ± 3.8% and 38.5 ± 18.1% (100 μM), respectively (n=3, mean ± SEM, $p < 0.05$). **Conclusion** Resveratrol reduced the secretion of inflammatory cytokines from peritoneal macrophages, which may contribute to the therapeutic effects of resveratrol on endometriosis.

IS-WS-3-5

The activation of PI3K/Akt/mTOR pathway is associated with the activation of primordial follicles in ovaries affected with endometrioma Arisa Takeuchi, Kaori Koga, Erina Satake, Tomoko Makabe, Ayumi Taguchi, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Tomoyuki Fujii, Yutaka Osuga *Graduate Schoool of Medicine, The University of Tokyo*

Objective It has been shown that endometrioma reduces ovarian reserve. Recent studies indicate that the activation of primordial follicles contribute to this reduction ; however, the mechanism is uncertain. We hypothesized that PI3K/Akt/mTOR pathway is associated with the mechanism. To test this hypothesis, we conducted following experiments. **Methods** Under informed consent, ovarian tissues were randomly collected from young patients with endometrioma (n=10, Em group) and cervical cancer without ovarian metastasis (n=10, controls). Activated primordial follicles was identified using immunohistochemical staining of Foxo3. Expressions of p-mTOR, p-Akt and PTEN within oocytes in primordial follicles were evaluated by immunohistochemical staining. The number of follicles with positively- or negatively-stained oocytes were counted and compared between groups. The statistical analysis was performed using Mann-Whitney U test. **Results** The percentage of primordial follicles containing oocyte with Foxo3 positive nu-

clear staining was significantly lower in Em group than in controls (15.1 ± 4.5% vs 61.2 ± 4.4%, mean ± SEM, $p<0.001$). The percentage of follicles containing p-Akt and p-mTOR positive oocyte was significantly higher in Em group than in controls (p-Akt 76.2 ± 6.3% vs 65.2 ± 4.2%, $p<0.05$, p-mTOR 70.9 ± 4.2% vs 62.1 ± 3.5%, $p<0.05$), whereas the percentage of follicles containing PTEN positive oocyte was significantly lower in Em group than in controls (42.1 ± 5.4% vs 73.2 ± 4.8%, $p<0.05$). **Conclusion** In ovaries affected with endometrioma, the percentage of activated primordial follicles are increased and this may be associated with the activation of PI3K/Akt/mTOR pathway.

IS-WS-4-1

The efficacy and safety of radical trachelectomy for early stage cervical cancer during pregnancy Kosuke Yoshihara, Nobumichi Nishikawa, Makoto Chihara, Tatsuya Ishiguro, Sosuke Adachi, Masanori Isobe, Kazufumi Haino, Koji Nishino, Masayuki Yamaguchi, Masayuki Sekine, Katsunori Kashima, Takayuki Enomoto *Niigata University*

Objective Cervical cancer is one of the most frequent diagnosed cancer in pregnancy. The aim of our study is to evaluate the efficacy and safety of radical trachelectomy for pregnant women with early stage cervical cancer. **Methods** A retrospective observational study was performed for stage IB1 cervical cancer (tumor size less than 2cm) patients who underwent abdominal radical surgery (ART) or radical hysterectomy (ARH) at our institution between February, 2013 and January, 2016. We compared the differences in perioperative and oncologic outcomes among ART during pregnancy (ART-DP) group, ART and ARH groups. **Results** A total of 28 patients were included in this analysis. Five, six, and eighteen patients were assigned as ART-DP, ART, and ARH groups, respectively. There were no significant differences in the frequency of diagnostic conization, pathological TNM classifications, histology, tumor size, stromal invasion, and lymphovascular space invasion. Patients in ART-DP was younger than those in ARH ($p=0.016$). The surgical time in ART-DP were longer than in ARH ($p=0.018$). Blood loss was higher in ART-DP compared to ARH ($p=0.021$). The number of total lymph node in ART-DP was lesser than in ARH ($p=0.020$). However, there were no significant differences in age, surgical time, blood loss, and lymph node count between ART-DP and ART. There were no significant differences in progression-free and overall survival times among three groups. No recurrence occurred in ART-DP group. **Conclusion** Radical trachelectomy might be a treatment option for pregnant women with early stage cervical cancer.

IS-WS-4-2

Identification of therapeutically targetable FGFR-fusion genes in cervical cancer through RNA sequencing Ryo Tamura[1], Kosuke Yoshihara[1], Yutaro Mori[1], Kaoru Yamawaki[1], Kazuaki Suda[1], Tatsuya Ishiguro[1], Yoichi Aoki[2], Seiya Sato[3], Hiroaki Itamochi[3], Takayuki Enomoto[1] *Niigata University[1], University of the Ryukyus[2], Tottori University[3]*

Objective The aim of our study is to identify and validate therapeutically targetable gene fusions in cervical cancer, leading to the development of new therapeutic strategies. **Methods** We analyzed RNA sequencing data of 253 TCGA cervical cancer samples to search for gene fusions, and validated recurrent fusions in our Japanese dataset (n=100). After transfection of targetable fusion transcript to a normal immortalized cervical keratinocyte (Ect1/E6E7) and 4 cervical cancer cell line (SiHa, ME180, HeLa, CaSki), we examined the molecular biological function of fusion transcript. This study was approved by the institute review board of each institute and all patients provided written informed consent. **Results** FGFR3-TACC3 fusion was identified in 2 of 253 TCGA samples and 2 of 100 our samples. Stable expression of FGFR3-TACC3 fusion led to anchorage-independent growth in cervical keratinocyte and the dramatically alteration of cell proliferation in all cancer cell lines. Stable fusion expression activated MAPK pathway in all cell lines but activated PI3K/AKT pathway in only ME180 and CaSki harboring PIK3CA mutation. Fusion specific siRNA and FGFR inhibitor showed high sensitivity in fusion transfected cell line. Although PI3K/AKT activated cell lines showed less effective against FGFR inhibitor compared to PI3K/AKT non-activated cell lines, combined inhibition of FGFR and AKT had a synergic effect in PI3K/AKT activated cell lines. **Conclusion** FGFR3-TACC3 is a driver mutation and a therapeutic target in a fraction of cervical cancer. When FGFR-fusion positive cervical cancer is treated by FGFR inhibitor, genomic background such as PI3K/AKT status should be considered.

IS-WS-4-3

Suppression of anti-apoptotic molecule, survivin, sensitizes TRAIL-induced apoptosis in TRAIL-resistant cervical cancer cells Hiroe Nakamura[1], Ayumi Taguchi[1], Kei Kawana[2], Akira Kawata[1], Juri Ogishima[1], Mitsuyo Yoshida[1], Masakazu Sato[1], Asaha Fujimoto[1], Katsuyuki Adachi[1], Katsutoshi Oda[1], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], School of Medicine, Nihon University[2]*

Objective Loss of p53 function by human papilloma virus (HPV) E6 induces resistance to apoptosis in cervical cancer cells. In addition, anti-apoptotic protein, survivin, is frequently overexpressed in cervical cancer, and the expression is known to inhibit apoptosis pathway of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a cytokine secreted by immune cells. As TRAIL induces apoptosis in a p53-independet manner, we aimed to clarify whether TRAIL-resistant cells can be sensitized to TRAIL by targeting survivin in cervical cancer. **Methods** SiHa was used as a TRAIL-resistant cervical cancer cell line. Cell viability and cell cycle were evaluated after knockdown of survivin by siRNA (si-survivin). A small molecule YM 155 and resveratrol (RVT ; a polyphenol with a potential to suppress survivin expression), were used as survivin inhibitors. Effects of si-survivin and these survivin inhibitors on TRAIL or cisplatin (CDDP)-induced apoptosis were analyzed by Annexin-V. **Results** Si-survivin reduced the number of viable cells by inducing G2/M cell cycle arrest in SiHa. Combination of si-survivin and TRAIL synergistically increased apoptotic cells (control : 8.7 ± 2.9% vs si-survivin : 46 ± 7.6%) ($p=0.004$). However, combination of si-survivin and CDDP only showed additive effect (control : 2.2 ± 0.2% vs si-survivin 5.5 ± 0.6%). Both YM155 (20 nM) and RVT (100 μ M) synergistically increased the TRAIL-induced apoptosis (control : 4.7 ± 1.0%, YM155 : 47 ± 15.8%, RVT : 64 ± 14.3%, respectively). **Conclusion** Our data suggest that survivin is essential for acquiring resistance to TRAIL-induced apoptosis in cervical cancer cells. Combination of survivin inhibitor and TRAIL, rather than CDDP, might be a promising strategy for TRAIL-resistant cervical cancer.

IS-WS-4-4

Novel effects of narrow-band low-energy middle-infrared radiation in enhancing the anti-tumor activity of paclitaxel Bor-Ching Sheu[1,2], Wen-Chun Chang[1], Shang-Ru Tsai[2] *National Taiwan University Hospital, College of Medicine, National Taiwan University, Taiwan[1], Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taiwan[2]*

OBJECTIVE Paclitaxel is used as an essential chemotherapy agent in treating a variety of human malignancies. Formally, radiation therapy with high-energy radiation often damages the

healthy cells surrounding cancer cells. Low-energy, middle-infrared radiation (MIR) has been shown to prevent tissue damage, and recent studies have begun combining MIR with paclitaxel. This study investigated the effectiveness of treating human HeLa cervical cancer cells with a combination of paclitaxel in conjunction with narrow-band MIR. **METHOD** A high-power, narrow-band triple layer Ag/SiO2/Ag waveguide thermal emitter (WTE) by waveguide modes was utilized. This study used WTEs to generate narrow-band MIR with full width at a half maximum (FWHM). We used a wideband blackbody source combined with a bandpass filter to achieve a narrow-band IR. A Fourier transform IR spectrometer was used to measure the emission spectra. The effectiveness of treating human HeLa cells with a combination of paclitaxel in conjunction with narrow-band MIR were measured. Annexin V-FITC/PI apoptosis detection and cell mitochondrial membrane potential analyses were performed. **RESULTS** The combined treatment significantly inhibited the growth of HeLa cells. Specifically, results from Annexin V-FITC/PI apoptosis detection and cell mitochondrial membrane potential analyses revealed an increase in apoptotic cell death and a collapse of mitochondrial membrane potential. **CONCLUSIONS** These Novel findings shad new lights on the combination of narrow-band MIR with paclitaxel as an alternative approach in the treatment of human malignancies.

IS-WS-4-5

The pathologic profile of the low grade results of uterine cervical smear for 20 years at one institution in Korea Eunseop Song, H Choi, E Cho, S Jung, S Chang, J Kim *Inha University, Korea*

Aims To analyze the low grade results of uterine cervical smear (LG-S) for 20 years. **Methods** From 1997 to 2016, LG-S were reviewed retrospectively through medical record. The pathologic results were analyzed according to the cervical smear and vice versa. **Results** For 20 years there were 588 patients whose cervical smears were low grade. The duration of follow-up was from 0 to 12.5 years. The patients age were between 21 to 91 years old. Among 588 patients, 216 (37%) had ASCUS, 38 (6%) had ASC-H, 273 (46%) had LSIL and 61 (10%) had CIN1. Among 216 patient with ASCUS, 129 had cervicitis at the pathologic results of biopsy, 64 had CIN1. There were 20 whose results were worse than CIN2 (9%). Among 38 with ASC-H, 19 had worse results than CIN2 (50%). Among 273 with LSIL, 30 had worse results than CIN2 (11%). Among 61 with CIN1, 6 had worse results than CIN2 (10%). There were 3 squamous cell cancers and 2 among them had ASCUS and 1 ASC-H. There were 1 adenocarcinoma and she had ASC-H. Among low grade cervical smear results, 75 (13%) had worse than CIN2 lesion, and among ASC-H, the frequency were increased to 50% and they had 20% of cancer. **Conclusion** Among patients with LG-S, 13% had worse than CIN2 lesions at the tissue biopsy and with ASC-H, 50% had worse than CIN2 and 20% had cancer.

IS-WS-4-6

Cervical Pre-Cancer Treatment in Cambodia Aun Korn[1], Kanal Koum[2], Soeung Sann Chan[2], Noriko Fujita[3], Takafumi Kuroda[4], Nozomu Yanaihara[4], Akiko Abe[5], Akira Kuwahara[5], Wataru Yamagami[6], Koji Banno[6], Yutaka Ueda[7], Tadashi Kimura[7] *Calmette Hospital, Cambodia[1], Cambodian Obstetrics and Gynecology Society, Cambodia[2], National Center for Global Health and Medicine[3], The Jikei University School of Medicine[4], University of Tokushima[5], Keio University School of Medicine[6], Osaka University[7]*

The three-year project to diagnose and treat an early stage cervical cancer was started as a joint project of SCGO and JSOG in October 2015. The Shimodaira High Frequency Surgical Instrument (thereafter Shimodaira) was introduced in June 2016 in three national tertiary hospitals in the capital of Cambodia. Cervical pre-cancer treatment for suspected CIN2 and more was performed initially in three national hospitals using Shimodaira. Among three hospitals, only one hospital has used LEEP, one hospital used to perform cold knife conization, and the last hospital has never performed any early treatment. Four cases were operated on by using Shimodaira under local anesthesia in an outpatient setting from June to September 2016. All the cases complained vaginal discharge to come to the hospital at first and biopsy followed by colposcopy after the positive result of VIA or cytology. Case1 32y.o.G3P0 was operated by loop electrode. Case2 56y.o.G7P4, by loop electrode. Case3 45y.o.G12P8, by triangle electrode. Case4 33y.o.G5P4, by loop electrode. There was no complication during the operation. Pathology of Case1, 3, 4 was CIN2 and margin negative. Case2 revealed CIN3 and margin positive, so a hysterectomy was performed. Shimodaira is suitable for use in an outpatient setting. It is beneficial as one stop treatment for the patients especially for those who has geographical and financial difficulties to come for regular follow-up. Cervical cancer screening is not commonly implemented, so early detection and treatment are still a challenge, but Shimodaira creates a choice for early treatment in Cambodia.

IS-WS-5-1

Periostin activates invasive potency of endometriotic epithelial cells Kazuaki Neriishi, Tetsuya Hirata, Shinya Fukuda, Akari Nakazawa, Miyuki Harada, Yasushi Hirota, Kaori Koga, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Our previous global gene profiling showed 371-fold increase in Periostin (POSTN) mRNA expression in endometriotic epithelial cells (EmoECs) compared to endometrial epithelial cells (EECs). The aim of this study is to clarify the expression and function of POSTN in endometriosis. **Methods** The experimental procedures were approved by the Institutional Review Board of our university, and signed informed consents were obtained from each patient. Immunohistochemistry (IHC) of ovarian endometrioma and endometrium was performed, and POSTN mRNA and POSTN concentration in cultured media of immortalized EmoECs (imEmoECs) stimulated by TGFβ or IL-4 were measured by quantitative PCR or ELISA. We then generated doxycycline (dox) inducible system of POSTN using imEmoECs (doxPostn-EmoECs) by lenti-viral infection and examined invasion capacity of doxPostn-EmoECs using matrigel under the presence or absence of dox. **Results** IHC staining showed that POSTN were overexpressed in EmoECs compared to endometriotic stromal cells or EEC. Stimulation by IL-4 or TGFβ increased POSTN mRNA and secretion of POSTN protein in cultured media of imEmoECs. The presence of dox resulted in 3.7-fold increase in POSTN mRNA expression in doxPostn-EmoEC ($p<0.05$), and the number of invasion cells was significantly elevated compared to imEmoECs ($p<0.05$). **Conclusion** Our result clearly indicated that POSTN activates invasive potency of endometriotic cells. Considering that POSTN is predominantly expressed in mesenchymal linage, our data suggested that EmoECs might possess EMT-like phenotype in contrast to EECs.

IS-WS-5-2

Snail promotes invasion and inflammatory reactions in endometriotic epithelial cells Shinya Fukuda[1], Tetsuya Hirata[2], Kazuaki Neriishi[1], Akari Nakazawa[2], Miyuki Harada[2], Yasushi Hirota[2], Kaori Koga[1], Osamu Hiraike[1], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1],*

Faculty of Medicine, The University of Tokyo[2]
Objective Epithelial–mesenchymal transition (EMT) is a biological process for invasive properties and was reported to be involved in the development of endometriosis. We examined the expression and function of snail, a key transcription factor of EMT, in endometriotic epithelial cells (EmoECs). **Methods** The experimental procedures were approved by the Institutional Review Board of the University of Tokyo. Snail expression in ovarian endometrioma and endometrium were confirmed by immunohistochemistry. Immortalized EmoECs (imEmoECs) were stimulated by TGFβ1 and we examined the expression of EMT-related genes by quantitative RT-PCR (qPCR) and invasive capacity by matrigel invasion assay. Then we examined the effect of repressing snail expression on TGFβ1-induced invasion using matrigel invasion assay. Finally, we introduced doxycycline-inducible snail overexpression system in imEmoECs. Using this cell line, we examined the expression of EMT and inflammation related genes by qPCR and invasive capacity by matrigel invasion assay. **Results** EmoECs showed intense staining of snail compared to endometrial epithelial cells. TGFβ1 upregulated EMT-related factors (N-cadherin, αSMA, fibronectin1, CTGF, MMPs) and increased the number of invading cells ($P<0.05$). Among the upregulated EMT-related transcription factors, the fold-change of snail was prominent. TGFβ1-induced invasion was significantly attenuated by snail-specific siRNA ($P<0.05$). Overexpression of snail induced 4-fold increase in the number of invading cells and significant increase in MMPs, COX2, IL-8 and CCL5 mRNA expression ($P<0.05$). **Conclusion** These results suggested that expression status of snail affects the invasion and inflammatory reaction in endometriosis, which indicates targeting snail could be a therapeutic candidate in endometriosis.

IS-WS-5-3

Daidzein-rich isoflavone aglycones inhibit proliferation of human endometriotic stromal cells and in a mouse endometriosis model Osamu Takaoka, Taisuke Mori, Fumitake Ito, Akemi Koshiba, Yukiko Tanaka, Hisashi Kataoka, Izumi Kusuki, Jo Kitawaki *Kyoto Prefectural University of Medicine*
Objective Daidzein-rich isoflavone aglycones (DRIAs), a dietary supplement, are known to relieve menopausal hot flashes without any severe adverse events or affecting hormone profiles. We therefore aimed to investigate the *in vitro* and *in vivo* effects of DRIAs on cellular proliferation in endometriosis. **Methods** Endometriotic stromal cells (ESCs) isolated from ovarian endometrioma (OE) and normal endometrium (NE) were cultured in the presence of DRIAs, each of the DRIAs components (daidzein, genistein, or equol), or conventional isoflavone glycosides (IG), precursors of DRIAs, as the control. A mouse model of endometriosis was established by transplanting donor-mouse uterine fragments into the abdominal cavity of recipient mice. **Results** The addition of DRIAs (0.2–20 μM) inhibited the proliferation of OE-ESCs ($P<0.05$ for 0.2 μM ; $P<0.01$ for 2 and 20 μM) but not of NE-ESCs. However, daidzein, genistein, equol, and IG did not inhibit proliferation. DRIA suppression was canceled when estrogen receptor (ER) β was inhibited by an antagonist, PHTPP ($P<0.05$), or by ERβ siRNA, but not by MPP, an antagonist to ERα. In OE-ESCs, DRIAs (20 μM) reduced the expressions of IL-6, IL-8, COX-2, and aromatase ; aromatase enzymatic activity, serum glucocorticoid-regulated kinase, and prostaglandin E_2 ($P<0.05$). Western blot and immunofluorescence assay revealed that DRIAs inhibited TNF-α-induced IκB phosphorylation and p65 uptake into the nucleus in OE-ESCs. In the mouse model, a DRIA-containing feed significantly decreased the number, weight, and Ki-67 proliferative activity of endometriosis-like lesions compared to those observed with an IG-containing feed ($P<0.01$) and the control feed ($P<0.05$). **Conclusion** DRIAs are potential therapeutic options for managing endometriosis.

IS-WS-5-4

Alpha-7 nicotinic acetylcholine receptor (nAChR) agonist inhibits the development of endometriosis by regulating inflammation Osamu Yoshino[1], Yosuke Ono[1], Tomoko Shima[1], Akitoshi Nakashima[1], Ikumi Akiyama[2], Yutaka Osuga[2], Shigeru Saito[1] *University of Toyama[1], University of Tokyo[2]*
Objective In the etiology of endometriosis, IL-1β produced by macrophages is known to be a key molecule to induce inflammatory milieu. Macrophages express nAChR, which is activated by nicotine, acetylcholine and specific agonists. In fact, several studies suggest that there are inverse associations between cigarette smoking and endometriosis. In the present study, we evaluated the suppression of macrophages by nAChR activation might represent a new therapy for endometriosis. **Methods** The study was approved by the IRB and informed consents were obtained from patients. Human peritoneal fluid mononuclear cells (PFMC) were stimulated with lipopolysaccharide (LPS) in the presence of α-7 nAChR agonists. In a murine endometriosis model α-7 nAChR modulators were administered. One or 3 weeks after the injection of endometrial fragments, mice were sacrificed and PFMC were collected. Laparotomy was performed, and the number and the total weight of endometriotic foci were measured. **Results** Human PFMC expressed α-7 nAChR at the mRNA and protein levels. Activation of α-7 nAChR with its agonists led to significant ($P<0.01$) suppression of LPS-induced IL-1β expression via suppressing p38 MAPK. In a murine model, 1 week after inoculation of endometrium to the peritoneal cavity, α-7 nAChR agonist significantly suppressed the expression of IL-1β mRNA in PFMC ($P<0.01$), which was negated with α-7 nAChR antagonist. α-7 nAChR agonist significantly suppressed the formation of endometriotic lesions in the numbers and the weight, which was reversed with α-7 nAChR antagonist. **Conclusion** We firstly showed that activation of nAChR might be a new candidate for treatment of endometriosis.

IS-WS-6-1

Investigation of uterine corpus cancer treatment in elderly women Takanori Yokoyama[1], Kazuhiro Takehara[2], Tomoya Mizunoe[3], Yoshie Kazusa[4], Masaru Sasaki[5], Hiroyuki Naitou[6], Hideki Teramoto[7], Takefumi Akagi[8], Hisaya Fujiwara[9], Takashi Kodama[10], Kenjiro Date[11], Yoshiki Kudo[1] *Hiroshima University[1], Shikoku Cancer Center[2], Kure Medical Center[3], Hiroshima General Hospital[4], JA Onomichi General Hospital[5], Hiroshima Prefectural Hospital[6], Hiroshima Asa Civilian Hospital[7], Miyoshi Sentral Hospital[8], Chugoku Rosai Hospital[9], Higashihiroshima Medical Center[10], Hiroshima Red Cross Hospital[11]*
Objective To investigate uterine corpus cancer treatment in elderly women (age, ≥75 years). **Methods** Totally, 151 uterine corpus cancer patients underwent primary treatment at 14 centers from 2007 to 2012. We retrospectively reviewed clinical status, treatment methods, reasons for treatment selection, and prognoses. **Results** Group A and B patients were aged 75–79 (n=90) and ≥80 (n=61) years, respectively ; the numbers of patients with progressive stages I, II, III, IV, endometrioid adenocarcinoma, others, and performance status 3–4 were 110, 5, 21, 15, 102, 49, and 15, respectively. The surgical treatment group comprised 117 patients (lymphadenectomy, 48 ; non-lymphadenectomy, 69), radiotherapy group comprised 16, and best supportive care (BSC) group comprised 18 (radiotherapy, 5 ; chemotherapy, 6). We performed surgical treatment and lymphadenectomy for 83% and 46% group A patients and 69% and 11% group B patients. Approximately 4% group A patients and

25% group B patients underwent non-surgical treatment because of age and 13% because of complications such as heart disease, and stroke. Three-year survival rates in the surgical treatment, radiotherapy, and BSC group were 82%, 84%, and 21%, respectively. Overall survival (OS) in the surgical treatment or radiotherapy group was significantly longer than that in the BSC group. **Conclusion** In many centers, patients aged ≥80 years prudently selected the surgical treatment. Approximately 10% elderly women with uterine corpus cancer selected radiotherapy instead of surgical treatment ; OS after radiotherapy was almost equivalent to OS after surgical treatment. In over half the patients, for diagnosis, lymph node assessment was substituted by an imaging study and lymph node biopsy.

IS-WS-6-2

Correlation between the tumor area and copies number of CK 19 mRNA expression by OSNA in sentinel lymph nodes of patients with endometrial cancer Satoshi Okamoto, Hitoshi Niikura, Tomoyuki Nagai, Hideki Tokunaga, Asami Toki, Masafumi Toyoshima, Michiko Kaiho, Ai Otsuki, Chiaki Hashimoto, Shoko Sakurada, Yusuke Shibuya, Nobuo Yaegashi
Tohoku University

Objective The aim of this study is to investigate the correlation between the copies number of one-step nucleic acid amplification (OSNA) assay using CK19 mRNA marker and metastatic tumor area in sentinel lymph nodes (SLNs) of patients with endometrial cancer. **Methods** Twenty-two sentinel lymph nodes (SLNs) with less than 4 mm^2 metastases from 8 patients (6 endometrioid, 1 serous, 1 clear) were tested for this study. Firstly, 22 SLNs were analyzed intraoperatively with frozen section. Each SLNs were serially sectioned at 2 mm intervals perpendicular to the short axis. All cut surfaces were subjected to histopathological examination with H&E stain. Next, metastatic tumor area was analyzed using Keyence BZ-9000 fluorescence microscope. After histopathological examination, even numbered sections were analyzed by OSNA assay using CK19 mRNA. We determined that there was no expression of the CK 19 mRNA at less than 250 copies/μL. **Results** The OSNA assay results of 4 SLNs were less than 250 copies/μL (group A). Seventeen SLNs were ranged from 250 to 3500 copies/μL (group B). One SLN was 1.7×10^4 copies/μL (group C). The patient who showed 1.7×10^4 copies/μL was clear cell carcinoma. On the other hand, the maximal metastatic tumor area of group A, B and C showed 0.002-0.007 mm^2, 0.002-2.506 mm^2, 2.598 mm^2, respectively. The copies number of OSNA assay were correlated with those of metastatic tumor area (r=0.633). **Conclusion** The OSNA assay using CK19 mRNA appears to associate a tumor area. We have to examine a large number of cases and perform a lot more analytic work.

IS-WS-6-3

***Transformed follicular lymphoma* as a novel prognostic biomarker for endometrial cancer** Senn Wakahashi[1], Tamotsu Sudou[2], Hideto Yamada[1] *Kobe University Graduate School of Medicine[1], Hyogo Cancer Center[2]*

Objective *Transformed follicular lymphoma* (*TFL*, *zc3h12d*) was first identified as a candidate tumor suppressor gene from a lymphoma patient whose disease was transformed from indolent to aggressive type along with the *TFL* downregulation. Here, we speculated that *TFL* plays a role as tumor suppressor gene even in other cancers and that assessed the significance of low TFL protein expression as a predictor of poor prognosis in advanced endometrial cancer. **Methods** Tissue samples were obtained from consecutive 103 patients with stage III-IV endometrial cancer. An association between TFL expression levels determined by immunohistochemistry and clinical outcome was evaluated using Kaplan-Meier method and Cox-regression model. **Results** Follow-up period was median 64 (range, 5-199) months. Twenty-one patients (20%) were negative for TFL expression, and their 10-year overall survival (OS) (49%) and progression-free survival (PFS) (25%) were lower than OS 71% (p=0.09) and PFS 64% (p<0.05) of TFL positive patients, respectively. Multivariate analyses demonstrated TFL status was a significant factor for OS (HR 2.6, 95%CI 1.2-5.7 ; p<0.05) and PFS (HR 4.1, 95%CI, 2.1-8.1 ; p<0.01), adjusted for age, stage, histologic type, myometrial invasion and peritoneal cytology. The *TFL* gene is mapped in human chromosome 6q25.1 where estrogen receptor gene (*ESR1*) is also located, and the vast majority of TFL negative samples were found to be negative for estrogen receptor as well, suggesting that prognostic significance of estrogen receptor may depend on TFL. **Conclusion** TFL may be a novel prognostic biomarker and useful to identify patients with advanced endometrial cancer who need a new treatment modality.

IS-WS-6-4

Polypeptide N-acetylgalactosaminyltransferase-6 (GalNAc-T6) is related to cell invasiveness and independently predicts good prognosis in patients with uterine endometrial carcinomas Tomoko Kurita[1], Chiho Koui[1], Midori Murakami[1], Seiji Kagami[1], Rie Urabe[1], Taeko Ueda[1], Toshinori Kawagoe[1], Yusuke Matsuura[2], Toru Hachisuka[1], Hiroto Izumi[3] *University of Occupational and Environmental Health[1], University of Occupational and Environmental Health[2], University of Occupational and Environmental Health[3]*

Objective GalNAc-T6 is related with prognosis of variable types of cancers, but this function remains unclear. We investigated the clinical significance, survival relevance and the molecular mechanism of GalNAc-T6 contributing to carcinogenesis of endometrial carcinomas. **Methods** Immunohistochemistry of GalNAc-T6 was done in the 218 patients with endometrioid adenocarcinoma of endometrium. Immunoreactivy of GalNAc-T 6 was scored based on intensity of staining. We investigated the relationship between the expression of GalNAc-T6 and clinicopathological values, prognosis. In vitro migration assay was conducted in GalNAc-T6 knockdown HHUA cells to investigate its role in metastatic character of cancer cells. Statistical analyses were performed using SPSS Version18.0 (Chicago, IL, USA). The Mann- Whitney U- test was used to evaluate relationship between clinicopathological variables with GalNAc-T6 expression. Univariate and multivariate Cox survival analysis were used to evaluate any independent prognostic factors associated with relative survival. P<0.05 - statistically significant. **Results** 152 tumors (69.7%) were determined to have positive GalNac-T 6 expression, and 66tumors (30.3%) had negative. The GalNAc-T6 expression correlated significantly with histological grade (p =0.002). In univariate survival analysis, the GalNac-T6 expression represented better overall survival (the 10-year overall survival rate : positive 94.9% vs negative 77.8%, p=0.003). In multivariate analysis, GalNac-T6 was significant predictors of high overall survival (P=0.013). In additional experiments, knockdown GalNac-T6 in endometrial cancer cell lines was involved in increasing cell invasion (p<0.05) and correlated significantly with E-cadherin expression (p=0.038). **Conclusion** The expression of GalNAc-T6 is related to cell invasiveness and is a useful marker for good prognosis of the patients with endometrioid adenocarcinoma of the endometrium.

IS-WS-6-5

Clinicopathological characteristics of hyperprolactinemic patients with endometrial cancer by immunohistochemical analysis Erdenebaatar Chimeddulam, Munekage Yamaguchi,

Fumitaka Saitou, Hironori Tashiro, Hidetaka Katabuchi *Kumamoto University*

Objective Prolactin (PRL) induces the phosphorylation of Janus Activating Kinase 2 (JAK2) via PRL receptor (PRLR) expressed on cell membrane and activates intracellular signal transduction. The aim of this study is to investigate whether preoperative serum PRL contribute to the tumorigenesis of endometrial cancer (EC). **Methods** We retrospectively reviewed 94 patients with EC treated at our hospital whose serum PRL levels were preoperatively examined. Excised cancer tissues were investigated by using immunohistochemistry with anti-PRLR, anti-phosphorylated JAK2 (pJAK2), anti-estrogen receptor arpha (ER- α), and anti-progesterone receptor (PgR) antibodies. Available preoperative biopsy tissues were also examined via immunohistochemistry with anti-Phosphatase and Tensin Homolog Deleted from Chromosome (PTEN) antibody because expressions of PTEN were more clearly detected in biopsy tissue than in excited cancer tissues due to short formalin-fixation time. **Results** Thirteen and 81patients were divided into high PRL group (HPG) and low PRL group (LPG) based on the PRL levels of 30 ng/ml. In 74 patients classified as type1 EC, expressions of both PRLR and pJAK2 were significantly higher in HPG compared to LPG ($p<0.01$). In 20 patients with type2 EC, these expressions were not significantly different in both groups. In patients with type1 EC and those with type2 EC, the expressions of ER- α and PgR were not different. In 62 patients with type1 EC, the rate of positive expression with PTEN was significantly higher in HPG than that in LPG ($p<0.05$). **Conclusion** These results suggest that PRL-PRLR signaling may be associated with the carcinogenesis of type1 EC in hyperprolactinemic women without involving PTEN mutation.

IS-WS-6-6

Endometrial surveillance in premenopausal breast cancer patients using tamoxifen Maria Lee, Hee Seung Kim, Jae Weon Kim *Seoul National University College of Medicine, Korea*

Objective To describe the endometrial pathologic lesions in premenopausal breast cancer patients with a history of tamoxifen (TMX) use. **Methods** We retrospectively reviewed the medical records of 120 premenopausal breast cancer patients with a history of TMX use that had undergone a hysteroscopic examination. **Results** Among 120 patients, 44.2% (n=53) were asymptomatic with an endometrial thickness ≥5mm, as assessed by transvaginal ultrasonography (TV-USG). Of the patients that reported abnormal uterine bleeding (AUB), 5% (n=6) had an endometrial thickness<5mm and 20% (n=24) had an endometrial thickness ≥5mm by TV-USG. The final group of patients were asymptomatic, but showed an abnormal endometrial lesion, such as an endometrial polyp, by TV-USG [30.8% (n=37)]. Of the 56 benign lesions that were histologically reviewed, 50 (41.7%) were endometrial polyps, 3 (2.5%) were submucosal myomas, 2 (1.7%) were endometrial hyperplasias, and 1 (0.8%) was chronic endometritis. There were 64 (53.3%) other non-pathologic conditions, including secreting, proliferative, and atrophic endometrium, or in some cases, there was insufficient material for diagnosis. In our data, only one case was reported as a complex hyperplasia without atypia arising from an endometrial polyp, and one patient was diagnosed with endometrioid adenocarcinoma. **Conclusion** For premenopausal breast cancer patients with a history of TMX use, the majority of the patients were asymptomatic, and endometrial polyps were the most common endometrial pathology observed. Therefore, we believe that endometrial assessment before starting TMX treatment, and regular endometrial screening throughout TMX treatment, are reasonable suggestions for premenopausal breast cancer patients.

IS-WS-7-1

Role of Type I Interferon and IRF-7 in anti-viral responses at the placenta Go Ichikawa, Hiromitsu Azuma, Erina Kato, Takehiro Nakao, Hideki Takahashi, Takuo Nakayama, Kaori Shinya, Chuyu Hayashi, Kenji Sugita, Fumihisa Chishima, Kei Kawana *Nihon University*

Objective The placenta plays a critical role in the protection of the fetus against viral transmission. Recently IFN-β has been shown to have anti-viral effects and its inhibition is associated with viral-induced preterm birth. Since the IRF family are major mediators against viral infection, we here addressed the anti-viral effects of IRF-7 in the placenta. **Methods** We examined IRE-7 expression in human first trimester trophoblast cell line (Sw.71) or in primary culture of trophoblast obtained from mice at mRNA and protein levels. Sw.71 was treated with or without IFN-β and its downstream signaling components were also evaluated. **Results** IRF-7 was expressed in not only Sw.71 cells but mouse placenta. IFN-β exposure to Sw.71 induced SOCS expression and then phosphorylation of STAT-1 in the trophoblast cells. The activation of the SOCS/pSTAT1 signaling pathway promoted expression of IRF-7 in the cultured cells. **Conclusion** IRF-7 was expressed in the human and murine placenta and regulated positively by IFN-β. IRF-7 may be a major downstream of IFN-β for anti-viral responses at placenta.

IS-WS-7-2

Newly developed promising oocyte activation with phospholipase C zeta 1 (PLCZ1) for treating repeated unsuccessful fertilization in ICSI Takashi Yamaguchi[1], Takuhiko Ichiyama[1], Tamito Miki[1], Motoi Nagayoshi[1], Atsushi Tanaka[1], Keiji Kuroda[2], Satoru Takeda[2] *Saint Mother Hospital[1], Juntendo University School of Medicine[2]*

Objective The biggest problem in ART is the repeated unsuccessful fertilization after ICSI into matured oocytes. It has been reported that about half of these cases are unsuccessful because of insufficient sperm induced oocyte activation. Previously, electrical stimulation, Ca ionophore and $SrCl_2$ have been used for oocyte activation. But, the results were different from that induced by in vitro fertilization. In this study, we examined the possibility of clinical application of the newly developed sperm-derived oocyte activation factor, PLCZ1. **Methods** M-II oocytes were incubated in 4μM Fluo-8H AM in SPS medium and optimal RNA concentrations for oocyte activation were examined by injecting various concentrations of in vitro transcribed PLCZ 1 mRNA 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) PLCZ1. **Results** From the pattern of Ca^{2+} concentrations and PN formation rate, optimal concentration of PLCZ1 mRNA to activate human oocytes was 100 ng/μl. The duration and interspike intervals of Ca^{2+} oscillations were similar to that of ICSI. In this study, figure1-6 are a variety of waves of Ca^{2+} oscillations. **Conclusion** We determined the best concentrations of PLCZ1 mRNA to activate human eggs physiologically. The egg activation by PLCZ1 mRNA injection showed similar pattern of Ca^{2+} oscillations to that of in vitro fertilization eggs and can improve the efficiency of egg activation.

IS-WS-7-3

Glucagon-like peptide-1 (GLP-1) increases kisspeptin mRNA expression in hypothalamic neurons Aki Oride, Haruhiko Kanasaki, Tomomi Hara, Satoru Kyo *Shimane University Faculty of Medicine*

Objective Energy balance has long been known to be closely re-

lated to female reproductive functions. Recent work has shown that the feeding-related peptide glucagon-like peptide-1 (GLP-1), which is produced by L cells in the small intestine and colon, can accelerate the hypothalamic-pituitary-gonadal (HPG) axis and influence reproductive efficiency. To examine the direct effect of GLP-1 on hypothalamic neurons, we examined the expression of kisspeptin and gonadotropin-releasing hormone (GnRH). **Methods** The clonal hypothalamic cell lines rHypeE-8 and GT1-7 and primary cultures of fetal rat brain were used for the experiments. Expression levels of kisspeptin mRNA were measured by real-time RT-PCR and signal transduction pathways evoked by GLP-1 were determined by reporter gene assay using luciferase vectors. **Results** Kisspeptin and GnRH were expressed in rHypeE-8 and GT1-7 cells and primary cultures of fetal rat brain. GLP-1 significantly and dose-dependently increased kisspeptin mRNA expression in rHypeE-8 cells. A similar effect of GLP-1 on kisspeptin expression was also observed in GT1-7 cells and fetal rat brain cultures. Another anorexigenic factor, leptin, similarly increased kisspeptin mRNA in rHypeE-8 cells but GLP-1 and leptin in combination failed to potentiate their individual effects. GLP-1 increased cAMP-mediated signaling pathways but failed to activate extracellular-signal regulated kinase (ERK) pathways. GLP-1 did not increase the expression of GnRH in these cells. **Conclusion** Our current observations suggest that the feeding-related peptide GLP-1 could directly regulate kisspeptin mRNA expression in the hypothalamus and affect the HPG axis.

IS-WS-7-4

M1 macrophages but not M2 macrophages are involved in folliculogenesis Yosuke Ono[1], Miwako Nagai[2], Osamu Yoshino[1], Kaori Koga[2], Azusa Sameshima[1], Kumiko Inada[1], Tomoko Shima[1], Akitoshi Nakashima[1], Tomoyuki Fujii[2], Shigeru Saito[1], Yutaka Osuga[2] *University of Toyama[1], University of Tokyo[2]*

Objective Although macrophages are known to be involved in folliculogenesis, there are no data which subtype, M1 or M2 macrophage, is essential. We evaluated the role of ovarian M1 and M2 macrophage using M1 or M2 macrophage specific depletion mouse model. **Methods** In CD11c- or CD206-diphtheria toxin (DT) receptor transgenic mice, which enable depletion of CD11c+ M1 or CD206+ M2 macrophages, respectively, were used. Upon depletion of M1 or M2 macrophage by DT, ovaries were obtained from mice superovulated with PMSG+hCG, followed by histological examination, flow cytometry and qPCR. To evaluate the number of ovulation, we have counted the number of oocytes extracted from tube. To study implantation rate, in vitro fertilized embryos were transfered to pseudopregnant mice. In human ovaries, the localization of M1 or M2 macrophage was examined by immunohistochemistry. **Results** In mice, flow cytometry and qPCR revealed the number and the mRNA of M1 and M2 macrophage was increased throughout folliculogenesis. In M1 macrophage depletion mice, folliculogenesis was impaired completely accompanying ovarian bleeding. In M 2 macrophage depletion mice, folliculogenesis was normal, and oocytes exhibited normal in the number of ovulation (17 ± 4.6; mean ± SE), fertilization rate ($73 \pm 9\%$) and implantation rate ($66 \pm 33\%$). We found the dominance of M1 macrophage in human ovary. This finding support the results in mice, suggesting that M1 macrophages play an important role for folliculogenesis in human. **Conclusion** M1 macrophages rather than M2 are essential for folliculogenesis.

IS-WS-8-1

Prenatal multifaced control to prevent low birth weight：the RAINBOW Project Sakura Chiga[1], Takashi Ohba[1], Junya Miyoshi[2], Hidetaka Katabuchi[1] *Kumamoto University[1], Japan Red Cross Kumamoto Hopital[2]*

Objective To evaluate the effect of the RAINBOW Project which is a multifaceted implementation trial for the prevention of preterm birth on the low birth weight (LBW). **Methods** This project was conducted on pregnant women in our prefecture from August 2012 to January 2014. Prophylactic oral antibiotics were recommended for pregnant women with high-risk on preterm birth. The subjects were also encouraged to undergo a periodontal examination both in the first and the second half of pregnancy. A guidance of proper tooth brushing was given and periodontal treatment was allowed if deemed necessary. This study was approved by the Institutional Review Board. **Results** Of 20,701 consented subjects in this project, 20,454 had bacterial examinations of vaginal secretions. Bacterial vaginosis was found in 2,472 (12.1%). Prophylactic antibiotics were prescribed for 1,233. During the first half of pregnancy, 9,527 women (46.0%) received periodontal examinations. Among subjects who underwent a periodontal examination, periodontal disease was found in 3,016 (32.2%). The number of subjects we could collect the birth outcome was 16,584. Comparing the incidences of LBW with the averages during the preceding 5 years in our prefecture, it was declined 0.8% in 2013 and 2014 (10.0% to 9.2%, $p<0.001$, χ^2test). We presumed that this project reduced 128 LBW infants per year. Both of dental treatment and the prophylactic oral antibiotics during pregnancy were not the isolated factors which decrease the incidence of LBW. **Conclusion** A multifaceted intervention including lifestyle guidance could reduce the incidence of LBW infants.

IS-WS-8-2

Progesterone inhibits preterm birth by suppressing the expression of contractile associated proteins and ion channels in mice with chronic dental *Porphyromonas gingivalis* infection Haruhisa Konishi[1], Hiroshi Miyoshi[1], Yuko Teraoka[1], Satoshi Urabe[1], Mutsumi Miyauchi[2], Takashi Takata[2], Yoshiki Kudo[1] *Hiroshima University[1], Department of Oral and Maxillofacial Pathobiology, Hiroshima University[2]*

Objective Progesterone (P4) is essential to maintain pregnancy by promoting uterine quiescence；however, this mechanism has not been well studied. We previously demonstrated that mice with dental Porphyromonas gingivalis infection (*P.g* mice) were useful as animal models for chronic inflammation-induced preterm birth. In *P.g* mice, the average gestational period was 2 days shorter and the uterine contractility was significantly enhanced at an earlier time. The aim of this study was to investigate whether P4 prevented preterm birth and to determine the effects of P4 on production of uterine contractile associated proteins (CAPs) and ion channels. **Methods** *P.g* mice were injected subcutaneously with (*P.g* +P4 mice) or without (*P.g* mice) 1 mg P4 daily at day 15.5-18.5 of gestation. We then observed the gestational period and examined the expressions of CAPs (i.e., oxytocin receptor and connexin 43) and ion channels (i.e., calcium channel and P2X7 receptor, a purinergic receptor) in the myometrium at day 18.0 of gestation using real-time polymerase chain reaction. **Results** The average gestational periods were 20.4 days in *P.g* +P4 mice (n=4) and 18.3 days in *P.g* mice. Treatment with P4 significantly reduced the enhancement of the expression of oxytocin receptor, connexin 43, L-type calcium channel and P2X7 receptor in the myometrium by 73%, 57%, 78%, and 50%, respectively ($P<0.001$；n=8). **Conclusion** P4 prevented preterm birth by suppressing the enhancement of CAPs and ion channels expressions in chronic inflammation-induced preterm birth model.

IS-WS-8-3

Metagenomic Analysis with Amniotic Fluid in Cases of Chorioamnionitis Daichi Urushiyama[1], Chihiro Kiyoshima[1], Masamitsu Kurakazu[1], Ryota Araki[1], Ayako Sanui[1], Fusanori Yotsumoto[1], Masaharu Murata[1], Shigeru Saito[3], Shingo Miyamoto[1], Kenichiro Hata[2] *Fukuoka University[1], National Research Institute for Child Health and Development[2], University of Toyama[3]*

Objective Chorioamnionitis, which is definitive evidence of an intrauterine infection, is highly associated with preterm births and poor perinatal prognoses. Microbiological studies suggest that intrauterine infections might account for at least 40% of preterm births. The aim of this study was to use metagenomic analysis to characterize the bacterial composition in amniotic fluid samples in cases with or without chorioamnionitis, and to verify that the condition can be diagnosed prior to delivery. **Methods** Amniotic fluid samples from 45 cases, who had undergone both amniocentesis and histological examination of the placenta, were divided into three groups according to the "Blanc's classification"：Group A (n=14), chorioamnionitis (stage III)；Group B (n=18), chorionitis (stage II)；and Group C (n=13), no infiltration or subchorionitis (stage ≤I). 16S rDNA amplicon sequencing was performed with two control groups：controls of amniotic fluid (Group D, n=18) and blank controls (Group N, n =14). **Results** The α-diversity index in Group A was significantly less than that in the other groups. In a principal coordinate analysis, plots of Group A were differently clustered than those of Groups C/D/N. In further analysis, we identified the group defined by seven specific species to be strongly related with chorioamnionitis and some parameters of perinatal prognosis. The accuracy in diagnosing chorioamnionitis was 100% for sensitivity and 77.4% for specificity. **Conclusion** We showed that it can be possible to diagnose chorioamnionitis with a high level of accuracy and to detect pathogenic bacteria prior to delivery.

IS-WS-8-4

Ultrasound Shear-Wave Elastography to evaluate the change of cervical stiffness in pregnancy Tetsuo Ono, Daisuke Katsura, Kazutaka Yamada, Kaori Hayashi, Syunichiro Tsuji, Akiko Ishiko, Fuminori Kimura, Kentaro Takahashi, Takashi Murakami *Shiga University of Medical Science*

Objective The aim of this study was to evaluate the change of cervical stiffness with ultrasound shear-wave elastography (SWE) during pregnancy. **Methods** A total of 280 women, ranging from the 10th to the 40th week of pregnancy, enrolled in this study between January 2016 and March 2016. Elastography was performed in routine prenatal visit. A measurement area was chosen at the anterior part of cervix, and the circular region of interest of 5 mm in diameter was set at two points, 5 to 10 mm (lower point) and 15 to 20 mm (upper point) from external cervical os. The generalized estimating equation was used to estimate the correlation between stiffness value and gestational age by generalized linear models. The Ethics Committee of our institution approved the study protocol, and informed consent was obtained from all patients. **Results** There were significant negative correlations between stiffness value and gestational age. The estimated regression equation of the lower and upper points showed $Y=-0.049X+3.675$ ($p<0.05$) and $Y=-0.060X+4.170$ ($p<0.05$), respectively. There was a significant difference in the gap between stiffness values of the upper point and those of the lower point. Softening of the cervix in the upper point was different between single pregnancy and twin pregnancy significantly ($p<0.05$), however, was not different between primiparous women and multiparous women. **Conclusion** Our data sug-

gest cervical elastgraphy using SWE could measure the change of cervical stiffness during pregnancy, and the relevant assessment point of the cervical softening may be upper area than lower area of the cervix.

IS-WS-8-5

Feasibility of Interval Cerclage in Preterm labor with Incompetent Internal Os of Cervix : Preliminary Study Jeongkyu Hoh, Mirang Seo, Jihyun Keum, Yoonseo Choi, Jongwon Lee, Eunsam Choi *Hanyang University, Korea*

Objective The aim of this study was to determine whether an interval cerclage reduced preterm delivery in those women who had undergone an emergency transvaginal cerclage due to dilated cervix and/or protruding fetal membrane with labor. **Study Design** A retrospective cohort study was conducted on 16 women with a transvaginal cervical cerclage. Among those, 7 women went over interval cerclage whereas 9 had elective cerclage due to bad obstetric history. Interval cerclage was performed on patients who previously had emergency cerclage due to symptoms of impending preterm delivery at a distance of time. Antibiotics and prophylactic tocolysis were given to all patients. Neonatal outcomes and perinatal complications were analyzed between two groups. **Results** Mean initial cervical length before the first surgery was 0.07cm in the interval cerclage group and 4.3cm in the elective cerclage group. Cervical length before second surgery in the interval cerclage groups was 1.94 cm. Of all 16 cases, no fetal loss was found during present pregnancy. Mean delivery weeks was 35+0 weeks in the interval cerclage group while 35+1 weeks in the elective cerclage group (P =0.4981). Mean birth weight in the interval cerclage group was 1920.0 g and 2145.0 g in the elective cerclage group (P=0.2901). Neonatal outcomes and perinatal complications were not different between two groups as well. **Conclusion** The results suggest interval cerclage as a potentially good emergent surgical procedure which could be used in preventing preterm delivery in patients with incompetent internal os of cervix having preterm labor.

IS-WS-8-6

Comparison between Nitroglycerin Dermal Patch and Nifedipine for Treatment of Preterm Labor, a randomized clinical trial Maryam Kashanian, Zahra Zamen *Iran University of Medical Sciences, Iran*

Objective To compare the effect of nifedipine and nitroglycerin dermal patch for taking control of preterm labor. **Method** Study was performed as a randomized clinical trial on women who had been admitted in hospital with complaint of preterm labor. In one group, nitroglycerin (NG) dermal patch and in other group, nifedipine were prescribed. The women of 2 groups were followed up to delivery and compared according to arrest of labor for 2 hours, 48 hours, 7 days, gestational age at the time of delivery and their adverse effects. The primary outcome was to postpone delivery for 48 hours. **Results** Women of 2 groups did not have significant difference according to age, BMI, primary Bishop Score, gestational age at the time of tocolytic therapy, history of abortion, rout of delivery and preterm labor. In more women in NG group delivery was postponed for 2 hours [59 (98.3%) VS 48 (80%), p=0.001], for 48 hours [52 women (86.7%) VS 41 (68.3%), p=0.016] and for 7 days [47 (78.3%) VS 37 (61.7%), p=0.046].Gestational age at the time of delivery was higher in NG group (35.6 ± 1.9 VS 34.3 ± 2.05 weeks, p=0.155), however, it was not significant.Apgar score of minute 5,(p=0.03) and neonatal weight (p=0.04), were more and cesarean deliveries, NICU admission and duration of NICU stay were less in NG group. Adverse effects were similar, minimal in both groups. **Conclusion** NG patch is more effective method for preterm labor control than nifedipine with minimal side effects.

IS-WS-9-1

mRNA splicing is novel homologous recombination regulator Michihiro Tanikawa[1], Osamu Hiraike[1], Katsutoshi Oda[1], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2]*

Objective Recent whole-exome sequencing studies of malignancies have detected recurrent somatic mutations in splicing factors. These novel mutations include homologous recombination (HR) repair genes, which might be correlated with sensitivity to PARP inhibitor. However, their roles have not been fully understood. The aim of this study is to clarify the functions of U2 snRNP splicing factors, especially SNRPA1 (Small Nuclear Ribonucleoprotein Polypeptide A1), in HR repair process. **Methods** SNRPA1 and other splicing factors were identified as HR repair genes by genome-wide screens. Each splicing factor was depleted by siRNA knockdown. The functions of SNRPA1 in DNA repair were analyzed by HR assay (DR-GFP assay), immunofluorescence, real-time laser micro-irradiation and comet assay (single cell gel electrophoresis). **Results** HR assay showed strong HR deficiencies in splicing factor's depleted cells. In these cells, accumulation of BRCA1 and Rad51, major HR factors, to DNA damage sites were severely impaired. Especially, live cell imaging showed recruitment of SNRPA1 to laser induced DNA damage sites and unveiled its direct involvement to DNA damage repair. Comet assay also showed that depletion of SNRPA1 markedly caused DNA damage with the tail of broken DNA fragments. **Conclusion** Recruiting HR factors to DNA damage sites is one of the DNA repair process by splicing factors, and SNRPA1 may have direct role in this process. Our data suggest that depletion of splicing factors can be one mechanism for HR deficiency (i.e. BRCAness).

IS-WS-9-2

Surgeon's role about genetic screening among endometrial cancer with regard to Lynch syndrome Min Kyu Kim, Eun Jin Heo *Sungkyunkwan University of Medicine, Samsung Changwon Hospital, Korea*

Objective Lynch syndrome increase risk of mostly endometrial cancer and colorectal cancer. There is not much study about detecting algorithm among Korean population by gynecologic oncology surgeon. We undertook this study to investigate this. **Methods** A retrospective review of endometrial cancer patients who was counseled about Lynch syndrome in Department of Obstetrics and gynecology, Samsung Changwon Hospital by single surgeon was done. Clinical information was extracted from the medical record including age, family and personal history of cancer, immunohistochemistry (IHC), microsatellite instability test (MSI), and gene sequencing results. Risk management and posttest education after result were offered about risk reducing options and cascade testing for affected individual. **Results** Total test was 16. There were two germline mutations (both MSH 2) (c.23C>T (p.Thr8Met), c.187delG (p.Val63*)). Both were negative for MSH2 IHC, But no patient matched criteria of Amsterdam. Four variation of unknown significance (VUS) was found (Three MSH2 and One MLH1). Among those all were abnormal in IHC and there was only one Amsterdam criteria matched patient. There were two unstable MSI patients, one was MSH2 germline mutation and the other was MSH2 VUS. Median age was 57 (41~76). Most cases were endometrioid type (11/16, 69%). Seventy five percent were stage I (12/16). **Conclusions** We found two MSH2 germline mutation patients among this population. Gynecologic oncology surgeon can be adapted to develop the ability to assess and evaluate genetic risk among endometrial cancer.

IS-WS-9-3

Novel strategy to overcome platinum resistance in leiomyosarcoma (LMS) ; blocking ATP7B by copper ion Mamoru Kakuda, Shinya Matsuzaki, Ruriko Nakae, Yusuke Tanaka, Tadashi Iwamiya, Akiko Okazawa, Eiji Kobayashi, Yutaka Ueda, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

Objective Resistance to platinum drugs remains a significant problem in uterine LMS. Our objective is to elucidate the role of ATP7B, a copper transporter which excretes intracellular platinum, in LMS and develop a method which can overcome the platinum resistance. **Methods** The expression of ATP7B was examined in cell lines and clinical samples of LMS by using western blotting (WB) analysis. IC50 values for cisplatin and intracellular platinum accumulation were measured by ICP-MS methods in SK-LMS cells and ATP7B-suppressed cell line (SK-LMS-7B cells), which permanently transfected the pRS ATP7B shRNA vector. We established xenografted tumors by inoculating SK-LMS cells or SK-LMS-7B cells and examined in vivo platinum sensitivity for both tumors. In addition, we attempted to improve platinum sensitivity by using CuSO4 for premedication. **Results** The expression of ATP7B was identified in the SK-LMS cells and 62.5% of clinical samples using WB analysis. By suppression of ATP7B in SK-LMS-7B cells, IC50-values for cisplatin decreased from 17 μM to 4.3 μM and intracellular platinum accumulation was elevated from 7.2 ng/dish to 52 ng/dish. A significantly higher anti-tumor effect of cisplatin was observed in SK-LMS-7B-inoculated xenografted tumor compared with SK-LMS-inoculated tumor. Premedication with CuSO4 (15 μM) significantly reduced IC50-values (17 μM to 3.9 μM) for cisplatin and elevated intracellular platinum accumulation by blocking ATP7B. In addition, a significant improvement of platinum sensitivity was observed in vivo model by the same premedication. **Conclusion** ATP7B is associated with platinum resistance in LMS. Premedication of Copper as a drag agent of ATP7B improved platinum sensitivity.

IS-WS-9-4

Comparison of relapse-rates and survival after sentinel node biopsy or inguinofemoral lymphadenectomy in patients with node-negative vulvar cancer Fabienne Schochter[1], Nikolaus De Gregorio[1], Antje Beyer[1], Thomas W.P. Friedl[1], Amelie Schramm[1], Thomas Blankenstein[2], Andreas Rempen[3], Wolfgang Janni[1], Florian Ebner[1] *Ulm University, Germany[1], Hospital of the Ludwig-Maximilians-University, Munich, Germany[2], Diakonie-Klinikum, Schwaebisch Hall, Germany[3]*

Introduction 2008 Hampl and Van der Zee presented the results showing sentinel node biopsy is possible, safe and reduces morbidity in patients with early vulvar cancer. Due to unclear follow-up data further investigations are recommended. **Methods** We compared patients with vulvar carcinoma undergoing sentinel node biopsy (SNB) vs. inguinofemoral lymphadenectomy (IFLA) regarding overall, local and inguinal relapse risk, disease free and overall survival in unselected patients of three German centers. **Results** We indentified 112 (56 SNB, 56 IFLA) complete data sets out of 239 available patient data sets. During follow up overall 29 % in SNB group relapsed of which 14 % were inguinal relapses. In IFLA group 46 % relapsed , 11 % of those in the inguinal region. No significant difference was seen in the rate of inguinal relapse (p=0,568). Multivariate Cox Regression analysis corrected for tumor size, performed surgery (total vulvectomy, partial vulvectomy and wide excision) and year of diagnosis showed no significant impact on disease free survival (HR 2.07, 95 %KI 0.97 - 4.46, p=0.062) and overall survival (HR 0.93, 95 %KI 0.23 - 3.77, p=0.924) for IFLA vs SNB. **Conclusion** SNB in Vulvar cancers seems to be a safe method in our cohort with equal rates of inguinal disease recurrence. However, overall rates for local as well as inguinal relapse were higher as compared to previous studies. This might be due to longer follow up and a retrospective selected cohort which may not include all initially treated patients at our centers.

IS-WS-9-5

Current knowledge and attitudes on HPV prevention among Japanese : A large-scale questionnaire Yukio Suzuki[1], Akiko Sukegawa[1], Yukihide Ota[1], Yuichi Imai[1], Aya Tokinaga[1], Tae Mogami[1], Yoko Motoki[1], Naho Ruiz Yokota[1], Tatsuya Matsunaga[1], Mikiko Sato[1], Takayuki Enomoto[1], Etsuko Miyagi[2] *Yokohama City University Graduate School of Medicine[1], Niigata University Graduate School of Medical and Dental Sciences[2]*

Objective Data representing knowledge and attitudes on human papillomavirus (HPV) prevention among Japanese men are greatly needed, yet still lacking. We sought clarification among the general population in Japan, with particular focus on males. **Methods** We conducted our study between October 2015 and June 2016 at various settings including public spaces, classrooms, companies, university festivals, and citizens' open forums. Recruited participants were 16 years or older, and filled out a 20-item, multiple-choice questionnaire. The 11 questions regarding HPV knowledge were scored and divided into low-, medium-, and high-knowledge groups. **Results** There were 2156 participants (1022 male, 1134 female ; mean age : 39.5 ± 16.6 years ; range : 16-90 years) ; 47.6% were married. Based on the grouping, males showed respectively lower HPV knowledge than females (low ; 61.3% vs. 27.2% ; medium : 30.9% vs. 48.9% ; high ; 7.8% vs. 23.9% ; $p<0.001$). Only 25.4% of males had heard of the positive effects of HPV vaccination, while 27.0% had heard of the negative effects. Males had lower recognition than females regarding both positive and negative effects of vaccination ($p<0.001$). Of males, 39.9% responded that they would approve of their daughters receiving the HPV vaccine. The high-knowledge group tended to be in favor of vaccination (49.0% vs 32.8% of the low-knowledge group ; $p<0.001$), while 59.6% of the low-knowledge group were undecided. **Conclusion** Our results indicate that knowledge about HPV prevention is lower among males in general. Further education for men on HPV prevention should be promoted in Japan.

IS-WS-9-6

Scientific data and Medical Evidence of Lymphatic Surgery for Lymphedema patients after gynecological cancer treatment Mihara Makoto, Hisako Hara *Saiseikai Kawaguchi General Hospital*

Objective The impact of lymphaticovenous anastomosis on lymphedema has yet to be defined. The authors investigated the clinical evidence regarding the effectiveness of lymphaticovenous anastomosis in lower limb lymphedema. **Methods** Eighty-four patients (162 limbs ; 73 female and 11 male patients) with lower limb lymphedema who underwent multisite lymphaticovenous anastomosis in the authors' clinic between August of 2010 and May of 2014 were included in this retrospective study. Lymphedema was diagnosed using lymphoscintigraphy and indocyanine green lymphography. All lymphaticovenous anastomoses were performed under local anesthesia. The lymphatic vessels that were identified were classified using the normal, ectasis, contraction, and sclerosis type (NECST) classification. Limb circumference, subjective symptoms, and frequency of cellulitis were evaluated. **Results** The average patient age was 60 years (range, 24 to 94 years) ; mean postoperative follow-up period was 18.3 months. The postoperative change rate in limb circumference indicated that 67 limbs (47.7 per-

cent) were classified as improved, 35 (27.3 percent) were classified as stable, and 32 (25 percent) were classified as worse. Postoperative interview revealed improvement in subjective symptoms in 67 limbs (61.5 percent), no change in 38 (34.9 percent), and exacerbation in four (3.7 percent). The postoperative mean occurrence of cellulitis was decreased to 0.13 times per year compared with 0.89 preoperatively, which was statistically significant (p=0.00084). Multiple regression analysis using the postanastomosis limb circumference and NECST classification confirmed the following results : change rate (percent) =−0.40 +(0.30*N)+(−0.84*E)+(0.22*C)+(−0.61*S). **Conclusion** Lymphaticovenous anastomosis is effective for lower limb lymphedema, in point of limb circumference, subjective symptoms, and the frequency of cellulitis.

IS-WS-10-1

Tumor suppressor p53 impairs cumulus cell–oocyte complex expansion and ovulation Hirofumi Haraguchi, Yasushi Hirota, Tomoko Fujita, Leona Matsumoto, Mitsunori Matsuo, Takehiro Hiraoka, Shun Akaeda, Tomoki Tanaka, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Tumor suppressor p53 has functions in various physiological and pathological processes beyond tumor suppression. Recent mouse studies have shown that uterine p53 controls embryo implantation and labor onset. Although its role in the ovary remains elusive, it has been reported that p53 is expressed in human granulosa cells. Mouse double minute 2 homolog (Mdm2) is the principal negative regulator of p53, and Mdm2–deleted cells show the heightened levels and activity of p53. We here established a mouse model of ovarian Mdm2 deficiency to clarify the influence of increased p53 on ovarian function. **Methods** Mice with deletion of ovarian Mdm2 (KO) and Mdm2/p53 (DKO) were generated by crossing Mdm2–floxed and p53–floxed mice with Pgr–Cre mice. These mice with or without superovulation treatment (SO) were mated with wild–type fertile males, and fertility and ovarian phenotype of KO and DKO mice were evaluated. **Results** Expression of p53 protein was upregulated and downregulated in granulosa cells of KO and DKO mice, respectively. KO mice were infertile with reduced number of ovulated eggs. In KO mice with SO, cumulus cell–oocyte complex (COC) expansion was markedly compromised, and few eggs were ovulated even after hCG treatment. Importantly, DKO showed normal fertility with normal COC expansion and normal ovulation. **Conclusion** Our findings suggest that aberrant activation of ovarian p53 is associated with ovulation disorder, mainly in COC expansion.

IS-WS-10-2

DNA methylation and its transcriptional regulation of preimplantation mouse blastocyst in the process of blastocyst activation Daiki Hiratsuka, Yasushi Hirota, Hirofumi Haraguchi, Tomoko Fujita, Mitsunori Matsuo, Leona Matsumoto, Takehiro Hiraoka, Shun Akaeda, Tomoki Tanaka, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective In the process of epigenetic reprograming, embryos undergo comprehensive DNA remethylation in the periimplantation period. A few hours before blastocyst attachment to the uterus, blastocysts change their global transcriptome status dynamically due to embryo–uterine interaction, known as blastocyst activation. To investigate the association of DNA methylation with blastocyst activation, we used the delayed implantation mouse model, which can control implantation only by ovarian hormone treatment. **Methods** Pregnant wild–type mice were ovariectomized a day before implantation, and daily injection of progesterone (P4) was performed to maintain pregnancy without implantation. To induce blastocyst activation and subsequent implantation, estrogen (E2) was injected into P4–treated mice in which implantation started a day after E2 injection. Activated blastocysts were collected 12 hours after E2 injection, and dormant blastocysts without E2 treatment were collected as the control. To evaluate global transcriptome and DNA methylation of activated and dormant blastocysts, RNA–Seq and MeDIP–Seq were performed. Transcripts of genes selected by their combination analyses were verified by qPCR. **Results** There was no significant difference of global DNA methylation status between dormant and activated blastocysts. Eight genes with more than ten–fold change of transcript level as well as significant change of DNA methylation level were identified. Two genes with downregulation of DNA methylation, *Akr1c14* and *Otogl*, showed significant upregulation of their transcripts in activated blastocysts compared to dormant ones. **Conclusion** These findings suggest that comprehensive DNA remethylation start after blastocyst activation, and DNA methylation is involved in epigenetic regulation of blastocyst activation.

IS-WS-10-3

CRISPR/Cas9–mediated gene disruption on Y chromosome Takashi Nakasuji[1], Hiroshi Asahara[2], Nobuyuki Kidera[1], Atsushi Yamamoto[1], Yuki Iwahara[1], Tomonori Ishikawa[1], Naoyuki Miyasaka[1] *Tokyo Medical and Dental University[1], Tokyo Medical and Dental University[2]*

Objective The Y chromosome plays a critical role in spermatogenesis. However, exact function of Y chromosome genes have not been completely elucidated because of difficulties to generate mutant mice with specific Y chromosome gene using conventional gene targeting strategies. Recently, artificial endonuclease was successfully used to generate mutation on the Y chromosome gene. **Methods** We applied CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR–associated protein 9) system for generation of mice model with a mutation in some gene encoded on the Y chromosome whose physiological function was unclear. **Results** The male mice with the mutation of the gene were infertile. Mutant sperm were morphologically abnormal and almost immotile. In vitro fertilization of mutant sperm failed to fertilize oocyte, and the rate of fertilization and blastocyst formation by intracytoplasmic sperm injections (ICSI) were significantly lower in the mutant sperm compared to wild type sperm. Furthermore, embryo transfer of ICSI–derived embryos did not generate any pups from the mutant sperm. Chromosome analysis on the mitotic embryos derived from mutant sperm showed chromosome breaks. **Conclusion** These results suggest that this gene are involved in sperm morphogenesis, fertilization, and the early embryonic development. Further investigation of the gene and its molecular network will contribute to understanding the failure of fertilization and early embryonic development in mammals.

IS-WS-10-4

The effects of chronic testosterone administration on body weight, appetite, and adipose tissue differ widely according to the estrogen milieu Takeshi Iwasa, Toshiya Matsuzaki, Kiyohito Yano, Maira Iriasu, Minoru Irahara *The University of Tokushima Graduate School, Institute of Health Biosciences*

Objective In females, estrogens play pivotal roles in preventing excessive body weight (BW) gain, whereas the roles of androgen in appetite and BW regulation systems have not been fully studied. Whether the roles of testosterone in the regulation of BW and appetite differ according to the estrogen milieu in females were evaluated. **Methods** Adult female rats were randomly divided into ovariectomized with estradiol supplementation (OVX

+E) or without supplementation (OVX) groups. These two groups were further divided into testosterone administered (T) or non-administered (Control) groups, respectively. After sixteen days' administration, samples were collected. BW change, food intake (FI), fat weight, adipocyte size, and peripheral and central metabolic/reproductive factors were compared between T and Control groups. **Results** In OVX+E groups, BW gain, fat weigh, and adipocyte size in T were higher than those in Control. In addition, leptin secretion from fat was lower and hypothalamic IL-1b mRNA level was higher in T compared with Control. On the other hand, in OVX groups, BW gain, FI, fat weight, and adipocyte size in T were lower than those in Control. Leptin secretion from fat and hypothalamic aromatase (CYP19a1) mRNA level were higher and hypothalamic TNF-a mRNA level was lower in T compared with Control. **Conclusion** Chronic administration of testosterone increase body weight and fat in the presence of estradiol, whereas, it decreases body weight, appetite and fat in the absence of estradiol. Changes in the hypothalamic aromatase and inflammatory cytokines, and leptin secretion from fat might be involved in such different effects of testosterone.

IS-WS-10-5

Investigation of Novel Genetic Candidates Causing Recurrent Abortions in Japanese Women Using Whole-Genome Single Nucleotide Polymorphism Arrays Taisuke Sato[1], Ohsuke Migita[3], Hiroka Hata[4], Aikou Okamoto[2], Kenichiro Hata[1] *National Research Institute for Child Health and Development[1], The Jikei University School of Medicine[2], St Marianna University School of Medicine[3], St Marianna University School of Medicine[4]*

Objective To investigate the genetic candidates linked to recurrent abortions (RAs). **Methods** We recruited 29 Japanese women who had a history of RAs without any underlying anatomical and medical causes. We extracted DNA from the villi of the aborted embryos from these women, and analyzed them using whole-genome single nucleotide polymorphism (SNP) arrays. **Results** Four cases (13.8%) could not be analyzed because of contamination with maternal-origin DNA, and chromosomal aneuploidies were observed in 10 cases (34.5%). By analyzing the array data from 15 euploidy cases, 33 copy number variations (CNVs) were identified. To enrich the more probable causative CNVs, we examined the overlap with the CNVs identified in phenotypically normal and parous Japanese women (Migita O, et al. 2014). Finally, we enriched 22 regions with 24 CNVs (Median : 0.278 Mb) as the precise genetic candidates causing RAs in Japanese. All these CNVs are too small to be detected by conventional chromosome binding techniques. Moreover, we could detect one CNV that caused the complete deletion of the miRNA cluster region. **Conclusion** We demonstrated that 22 CNV regions are causative candidates of RAs. Our analysis method using high-resolution whole-genome SNP arrays was beneficial for effectively investigating the novel genetic causative factors of RAs. To enrich the probable causative CNVs of RAs with greater efficacy, a more appropriate reference CNV list might be necessary. Moreover, our findings reaffirmed that the regulatory mechanism of gene expression with non-coding RNAs and other epigenetic factors could also be considered while identifying the unknown causes of miscarriages.

IS-WS-11-1

Analysis of maternal death autopsies in Japan Junichi Hasegawa[1], Naohiro Kanayama[2], Hiroaki Tanaka[2], Shinji Katsuragi[2], Masahiko Nakata[2], Takeshi Murakoshi[2], Kazuhiro Oosato[2], Masamitsu Nakamura[2], Akihiko Sekizawa[2], Isamu Ishiwata[2], Tomoaki Ikeda[2] *St. Marianna University School of Medicine[1], The Maternal Death Exploratory Committee in Japan[2]*

Objective To clarify the necessity for and problems related to autopsy for determining the cause of maternal death in Japan. **Methods** Women who died during pregnancy or within a year after delivery were analyzed between 2012 and 2015 in Japan to verify the requirement of autopsy in cases in which autopsy was performed and the need for autopsy in cases in which it was not performed. This study was approved by institutional ethical review board. **Results** Autopsies were performed in 49 cases of maternal death (37%). Among the 49 cases, the final diagnosis was compatible with the clinical course in 23, while the autopsy diagnosis was incompatible with the clinical course, and the final diagnosis was made using pathological findings in 13 cases. In two cases, the final diagnosis was based on the clinical course, but an autopsy was performed to exclude other possible causes. In three cases, no exact cause of maternal death was identified after autopsy. In seven cases that did not involve an autopsy, the diagnosis was made using ante-mortem surgical specimens. Fourteen cases were diagnosed based on operative findings. Three cases were diagnosed using post-mortem imaging. Twenty-eight cases were clinically diagnosed. The cause of death was determined by clinical findings in 25 cases without autopsy, and the cause of death could not be identified in eight cases. **Conclusion** We suggest that in these 33 cases (39%), autopsy should have been performed. Autopsy is necessary and important to determine the exact cause of maternal death.

IS-WS-11-2

A prospective study of maternal toxoplasma screening with use of IgG avidity and PCR method Ryosuke Takahashi[1], Akira Nishikawa[2], Mayumi Morizane[1], Shinya Tairaku[1], Ayumi Shimizu[2], Hideto Yamada[1] *Kobe University[1], NTT East Sapporo Medical Center[2]*

Objective Acute infection with Toxoplasma gondii (T. gondii) during pregnancy cause congenital toxoplasma infection of newborns. The aim of this study was to evaluate whether maternal screening with use of IgG avidity and PCR method effectively detect a high risk pregnancy for congenital infection. **Methods** In a prospective study serum T. gondii IgG avidity was measured in 472 pregnant women with positive tests for T. gondii antibody and positive/equivocal tests for IgM. Multiplex-nested PCR for T. gondii DNA on amniotic fluid, maternal blood and umbilical cord blood were performed with informed consent. **Results** Ninety-five (20%) women had low IgG avidity (<30%), thirty-four (7%) borderline avidity (30-35%), and three hundred and twenty-six (69%) high avidity (>35%) indices. Amniotic fluid obtained at amniocentesis or delivery showed positive PCR results in a total of 12 women with low IgG avidity indices. Of the 12 women 7 had congenital toxoplasma infection of their newborns. None of women with high or borderline IgG avidity indices had a positive PCR result in the amniotic fluid or congenital infection. No congenital infections was found in women whose amniotic fluids showed negative PCR results. **Conclusion** Maternal toxoplasma screening with a combination of IgG avidity in the blood and multiplex-nested PCR in the amniotic fluid was useful for detecting a high risk pregnancy of congenital toxoplasma infection.

IS-WS-11-3

Perinatal outcomes in women with systemic lupus erythematosus Eun Seok Seo, Suk Young Kim, Sun Young Jung, Seung Joo Chon, Jin Woo Shin *Gachon University, Korea*

Purpose Pregnancy in women with SLE carries various maternal and fetal risks. Recently we have experienced two cases of congenital heart block in neonatal lupus from women with SLE,

so for 10 years retrospective review of their clinical and perinatal outcomes is reported. **Methods** 15 cases of births in 13 peoples who had diagnosed to SLE during pregnancy were investigated between 2006 and 2016. 11 cases of women with SLE and their neonate were enrolled finally. Maternal obstetric characteristics, maternal complication, laboratory findings, and perinatal outcomes were investigated and compared their incidence, obstetric complication and neonatal outcomes. **Results** The incidence of women with SLE is 17/10,000 pregnancy during study period.(general population 14.6–50.8 cases per 100,000//the incidence of SLE during the child baring age being 1/500). There were 11 live births, 5 were premature, 5 had suffered intrauterine growth restriction and 2 had congenital heart block. Preeclampsia (2), gestational diabetes (2) thrombocytopenia (1), and pulmonary edema (1) had revealed to maternal complications. 50% of women with SLE had Anti Ro/SSA positive and two cases of congenital complete heart block in neonates were identified in positive the Anti Ro/SSA antibody patients. One of them required permanent pacemaker placement. And the other was dead in 24hr after delivery because of RDS. **Conclusion** Closed prenatal monitoring in fetus with arrhythmia by ultrasonography in women with SLE should be need and multidisciplinary approach with obstetrician, neonatologist, neonatal cardiologist and rheumatologist might be improved clinical outcomes both mother and infant.

IS-WS-11-4

Cesarean scar defect (Niche) : Prevalence and best diagnostic tools at an Egyptian University hospital Fady Moiety, Hesham Salem, Banan Aboulazm *Alexandria University, Egypt*

STUDY OBJECTIVE To report, and estimate the prevalence of Cesarean scar defects (CSD)/Niche at Shatby university hospital using both saline infusion sonohysterography (SIS) and office hysteroscopy (OH), thus comparing their diagnostic performance. **SETTING** University Gynecology Hospital. **PATIENTS** 200 consecutive patients with previous Cesarean sections were included. **INTERVENTIONS** All underwent Transvaginal 2D sonographic scan, SIS, and OH. Main Outcome Measures : Prevalence of CSD, and the diagnostic efficacy of each modality. **RESULTS** CSD/niche was detected in 56 cases (28%) at SIS and in 62 cases (31%) at OH. SIS was comparable to OH (the gold standard for diagnosis of intrauterine lesions) with a sensitivity, specificity, and overall accuracy of 87%, 100%, and 96%, respectively. **CONCLUSIONS** Prevalence of CSD/Niche is relatively high and should be considered with symptoms including ; abnormal uterine bleeding, secondary infertility and chronic pelvic pain. Sonohysterography is comparable to office hysteroscopy with an overall accuracy of 96% in the diagnosis of scar defects.

IS-WS-12-1

The Great East Japan Earthquake and following big tsunami impacted mental condition of pregnant women in the seriously affected area, Miyagi : The Japan Environment and Children's Study Zen Watanabe[1], Noriyuki Iwama[1], Hidekazu Nishigori[1], Takahiro Arima[1], Takashi Takeda[2], Junichi Sugawara[1], Hirohito Metoki[1], Nobuo Yaegashi[1] *Tohoku University[1], Kinki University[2]*

Objective The Great East Japan Earthquake hit the northeast coast of Japan on March 11, 2011. Miyagi prefecture was one of the most seriously affected areas by the earthquake and the following tsunami. The Japan Environment and Children's Study (JECS) was already underway when the earthquake occurred. We examined psychological distress among pregnant women in Miyagi and compared other less-damaged areas of Japan. **Methods** We examined eligible 7,473 Japanese pregnant women in the primary fixed data of the JECS : Miyagi unit center ("Miyagi-UC" ; n=998) and the other thirteen unit centers ("13UCs" ; n=6,475) as control. Further "Miyagi-UC" was divided into two groups : "Coast"(n=670) and "Inland"(n=328). The Kessler 6-item psychological distress scale was administered to assess psychological distress in the second-third trimester. We performed statistical comparisons in terms of the prevalence and the risk of psychological distress during pregnancy. **Results** The prevalence of pregnant women with psychological distress in "Miyagi-UC"(4.9%), especially "Coast"(5.5%) was significantly higher than in "13UCs"(3.1%). In multivariable logistic analyses adjusted for baseline characteristics, there was the association between psychological distress and areas, "Miyagi-UC"(adjusted odds ratio ; aOR=1.488 ; 95%CI, 1.059-2.090). After further adjusting for negative life events which probably reflected disaster situations, the association was diminished. In "Coast", the prevalence of psychological distress was almost equal and high without (5.5%) or with (5.4%) negative life events. **Conclusion** After the earthquake, pregnant women in Miyagi had psychological vulnerability. In seriously affected areas after a large-scale natural disaster, mental supports for pregnant women are important.

IS-WS-12-2

Development of "Disaster Liaison in Pediatrics and Perinatal Medicine (DLPPM)" Nobuya Unno[1], Miho Tsuruwa[2], Naotake Tsuda[3], Yoshiko Nishigaya[4], Kyoko Hattori[1], Junichi Sugawara[5], Makoto Suzuki[6], Akihito Nakai[7], Hideaki Masuzaki[8] *Kitasato Univsersity[1], National Disaster Medical Center[2], Kurume University[3], Kyorin University[4], Tohoku Medical Megabank Organization[5], Kameda General Hospital[6], Nippon Medical School Tama Nagayama Hospital[7], Nagasaki University[8]*

Objective After large scale earthquakes, to continue health care service to pregnant women and neonates in affected areas, an efficient information system is required between headquarters for disaster control in the local government and local perinatal facilities in affected areas. **Methods** In February, 2016, a new "DLPPM" training system was proposed to the Government by academic societies related to pediatric and perinatal medicine including JSOG. Supposedly, a DLPPM collects the support needs for maternal-fetal-neonatal medicine in the affected area, and plays a role in logistic arrangements such as patient transportation to perinatal centres in unaffected areas. In April 16, 2016, a huge earthquake struck Kumamoto Prefecture. In response to the request of disaster control headquarters in Kumamoto, a team including 3 obstetricians experienced with disaster medicine were sent to Kumamoto to serve as DLPPMs. **Results** After 10 days activities in the headquarters and evacuation shelters, the DLPPM team withdrew and took over their mission to local physicians. In Kumamoto area, no serious damage was observed in pregnant women or in the neonates obliged to be transported after the earthquake. **Conclusion** Although not well-prepared, an instant team of DLPPM played a significant role in the Kumamoto Earthquake. A training system of DLPPM may enhance our ability of disaster control in the field of pediatrics and perinatal medicine.

IS-WS-12-3

Assessment of the effectiveness of Tertiary Hospital-Recognized Partnership (THRP) program, a Public-Private Partnership program on Service Delivery Network (SDN) as an intervention to reduce Maternal and Neonatal Mortality Joanna Marie Paulino-Morente, Ma. Theresa Vergara, Eleanor Angulo De-Vera *Quirino Memorial Medical Center, Philippines*

Objective To evaluate the effects of Tertiary Hospital-Recognised Partnership or THRP program as a strategy to reduce ma-

ternal and neonatal mortality. **Methods** From June two thousand fourteen to April two thousand fifteen, data was collected from the medical records, Quezon City health department, ER log books, and database from the THRPs. The data for the years two thousand and ten to two thousand fifteen were also collected for comparison and analysis. **Results** The hospital maternal mortality rate decreased significantly over the study period using simple linear regression and Shapiro Wilk test. The hospital neonatal mortality rate did not decrease significantly. Interestingly, the pediatrics census revealed that the incidence of perinatal asphyxia was decreased significantly. There were two hundred forty five referrals from THRPs. The median time of transfer from THRPs to the tertiary hospital was forty five minutes. The expected mean transfer time of less than one hour was met using the Sign test. Those cases which were not coordinated were associated with a significantly higher risk of maternal death and neonatal death versus those which were coordinated. **Conclusion** This study demonstrates that this program is an effective referral system whose focus was to improve maternal and neonatal outcomes, strengthen the healthcare system, and remove the barriers between patient and good obstetric care. This strategy could be considered for use in other regions of the country as an intervention for improving the safety of pregnancy.

IS-WS-12-4

Horizontal transmission of HTLV-1 in Japanese reproductive-aged women Naoki Fuchi, Kiyonori Miura, Takashi Tsukiyama, Hideaki Masuzaki *Nagasaki University*

Objective The major route of Human T-cell leukemia virus type 1 (HTLV-1) infection is vertical transmission via breast-feedings during infancy. However, the incidence of horizontal transmission has not been unknown. We conducted retrospective analysis to investigate the incidence of seroconversion in the antenatal HTLV-1 screening test. **Methods** A total of 56,264 antenatal HTLV-1 screening samples gathered in Nagasaki prefecture between January 2011 and August 2016 were analyzed retrospectively. We extracted the pregnant women who had examined the screening test of HTLV-1 more than twice during this period, to assess the number of women who seroconverted to HTLV-1 positive. When western blot (WB) and/or PCR tests showed positive, women were confirmed as HTLV-1 carrier. All samples were obtained after receiving written informed consent, and the IRB of University approved the study protocol. **Results** Out of 56,264 samples, we included 8,659 pregnant women, who got HTLV-1 test twice or more ; the total number of samples was 18,139. Among them, 181 samples were confirmed as HTLV-1 carrier. Of the 181 samples, 6 pregnant women had seroconverted (6/8,659 ; 0.069%). **Conclusion** In this study, we detected seroconverted cases in the HTLV-1 screening test of pregnant women, suggesting that women have a risk of horizontal transmission from their partners with HTLV-1 infection. The HTLV-1 screening test in pregnant women should be performed in their each pregnancy.

IS-WS-12-5

Prevalence of repeat pregnancies among adolescent mothers at Siriraj Hospital Kanokwaroon Watananirun, Dittakarn Boriboonhirunsarn *Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

Objectives To study the prevalence of repeat pregnancies, the contraceptive use before getting pregnant and trend of contraceptive use after delivery among adolescent mothers at Siriraj Hospital. **Methods** A total of 220 adolescent mothers aged 13-19 years at delivery were enrolled. Each woman was interviewed regarding her current and past pregnancies, including demographic and social background, previous pregnancy, intention of current pregnancy, and contraceptive use. Prevalence of repeat pregnancy was estimated. Various characteristics were compared between those in their first pregnancy and those with repeat pregnancy. **Results** The mean age of all participants was 17.4 ± 1.4 years and mean age at first intercourse was 15.3 ± 1.4 years. Most of them have already quit school and live with their partner. Only 23.2% of them were planned pregnancies. Almost all of them knew about contraceptive methods (95.4%), but less than half (46.8%) used contraception. Reasons for not using contraception were planned pregnancies (35.9%), unawareness (48.7%), experiencing side effects (13.6%) and had no access to health care (2.5%). Those who declare using contraception, less than 25% use it regularly and correctly. Prevalence of repeat pregnancy was 16.8%. There was no significant difference between women in their first pregnancy and those with repeat pregnancy in terms of demographic and social characteristics, intention of pregnancy, and contraceptive use. **Conclusion** Prevalence of repeat pregnancy was 16.8%. These women had similar characteristics to adolescent mothers in their first pregnancy. The awareness and knowledge of contraceptive use should be intensively provided in order to prevent unplanned pregnancies among adolescents.

IS-WS-13-1

Relation between CHOP score and each parameter of fetal cardiac function in twin-to-twin transfusion syndrome and selective intrauterine growth restriction Katsusuke Ozawa, Riho Fukutani, Takuya Kushimoto, Rina Akaishi, Rika Sugibayashi, Seiji Wada, Haruhiko Sago *National Center for Child Health and Development*

Objective CHOP score is useful for assessing the cardiac function of recipient twins with TTTS ; however, it is not convenient because it entails the measurement of many parameters. We studied the relation between CHOP score and each parameter of fetal cardiac function in TTTS and selective IUGR. **Methods** One hundred and thirteen patients with TTTS or selective IUGR whose CHOP scores were measured at our center between June 2014 and August 2016 were included. The parameters of fetal cardiac function of recipient or larger twins were myocardial performance index (MPI), umbilical vein (UV) flow volume, ICT/ET, IRT/ET, pulsatility index (PI) of ductus venosus (DV), E/e, and inflow time/cardiac cycle length (CCL). The relationship between CHOP score and each parameter was analyzed using Pearson correlation and ROC curve. **Results** Median gestational age at measurement was 19 weeks and 6 days ; median CHOP score was 4 (0-16). The correlation coefficient of CHOP score and each parameter was −0.24 in UV flow volume, 0.34 in LV MPI, 0.67 in RV MPI, 0.39 in LV ICT/ET, 0.23 in LV IRT/ET, 0.59 in DV PI, 0.51 in RV ICT/ET, 0.40 in RV IRT/ET, 0.27 in LV E/e, 0.36 in RV E/e, −0.54 in LV inflow time/CCL, and −0.71 in RV inflow time/CCL. Sensitivity and specificity of RV inflow time/CCL for predicting CHOP score of >9 were 0.60 and 0.76, respectively (inflow time/CCL 34.4%, AUC 0.804). **Conclusion** Inflow time/CCL in the RV had a strong correlation with CHOP score in the recipient twins with TTTS and larger twins with selective IUGR.

IS-WS-13-2

Atmospheric pressure plasma irradiation promotes axonal growth in neonatal rat organ co-cultures Shiori Shinagawa, Norihumi Tanaka, Takako Sadakane, Yukie Kidani, Hiroshi Miyoshi, Yoshiki Kudo *Hiroshima University*

Objective Perinatal brain injury is a major cause of acute mortality and neurological complications in the new born. Although some new treatments have been developed, they have had lim-

ited therapeutic effects. Therefore, the development of new strategies for treating perinatal brain injury is urgently needed. Atmospheric pressure plasma, which increases cell proliferation, enhances cell transfection efficiency, and improves wound healing, is currently being developed for a wide range of medical applications. Thus, we hypothesized that plasma may become a new treatment modality for patients with perinatal bran injury. As a preliminary experiment, we examined the effects of plasma on axonal regeneration. **Methods** We used anterograde axonal tracing in organ cocultures of the cortex and the spinal cord from 3-day-old neonatal rats. The organ cocultures were irradiated with plasma on day 3 in culture. Axonal growth was evaluated by counting the number of axons labeled with 1,1'-dioctadecyl-3,3,3', 3'-tetramethylindocarbocyanine perchlorate passing through a reference line running parallel to the junction between the cortex and the spinal cord at 500, 1,000, and 1,500 μm from the junction. **Results** The mean numbers of axons extending to 500 or 1,500 μm were 22.0±3.9 and 1.6±0.6 in the flow control group and 39.0±4.9 and 6.7±2.0 in the plasma group. The mean numbers of axons extending to 500 or 1,500 μm in the plasma group were significantly greater than in the flow control group. **Conclusion** Our results showed that plasma irradiation promoted axonal growth in organ cocultures.

IS-WS-13-3

Fetal heart rate variability in preterm fetal sheep with lipopolysaccharide-induced endotoxemia Hyo Kyozuka, Tsuyoshi Hiraiwa, Shun Yasuda, Keiya Fujimori *Fukushima Medical University*

Objective The aim of this study was to investigate the effects of lipopolysaccharide (LPS)-induced endotoxemia on fetal heart rate (FHR) variability in chronically instrumented preterm fetal sheep. **Methods** The change in short-term variability (STV) due to intra-amniotic endotoxin infusion was measured in five chronically instrumented preterm fetal sheep at 111 to 120 days of gestation. Granulocyte-colony stimulating factor was injected intravenously into the fetuses on postoperative days 3 to 6, and 40 mg of lipopolysaccharide (LPS) was infused in the amniotic cavity on postoperative days 5 and 6. The quantification of STV was calculated according to *Huey et al*. The STV was recorded throughout the study and a 1-hour average was calculated. A Joinpoint regression model was used to analyze the trends regarding each 1-hour average of STV. All umbilical cord, amnion, and chorion membranes were evaluated histologically. **Results** STV was significantly decreased 18 hours after the first LPS administration ($p<0.05$) without any significant changes in fetal arterial blood gas (ie : pH, pO_2, pCO_2, and Base Excess). All intrauterine fetal deaths occurred within 15 to 28 hours after the second LPS administration. STV showed a significant linear increase from 30 hours before intrauterine fetal death ($p<0.05$). Histologic chorioamnionitis was confirmed in all cases. **Conclusion** Acute exposure to LPS suppressed STV however direct to an increase during the perimortem period in fetal sheep. This finding may be useful marker to the early detection of intra-amniotic infection.

IS-WS-13-4

Impact of degree of right ventricular outflow tract obstruction on cerebrovascular resistance in tetralogy of Fallot Mitsuhiro Tsuritani[1], Zhiyun Tian[2], Masami Sawada[1], Tetsuya Ide[1], Chinami Horiuchi[1], Takekazu Miyoshi[1], Yusuke Ueda[1], Chizuko Kamiya[1], Naoko Iwanaga[1], Reiko Neki[1], Jun Yoshimatsu[1], Jack Rychik[2] *National Cerebral and Cardiovascular Center[1], The Children's Hospital of Philadelphia, USA[2]*

Objective A relationship between various forms of congenital heart disease (CHD) and fetal cerebral blood flow patterns has been demonstrated. We sought to determine impact of degree of right ventricular outflow tract (RVOT) obstruction on cerebrovascular resistance in a large cohort of fetuses with a single CHD, that of tetralogy of Fallot (TOF). **Methods** We reviewed fetal echocardiograms of 256 fetuses (628 examinations) with TOF. Subjects were divided into 4 groups : Group 1=mild pulmonary stenosis (pulmonary artery > half size of aorta) ; Group 2=moderate-to-severe stenosis (pulmonary artery < half size of aorta but patent) ; Group 3=pulmonary atresia ; Group 4 =absent pulmonary valve syndrome. Subjects were compared to 184 age-matched normal controls. Pulsatility indices (PIs) were recorded for middle cerebral artery (MCA), umbilical artery (UA) and uterine artery (UTA). Cerebroplacental ratio (CPR) was calculated as MCA PI/UA PI. For subjects with more than 2 examinations, comparisons were made between values prior to 26 and after 34 weeks gestation. **Results** CPR was significantly lower in Group 1 compared with groups 3 and 4 ($p<0.01$, $p<0.01$) and moreover lower in Group 1+2 compared to Group 3. CPR declined when comparing 2nd to 3rd trimesters. There were no significant changes between groups 1, 2, and 3 for UA or UTA. **Conclusion** Degree of RVOT obstruction influences cerebral blood flow. Fetuses with pulmonary atresia have the highest cerebrovascular resistance. Anatomical variability within TOF influences cerebral blood flow patterns and thus may influence neurological development in survivors after postnatal surgery.

IS-WS-13-5

Determination of Fetal Gestational Age by Ultrasonographic Measurement of Fetal Humeral Length among Patients Seen at a Tertiary Government Hospital : A Preliminary Study Leslie Barba, Amaryllis Digna Yazon, Cristina Fabella *Amang Rodriguez Memorial Medical Center, Philippines*

Ultrasonography is a non-invasive and relatively inexpensive tool in estimating fetal gestational age. Measurement of humerus length is less commonly used, but studies have shown comparable accuracy with the other parameters - head circumference (HC), biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC). There have been no local studies on fetal humeral length (HL) measurement among Filipinos. This study was done to determine fetal gestational age by ultrasonographic measurements of fetal humerus. The data collected serve as an initial database for the construction of intrauterine fetal growth chart using this parameter. A cross-sectional study was done on 335 uncomplicated pregnant patients at gestational ages 20-40 weeks by conducting fetal sonographic biometrics including the fetal humeral length. Its correlation with menstrual age was evaluated. Results were compared with that of biparietal diameter and femur length. Analyses of the data were done using SPSS version 10. BPD, FL, and HL were plotted against age of gestation by last normal menstrual period. HL measurement is used as an alternative parameter for estimating gestational age, with correlation coefficient of 0.918 compared to BPD (0.943) and HL (0.924). The combination of BPD, HL and FL increased the correlation to 0.951. While combination of the BPD and HL have the same correlation coefficient of 0.951, indicating that using the two parameters can also estimate fetal gestational age.

IS-WS-13-6

Factors affecting the Quality of Nuchal Translucency Measurements Nalat Sompagdee, Tuangsit Wataganara, Chayawat Phatihattakorn *Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

Objectives To evaluate factors affecting the quality of nuchal translucency (NT) measurements. **Methods** The NT measure-

ments performed at Maternal-Fetal Medicine Unit, Siriraj Hospital from 2008-2013 by well-trained obstetricians were retrospectively reviewed with regard to quality control standard (median NT-MoM). The NT-MoM values were calculated using Nicolaides formula. The quality of the measurements according to years of experiences of the sonographers (comparing the first and the second chronological period ; 2008-2010 and 2009-2013), maternal body mass index and crown-rump length values were evaluated. **Results** A total of 716 NT measurements were retrieved from the database. Overall, years of experiences of the sonographers had a statistically significant impact improving this standard. The second chronological period measurements had a more accurate median NT-MoM as compared to the first chronological period (mean of medians of 1.05 VS 1.13, $P<0.05$), which targeted value of the mean of medians was 1.0. Body mass index $\leq$ 25 kg/m^2 and crown-rump length $\leq$ 60 mm had a tendency to improve the accuracy of measurements although without statistical significance. **Conclusion** More years of experiences of the sonographers in performing the NT measurements statistically significant improves the quality of the measurements. Body mass index $\leq$ 25 kg/m^2 and crown-rump length $\leq$ 60 mm have a positive impact on the quality without statistical significance.

IS-WS-14-1

Genome-wide DNA methylation sequencing showing that miR-663a is a novel epimutation candidate in endometrial cancer with CpG island methylator phenotype-high Megumi Yanokura, Kouji Banno, Masataka Adachi, Haruko Kunitomi, Miho Iida, Kanako Nakamura, Yusuke Matoba, Keiko Watanabe, Yusuke Kobayashi, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki *Keio University*

Objective Concurrent DNA methylation of multiple genes occurs in endometrial cancer and is referred to as the CpG island methylator phenotype (CIMP). However, the features and causes of CIMP-positive endometrial cancer are not well understood. We hypothesized that normal tissue in cases of CIMP-positive endometrial cancer has features that increase DNA methylation, and that such methylation plays important roles in carcinogenesis of CIMP-positive endometrial cancer. Therefore, the aim of this study was to investigate the DNA methylation status in normal tissue from patients with CIMP-positive endometrial cancer. **Methods** The study was approved by the Ethics Committee. The subjects were 25 patients with endometrial cancer from whom cancer tissue and peripheral blood cells (PBCs, serving as normal cell) were obtained. The 25 cancer samples were classified as CIMP-high (CIMP-H) and CIMP-negative (CIMP (-)) by methylation-specific PCR analysis of three genes (*MLH1*, *APC* and *E-cadherin*). DNA libraries were prepared from PBCs DNA from 2 CIMP-H and 2 CIMP (-) patients. Methylation targets were detected using bisulfite sequencing data and DNA Methyltransferases (DNMTs) expression were analyzed. **Results** Based on genome-wide bisulfite sequencing, PBC DNA in CIMP-H cases had significant hypermethylation in the miR-663a promoter region, compared to CIMP (-) cases (meth. Diff.$>$25%, q-value$<$0.01). Consistent with this methylation status, miR-663a expression was lower in CIMP-H PBCs than in CIMP (-) PBCs. DNMTs expression levels in CIMP-H endometrial cancer were higher than those in CIMP (-) endometrial cancer. **Conclusion** These results raise the possibility that aberrant methylation of the miR-663a promoter region is an epimutation candidate in CIMP-H endometrial cancer.

IS-WS-14-2

The MIR130 families suppress epithelial-to-mesenchymal transition of uterine endometrial cancer cells by inhibiting the expression of BHLHE40 and BHLHE41 Kazuo Asanoma, Hiroshi Yagi, Ichiro Onoyama, Kenzo Sonoda, Kiyoko Kato *Kyushu University*

Objective For the purpose of elucidating a novel molecular mechanism of human uterine endometrial cancer (HEC) development, we studied the impact of the onco-microRNA MIR130 families in HEC cells. **Methods** HEC specimens, which were surgically removed under patients` informed consents, were examined for the expression levels of the MIR130 families, MIR130A, MIR130B, MIR301A, MIR301B, and MIR454. The mimics of the MIR130 families were transfected into HEC cell lines. Invasive activity of the manipulated cells was assayed *in vitro*. Expression of the epithelial-to-mesenchymal transition (EMT) markers was also examined on the cells. We identified tumor suppressor genes, BHLHE40 and BHLHE41 (BHLHEs) as targets of MIR130 families. Reporter assay was applied to demonstrate the direct regulation of BHLHEs by the MIR130 families. **Results** The expression levels of MIR301A and MIR301B were higher in advanced stage of HEC tissues compared with those of early cases. Forced expression of MIR130A, MIR130B, and MIR 301B in HEC cells resulted in enhancement of EMT and *in vitro* cell invasion. The expression of both BHLHE40 and BHLHE41 was suppressed by transfection of MIR130 family mimics. Reporter assay revealed critical sites in 3`-UTR of BHLHEs for association with MIR130 families. **Conclusion** Our data suggested that upregulation of MIR130 families in the process of HEC progression suppresses the expression of BHLHEs and enhances EMT and cell invasion in HEC cells. We propose that MIR130 families are promising markers to predict the aggressiveness of each HEC cases, and that molecular targeting strategies involving MIR130 families and BHLHEs may effectively regulate HEC progression.

IS-WS-14-3

The recurrence prediction score for predicting the baseline risk of recurrence of stage I-II endometrial carcinoma Kenta Takahashi[1], Mayu Yunokawa[2], Yutaka Yoneoka[1], Mayumi Kobayashi[1], Yae Takehara[1], Keisei Tate[1], Takafumi Tsukada[1], Hanako Shimizu[1], Takashi Uehara[1], Mitsuya Ishikawa[1], Shun-Ichi Ikeda[1], Tomoyasu Kato[1] *National Cnancer Center Hospital[1], National Cnancer Center Hospital[2]*

Objective To develop and validate the recurrence prediction score (RPS) system for predicting the baseline risk of recurrence of stage I-II endometrial carcinoma. **Methods** After obtaining approval from of our institutional review board, we reviewed 427 patients with International Federation of Gynecology and Obstetrics stage I-II endometrial carcinoma who underwent surgery without any adjuvant therapy at our institution from 2005 to 2013. Multivariate analysis was performed with age, pathological type, myometrium invasion, lymphovascular invasion, cervical stromal invasion, and ascites cytology to identify the risk factors for recurrence-free survival (RFS) in 251 patients treated in odd-numbered years (test cohort). We developed the RPS system to estimate scores of recurrence using prognostic factors, and applied the system for 176 patients treated in even-numbered years (validation cohort). **Results** Multivariate analysis revealed that the significant risk factors were age $>$60 years, pathological type II, positive cervical stromal invasion, and positive ascites on cytology. We gave each risk factor 1 point, and defined the sum of the risk factor scores as the RPS. In the test cohort, the 5-year RFS was RPS 0 : 100%, RPS 1 : 95.8%, RPS 2 : 79.9%, and RPS 3 : 33.3%. In the validation cohort, the 5-year RFS was significantly higher in the low-risk group (RPS 0 or 1) than that in the high-risk group (RPS 2 or 3) (94.2% vs. 75.9%, $p<0.01$). **Conclusion** The RPS system shows significant reproducibility for predicting the baseline

risk of recurrence. The system could potentially impact treatment choices for stage I–II endometrial carcinoma.

IS-WS-14-4

Clinicopathologic analysis of synchronous ovarian malignancy in young women with endometrial cancer Mika Sakai, Takanori Yokoyama, Etsuko Fujimoto, Shinichi Ookame, Yuko Shiroyama, Takashi Yokoyama, Kazuhiro Takehara *National Hospital Organization Shikoku Cancer Center*

Objective To examine the clinicopathologic feature of synchronous ovarian malignancy in young women with endometrial cancer (EC). Lynch syndrome (LS) has been recognized as a familial clustering of cancers of the colon, endometrium, stomach, ovary, and ureter, caused by a dominantly inherited germ-line mutation in DNA mismatch repair (MMR) genes. For patients with LS, the average age of onset of endometrial or ovarian cancers is 46–48 years. Meanwhile, in premenopausal women with EC, ovarian preservation may be a consideration. **Methods** With institutional review board approval, a retrospective chart review was conducted on patients with EC, aged＜50 years, identified at a hospital specialized in cancer for 12 years. **Results** Among 106 patients (aged＜50 years) who underwent surgery for EC, 23 (21.7%) were found to have synchronous ovarian malignancies. The histology of endometrium and ovary were same among 18 cases (endometrioid adenocarcinoma (EA) in 17 ; clear cell carcinoma (CCC) in 1), but different among 5 (EA/CCC in 4 ; EA/endometrioid borderline tumor in 1). The expression of MMR proteins by immunohistochemistry was decreased in the endometrium and ovary in 6 cases. Of 6 cases, 3 showed different histology (EA/CCC) but similar pattern of the expression of MMR proteins between the endometrium and ovary. **Conclusion** We found a high incidence of synchronous ovarian malignancy in young women with EC. The patients suspected to have LS who desire ovarian preservation should be counseled regarding the high rate of synchronous ovarian malignancy. Interestingly, it is indicated that the histology of synchronous ovarian malignancy may be associated with CCC.

IS-WS-14-5

Oncogenic histone methyltransferase EZH2 : A novel prognostic marker and therapeutic target in endometrial cancer Shinya Oki[1], Kenbun Sone[1], Katsutoshi Oda[1], Michihiro Tanikawa[1], Kazunori Nagasaka[1], Yuji Ikeda[1], Takahide Arimoto[1], Hiroyuki Kuramoto[2], Osamu Hiraike[2], Kei Kawana[3], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Kanagawa Health Service Association[2], Faculty of Medicine, Nihon University[3]*

Objective Dysregulation of a histone methyltransferase EZH2, a key epigenetic regulator, is associated with human tumorigenesis. Here, we investigated the prognostic significance of EZH2 expression and ant-tumor effect of EZH2 inhibition in endometrial cancer. **Methods** EZH2 expression was analyzed by quantitative real-time PCR in 11 endometrial cancer cell lines and 52 clinical endometrial cancer specimens. The prognostic importance of EZH2 expression in endometrial cancer was evaluated by Kaplan-Meier survival analysis of the Cancer Genome Atlas (TCGA) microarray database (n=540). EZH2 was inhibited by either siRNA-mediated knockdown of EZH2 or treatment with GSK126, a selective EZH2 inhibitor in endometrial cancer cell lines. The anti-tumor effects were examined using western blotting, MTT assay, and Annexin V-FITC. GSK126 was combined with other anti-cancer drugs (cisplatin and doxorubicin). **Results** EZH2 was significantly overexpressed in endometrial cell lines ($p<0.01$) and clinical samples ($p<0.01$), compared with the control. High expression of EZH2 was significantly associated with poor progression free survival ($p=0.008$) and poor overall survival ($p=0.01$) in the TCGA dataset. EZH2 knockdown caused significant growth suppression and increased the ratio of apoptotic cell death (9–11%) in all the endometrial cancer cells through decreased H3K27 trimethylation. GSK126 treatment suppressed endometrial cancer cell growth and decreased the number of cancer cell colonies in a dose-dependent manner. Furthermore, GSK126 significantly sensitized the endometrial cancer cells to cisplatin- and doxorubicin-induced growth inhibition. **Conclusion** High EZH2 expression may be a useful poor prognostic marker, and EZH2 inhibitor, such as GSK126, may serve as a novel molecular targeted therapy in endometrial cancer.

IS-WS-15-1

In vitro* characteristics of intravaginal *Lactobacilli Kazuaki Yoshimura[1], Toru Hachisuka[2] *Wakamatsu Hospital of University of Occupational and Environmental Health[1], University of Occupational and Environmental Health[2]*

Objective Recently, the clone library method of broad-range 16 S rRNA gen sequencing has been applied for intravaginal microbiome analysis. The results of clone library method are occasionally different from that of traditional methods. *L. iners* which is gram negative short rod and is detected in BV case. In this study, *in vitro* characteristics of 4 species of intravaginal *Lactobacilli* were examined. **Methods** 1. By using the standard strain of *L. crispatus, L. iners, L. gasseri, L. jensenii*, growth curves were drawn (OD_{600}) accompanied with Gram stain, culture pH, and bacterial count. 2. MRS mediums were prepared for pH 3/6 and growth curve of 4 species of *Lactobacilli* were drawn with Gram stain, culture pH, and bacterial count for each medium. **Results** 1. The growth speed was faster in order of *L. gasseri, L. jensenii, L. crispatus, L. iners*. Bacterial counts of all *Lactobacilli* decreased in the middle of log-phase of the growth curve. In particular, *L. iners* grew to 10^6 CFU/mL and the others grew to 10^8 CFU/mL. 2. *L. iners* was almost gram-negative short rod and the others were gram-positive rod. 3. *L. iners* was almost killed in the pH3 medium and the others grew in 1/100 order compared with pH6 medium. **Conclusion** *L. iners* was thought to be weak against acid and it presented low anti-bactericidal activity. Therefore, the morbidity of BV will be higher in the *L. iners*-dominant case than the other *Lactobacilli*-dominant cases. In addition, *L. iners* was presumed to be misread as BV-related bacteria instead of *Lactobacilli* during the NS scoring.

IS-WS-15-2

Estrogen enhances endothelial differentiation and angiogenic activity in rat adipose-derived stromal cells Hsin-Ju Chiang[1], Steve Leu[2] *Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan[1], Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan[2]*

Objectives Previous studies have shown that rapidly deteriorating endothelial function led to poor prognosis of cardiovascular event in menopause women. Recent studies also demonstrated that the endothelial differentiation of mesenchymal stem cells (MSCs) modulated the therapeutic efficacy of cytotherapy in ischemic organ injury. In this study, we applied the cultured cell model to examine the effect of estrogen on regulating endothelial differentiation and angiogenesis in adipose-derived MSCs. **Methods** adipose-derived MSCs were isolated form abdominal adipose tissues of male Sprague Dawley (SD) rats and cultured in endothelial cell growth medium (EGM-2) with or without estrogen treatment (l00 nM of 17α-estradiol) for 14 days to induce endothelial differentiation. After culturing, Flow cytometric analysis, Matri-gel and trans-well examination, and im-

munofluorescent stainings were performed to examine the endothelial differentiation and angiogenic activity. **Results** Restuls from immunofluorecent stainings showed the nuclear translocation of estrogen receptor β (ER-β) in adipose-derived MSCs after culturing with estrogen. Expression levels of endothelial progenitor cell markers (CXCR4/CD34, Sca-1/KDR, c-Kit/CD 31) were increased with estrogen treatment in flow cytometric analysis. The migratory and in vitro angiogenic activity of adipose-derived MSCs were also enhanced by estrogen treatment. In addition, abundant expression level of angiogenic factors VEGF was found in adipose-derived MSCs treated with estrogen. **Conclusion** The endothelial differentiation of adipose-derived MSCs could be enhanced by the estrogen treatment.

IS-WS-15-3

Eldecalcitol increases the bone mass in patients with Turner syndrome whose bone mass acquisition is insufficient even after estrogen replacement therapy Taku Tsuburai[1], Tomomi Nakamura[1], Hiromi Yoshikata[1], Hideya Sakakibara[2] *Yokohama City University[1], Yokohama City University Medical Center[2]*

Objective Most patients with Turner syndrome (TS) are at high risk for osteoporosis due to ovarian dysfunction. However, it is not rare for insufficient bone mass acquisition even after estrogen replacement therapy (ERT). The objective of this study was to identify the characteristics of bone metabolism in TS with low bone mass after ERT, and to investigate the effectiveness of eldecalcitol (ELD) as an adjuvant therapy for bone mass acquisition. **Methods** We recruited 52 TS patients undergoing ERT, and sorted them into a low bone mass group (LB group ; n =23) and a normal bone mass group (NB group ; n=29). TS individuals with ovarian function were grouped in a spontaneous menstrual cycle group (MC group ; n=7), and bone metabolism markers were compared between the three groups. Furthermore, the LB group used ELD together with ERT for 12 months of treatment, and the bone density and bone metabolism markers were compared between before and after the treatment. **Results** uNTX (nmol BCE/mmol Cr) was significantly higher in the LB group (44.8 ± 17.7) than in the NB group (36.0 ± 18.0 ; p= 0.004) and the MC group (30.2 ± 9.8 ; p=0.005). Furthermore, when ELD was used together with ERT in the LB group, BMD (g/cm^2) increased significantly (pre-treatment 0.710 ± 0.056 vs. 0.736 ± 0.062 after 12 months ; $p<0.001$). **Conclusion** TS individuals with insufficient bone mass acquisition even after ERT are characterized by a higher turnover in bone metabolism. Therefore, the concomitant use of ELD for such cases was considered to be an effective adjuvant therapy for increasing bone mass.

IS-WS-15-4

High intake of sucrose is associated with anxiety and depression in Japanese middle-aged women Asuka Hirose, Masakazu Terauchi, Mihoko Akiyoshi, Naoyuki Miyasaka *Tokyo Medical and Dental University*

Objective In this study, we investigated the dietary patterns associated with anxiety and depression in Japanese middle-aged women. **Methods** This study used baseline data collected in a previous study in 88 women aged 40 to 60 years. Participants were assessed for age, body composition, psychological symptoms using HADS questionnaire, and dietary habits using the brief-type self-administered diet history questionnaire, which provides information about the amounts of 70 foods and 100 nutritional factors consumed during the previous month. Classifying HADS-Anxiety/Depression score >7 as high, we sought to identify the nutritional factors and dietary habits associated with anxiety and depression. **Results** First, we investigated about the nutritional factors and body composition, and multiple logistic regression analysis revealed that both of high HADS-Anxiety and Depression score were associated with high intake of sucrose (adjusted odds ratio, 1.06 and 1.07 per 1g/day increase of intake of sucrose ; 95% confidence interval, 1.03-1.16 and 1.01-1.14). All the other nutritional factors and body composition were not significantly different between high and low HADS-Anxiety/Depression score groups. Next, we investigated about the dietary habits. Multiple logistic regression analysis revealed that high HADS-Anxiety score was associated with high intake of western confectionery and low intake of fried food (1.02 and 0.97 per 1 g/day increase of intake ; 1.01-1.05 and 0.95-0.99), and high HADS-Depression score was associated with high intake of Japanese confectionery (1.07 per 1 g/day increase of intake ; 1.01-1.13). **Conclusion** High intake of sucrose is associated with anxiety and depression in Japanese middle-aged women.

IS-WS-15-5

A new protocol for reducing lower urinary tract symptoms after anterior transvaginal mesh surgery for pelvic organ prolapse Kaori Hoshino[1], Kazuaki Nishimura[1], Kazuaki Yoshimura[1], Toru Hachisuka[2] *Wakamatsu Hospital of University of Occupational and Environmental Health[1], University of Occupational and Environmental Health[2]*

Objective Anterior transvaginal mesh surgery (A-TVM) is an excellent procedure for cystocele. However, lower urinary tract symptoms (LUTS) after A-TVM, which includes de novo stress urinary incontinence (SUI) and voiding difficulty, is one of the serious postoperative problems which impair patients' QOL. To reduce the postoperative complications, we established a new protocol for the fixing methods of mesh according to the preoperative uroflowmetry results. **Methods** The patients who underwent A-TVM during April 2016 and September 2016 were enrolled. We categorized them into two groups according to the results of uroflowmetry. Twenty patients, whose maximum flow rate (Qmax) was over 10ml/s, were included in group A. Three fixing sutures of mesh by non-absorbable string were placed at 1cm proximal site from urethral meatus. Seventeen patients, whose Qmax was less than 10ml/s, were included in group B. Only one fixing suture of mesh was placed at the same point. Post-void residual urine volume (PVR) and Core Lower Urinary Tract Symptom Score (CLSS) questionnaire were used for assessment of LUTS. **Results** The PVR on postoperative day 3 of group A/B were 71.9 ± 78.9ml and 47.6 ± 70.9ml, respectively (p =0.75). None of them required clean intermittent catheterization. The evaluation of SUI and voiding difficulty by CLSS did not worsen at one month after the surgery. **Conclusion** Our protocol of mesh fixation will reduce the postoperative LUTS after A-TVM.

IS-WS-15-6

Comparisons of clinical outcomes and urodynamic effects in female overactive bladder patients after 3-month versus 6-month solifenacin treatment : A randomized prospective study Ho-Hsiung Lin[1], Sheng-Mou Hsiao[1,2] *National Taiwan University Hospital, Taipei, Taiwan[1], Far Eastern Memorial Hospital, Taiwan[2]*

This aim is to elucidate whether prolonged antimuscarinic treatment could decrease the recurrence of significant OAB symptoms that need retreatment. A prospectively randomized controlled trial was performed. Consecutive women with OAB symptoms were randomized assigned to receive solifenacin 5 mg once a day for 3 months or 6 months. Baseline characteristics, including urodynamic parameters, 20 minute pad weights, 3 day bladder dairies, questionnaires and urine nerve growth factors, were compared. Recurrence free interval was measured

from the date of the date of last antimuscarinics prescription to the date of documented OAB symptoms recurrence while received antimuscarinics retreatment, or last followup. A total of 182 women were analyzed. Ninety one patients received 3 months therapy and the other 91 patients received 6 months therapy. Most baseline data were not statistically different between these two groups. However, the recurrence free curves did not differ between these two groups. Multivariate analysis revealed that the strong desire amount and nocturia episodes were the sole two independent factors affecting recurrence free interval. The intension to treat duration did not affect the recurrence free interval. After treatment, significant better improvements of corrected NGF, Overactive Bladder Symptoms Score, Patient Perception of Bladder Condition, daytime frequency episodes, some Kings Health Questionnaires subscores were noted in the 6 months group, compared with the 3 months group. In conclusion, prolonged antimuscarinic treatment has better impacts on OAB symptoms and health related quality of life, but may not result in the decrease of the recurrence of OAB symptoms.

IS-WS-16-1

Prognostic factors and effect of fertility-sparing surgery for ovarian clear cell carcinoma in women of reproductive age : a propensity score-weighted analysis Masato Yoshihara, Hiroaki Kajiyama, Kiyosumi Shibata, Fumitaka Kikkawa *Nagoya University*

Objective Ovarian clear cell carcinoma (CCC) is one of the leading causes of death from gynecologic malignancies, which can arise in women in reproductive age. We investigated clinical characteristics of young patients with CCC and evaluated prognostic factors of them. **Methods** This is a regional population-based study between 1986 and 2015, collecting clinicopathological data of 161 young women with CCC. We evaluated characteristics, and clinical and survival outcomes of the patients. Additionally, to analyze prognostic effects of fertility-sparing surgery (FSS) in particular, baseline imbalance between patients with and without FSS was adjusted using an inverse probability of treatment weighting using propensity scores composed of independent clinical variables. **Results** The mean age was 39.5 years (Range, 27-45) and the median follow-up period for surviving patients was 55.6 months. In multivariate analysis, the substage group (IA-IC1 vs. IC2/3), was the only independent prognostic factor of recurrence free survival and overall survival in Stage I patients (hazard ratio, 12.0 ; $p<0.001$ and 18.6 ; $p<0.001$, respectively). Regarding FSS, the 10-year recurrence rates were 0.850 (SD=0.08) and 0.781 (SD=0.55) in the FSS and non-FSS groups, respectively. Noninferiority of FSS on the survival outcome was confirmed after propensity score adjustment. Uni- and multivariate analysis also demonstrated that FSS was not a significant prognostic factor for their survival outcomes. **Conclusion** Based on the results, the substage group was the only independent prognostic factor for young patients of Stage I CCC. FSS can be considered in CCC patients who strongly hope bear children in the future.

IS-WS-16-2

Prediction of platinum resistance by metabolome analysis and RNA sequence analysis of cancer stem-like cells in ovarian cancer Masakazu Sato[1], Kei Kawana[2], Katsuyuki Adachi[1], Akira Kawata[1], Juri Ogishima[1], Mitsuyo Yoshida[1], Ayumi Taguchi[1], Osamu Hiraike[1], Katsutoshi Oda[1], Takeshi Nagamatsu[1], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], School of Medicine, Nihon University[2]*

Objective It is now evident that there exists heterogeneity in tumors. Especially, cancer stem cell (CSC) theory is well-documented, and CSCs are involved in treatment resistance and tumor relapse. We aimed to characterize CSCs with both metabolome-based and mRNA-based comprehensive analyses, and to address whether CSCs-specific elements are useful to predict platinum-resistance in ovarian cancer. **Methods** We obtained CSC-like cells by culturing ovarian cancer cell line, OVTOKO in non-adherent plates (with formation of spheroids). We compared those properties with cells cultured in adherent plates (non-CSCs). We performed metabolome analysis (C-SCOPE, HMT, Inc.) and RNA sequence (Illumina HiSeq2000). Gene-set enrichment analysis from the data of RNA sequence was performed with DAVID tool based on Kyoto Encyclopedia of Genes and Genomes (KEGG). We also obtained dataset of RNA-sequence of 274 ovarian cancer patients derived from the Cancer Genome Atlas network (TCGA). **Results** Metabolome analysis showed that the concentrations of glutamine and serine were significantly higher in CSCs compared to non-CSCs (about nine times and five times, respectively). Meanwhile, RNA sequence showed that focal adhesion pathway was the key pathway in CSCs. We combined these data, by considering gene expressions involved in glutamine or serine metabolism, and focal adhesion kinase (27 genes in total). With computed analysis, considering those gene expressions could predict platinum-resistant cases from TCGA database at 88% accuracy, and platinum-sensitive cased at 93% accuracy. **Conclusion** Specific metabolomic and focal adhesion pathways can be a useful marker to predict platinum-resistant patients in ovarian cancer. Comprehensive analyses of CSCs might be a powerful strategy to clarify tumor biology in ovarian cancer.

IS-WS-16-3

Long term follow-up and prognosis of endometriosis associated ovarian cancer Yasuhito Tanase, Sumire Sugimoto, Kana Iwai, Emiko Niiro, Sachiko Morioka, Yuki Yamada, Fuminori Ito, Natsuki Koike, Hiroshi Shigetomi, Ryuji Kawaguchi, Toshiyuki Sado, Hiroshi Kobayashi *Nara Medical University*

Objective Most studies on patients with endometriosis-associated ovarian cancer (EAOC) have revealed an association between EAOC and younger age, earlier stage, specific histological type (i.e., clear cell carcinoma and endometrioid carcinoma), and relatively better prognosis. However, there have been few reports on patients with EAOC who were followed-up for long term. This study aimed to evaluate the long-term prognosis of EAOC. **Methods** We identified EAOC among 210 patients diagnosed with ovarian cancer at our institution from January 2008 to January 2015. Overall survival (OS) and progression-free survival (PFS) were compared between patients with EAOC and those with non EAOC. **Results** The median follow-up period was 26 months (range : 1-113). EAOC was present in 68 patients (32.4%), with a significant increase in the frequency of diagnosis at an earlier stage of disease and at a younger age ($p<0.01$ and $p<0.01$, respectively). Patients with EAOC had improved PFS and OS at a median follow-up period of 24 months and 27 months, respectively, [(HR=0.76 ; 95% CI, 0.54-0.88 ; $p<0.001$), (HR=0.71 ; 95% CI, 0.54-0.82 ; $p<0.001$), respectively], compared with those with non EAOC. Even in a multivariate Cox regression analysis, endometriosis was independently associated with OS and PFS [(HR=0.37 ; 95% CI, 0.18-0.79 ; $p<0.001$), (HR=0.44 ; 95% CI, 0.25-0.80 ; $p<0.001$), respectively]. **Conclusion** EAOC appears to be more frequently diagnosed at an earlier stage and younger age and confers a better OS and PFS than those of non EAOC. Compared with patients with non EAOC, those with EAOC have a more favorable long-term prognosis ; however, larger studies are required to validate these results.

IS-WS-16-4

Identification of two major subgroups (BRCA-related and aging-related) on basis of mutational signatures by whole-exome sequencing in high-grade ovarian serous carcinoma Kayo Asada[1], Katsutoshi Oda[1], Akira Nishijima[1], Kosei Hasegawa[2], Yuji Ikeda[1], Akira Kurosaki[2], Takahiro Kouso[1], Aki Miyasaka[1], Kei Kawana[3], Keiichi Fujiwara[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Saitama Medical University International Medical Center[2], Nihon University School of Medicine[3]*

Objective Homologous recombination deficiency (HRD) by mutations in *BRCA1/BRCA2* and other related genes is known to be essential for tumorigenesis in high-grade serous ovarian carcinoma (HGSOC). However, other types of HGSOC have not been well characterized. We aimed to identify an HRD-independent subgroup and clarify its genomic characteristics in HGSOC, using whole exome sequencing (WES) and methylation analysis. **Methods** We performed WES in 78 clinical HGSOC samples under informed consent and approval of our institutional ethics committee. Predominant mutational signature in each case was identified from 30 patterns on basis of nucleotide

substitution types in our samples and other 396 HGSOC samples from public database. Methylation levels across the genome were examined by Infinium Human Methylation 450 Bead Chip (Illumina). **Results** Two major mutational signatures were identified in HGSOC. One is "BRCA signature"(60/78 and 254/396 samples, respectively) and the other is "Age signature". "Age signature" group showed significantly poor overall survival, compared with "BRCA signature" group (p=0.0017 from our samples). "Age signature" was not associated with patients' age, as well as stage and residual tumor volume. DNA hypermethylation in *protocadherin*, one of aging markers, was significantly more frequent in "Age signature" group, compared with "BRCA signature" group (p<0.0001). In contrast, "BRCA signature" group include all the *BRCA1/2* mutant tumors (n=27) (p=0.0037). **Conclusion** Accumulation of mutations by aging and hypermethylation of *protocadherin* may contribute to carcinogenesis in HRD-independent HGSOC. Subclassification by genomic characterization may be useful to predict HRD- dependency in HGSOC.

IS-WS-16-5

Suppression of Warburg effect enhances cisplatin sensitivity in ovarian clear cell carcinoma Sachiko Kitamura, Ken Yamaguchi, Ryusuke Murakami, Kaoru Abiko, Junzo Hamanishi, Tsukasa Baba, Noriomi Matsumura *Kyoto University*

Objective Ovarian clear cell carcinoma (OCCC) exhibits resistance to chemotherapy including platinum agents. We have identified that HNF1B promotes Warburg effect and contributes to chemoresistance in OCCC. In this study, we aimed to identify a factor associated to drug resistance and a therapeutic target in glucose metabolism in OCCC. **Methods** Whole exome sequencing and expression microarray were conducted using 39 OCCC clinical samples and 13 OCCC cell lines. Expression microarray using sh-HNF1B OCCC cell line were performed. Cell viability of 13 OCCC cell lines against cisplatin was measured using WST-1 assay. Publicly available datasets of IC50 values and SNP array of ovarian cancer cell lines were used for validation. **Results** Chromosome (Chr) 17q21-24 is significantly amplified in recurrent OCCC cases compared to patients who did not recur. Positive correlation between chr17q21-24 amplification and IC50 for cisplatin was observed both in 13 OCCC cell lines (r>0.4) and 10 validation ovarian cancer cell lines but not in non-ovarian tumor cell lines. Of the down-regulated genes by HNF1B, overlapping genes located in chr17q21-24 and associated with glycolytic pathway is PDK2. PDK2 amplification was significantly correlated with IC50 values for cisplatin (p=0.0057). WST-1 assay showed that PDK2 inhibitor, dichloroacetate, have increased cisplatin sensitivity in OCCC cell lines (Combination Index<1). **Conclusion** Chr17q21-24 amplification was a predictor of platinum resistance. Suppression of Warburg effect through targeting PDK2 is a promising therapeutic strategy against OCCC.

IS-WS-17-1

Inflammation on the amniotic membrane induces preterm delivery via Toll-like receptor 2 in mice with chronic dental *Porphyromonas gingivalis* infection Yuko Teraoka[1], Hiroshi Miyoshi[1], Haruhisa Konishi[1], Satoshi Urabe[1], Mutsumi Miyauchi[2], Takashi Takata[2], Yoshiki Kudo[1] *Hiroshima University[1], Department of Oral and Maxillofacial Pathobiology, Hiroshima University[2]*

Objective It is now widely accepted that inflammation induces preterm delivery. We previously reported that mice with the dental *Porphyromonas gingivalis* (*P.g*) infection (*P.g* mice) could be used as an effective model of preterm delivery. In this model, inflammation on the amniotic membrane is thought to be the main cause of preterm delivery as cyclooxygenase 2 and interleukin (IL)-1β levels are highly upregulated in the amniotic membrane. Here, we aimed to investigate the mechanism through which inflammation was induced on the amniotic membrane in *P.g* mice. **Methods** We observed *P.g* colonies in the placenta of *P.g* mice using immunohistochemistry. We evaluated toll-like receptor 2 (TLR2) and TLR4 levels in the amniotic membrane using real-time polymerase chain reaction on day 18 of gestation in control and *P.g* mice. TLR2 plays an important role in the recognition of *P.g*-lipopolysaccharide (LPS) and the activation of inflammatory pathways. Western blot analysis was performed for detection of nuclear factor kappaB (NF-κB; phospho-p65), and mitogen-activated protein kinases (MAPKs; phospho-p38, and, phopho-JNK). **Results** Immunohistochemistry revealed that the *P.g* colonies were expressed in the embryo side of the placenta and amniotic membrane. TLR2 levels in the amniotic membrane were increased by 2.4-fold in *P.g* mice; however, TLR4 levels were not elevated. NF-κB and MAPK expression levels were enhanced on the amniotic membrane but not in the placenta and myometrium in *P.g* mice. **Conclusion** NF-κB and MAPK signaling pathways were activated via TLR2 leading to release cytokines. Inflammation on the amniotic membrane is suggested to induce preterm delivery.

IS-WS-17-2

Effects of human amniotic fluid stem cells on cutaneous wound healing in a mouse excisional model Marie Fukutake, Daigo Ochiai, Hirotaka Masuda, Yu Sato, Youhei Akiba, Toshimitsu Ohtani, Yoshifumi Kasuga, Satoru Ikenoue, Tadashi Matsumoto, Kei Miyakoshi, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective Adult wound healing sometimes results in pathologic scars, characterized by excessive deposition of type I collagen. In contrast, fetal wound healing always results in complete regeneration without scars. Our aim is to determine the effects of human amniotic fluid stem cells (hAFSs) on cutaneous wound healing using a mouse excisional model. **Methods** The study protocol was approved by the institutional review board of our university and informed consent was obtained from all patients. hAFSs were isolated as CD117 positive cells from human amniotic fluid. Two full-thickness skin wounds were created by a biopsy punch in the dorsal region of BALB/c mice, and hAFSs or PBS (control) were injected into the dermis around each wound. We performed macroscopic measurements and histological examination such as hematoxylin and eosin, Masson's trichrome (to evaluate re-epithelialization of the epidermis), and Elastica van Gieson staining (to evaluate granulation area in the dermis), 7, 14, and 21 days after the biopsy. **Results** Macroscopic and histological analyses of the cutaneous wounds revealed that hAFSs treatment significantly accelerated wound closure associated with re-epithelization as compared to control. Nevertheless, there were no significant differences in granulation area between the two groups. Picrosirius red staining demonstrated less deposition of type I collagen in the scars of hAFSs group compared to control. We also investigated collagen components of the scar in regenerated tissues by Picrosirius red staining 21 days after the biopsy. **Conclusion** hAFSs treatment accelerated cutaneous wound closure with fewer scars in a mouse excisional model.

IS-WS-17-3

Adipose-derived-mesenchymal stem cells could be a promising cell source of tissue regeneration in congenital neural degeneration Akihiro Kawashima, Akihiko Sekizawa, Ryu Matsuoka, Keiko Koide *Showa University*

Objective Genetic brain disorders including Down-syndrome cause abnormal development and function of the brain due to dysregulation of the central nervous system. Experimental cell therapy has been tried to fetus by intra-uterine injection. The aim of this study is to define the neural commitment of adipose-derived-mesenchymal stem cells (ADSCs) in vitro and analyze cellular distribution, survival, and tissue integration in vivo. **Methods** ADSCs were isolated from the inguinal adipose tissue of 8-week-old-mice by enzymatic digestion. To generate neural differentiation, the cells were stimulated with retinoic acid for 24 hours following bFGF, forskolin and GGF5 for 5 days. Neural specific mRNAs and proteins were examined by RT-PCR and immunocytochemistry (ICC). To clarify the effect of ADSCs on brain tissue in vivo, cells obtained from CAG-EGFP Tg mice were injected into fetal-brain ventricle at E14.5, then microscopically confirmed GFP positive cells after 3 days. **Results** ADSCs after neural induction expressed the neuron-specific markers, GFAP, S100 and Tuj1 by ICC. Also, GFAP and NSE mRNA were increased in ADSCs by the induction stimulation. These results suggest that ADSC may have a differentiation potential beyond the neural lineage. Furthermore, transplanted GFP-positive ADSCs into brain grew tightly around venticle and migrated deep into the brain. These data suggest that ADSCs can be differentiated into neural cell and tissue integration in vivo. **Conclusion** Taken together, ADSCs could be a promising cell source of tissue regeneration in congenital neural degeneration.

IS-WS-17-4

Sumoylation of Basonuclin1 highly expressed in oocyte is enhanced by Pias4 Motomasa Ihara, Masahiro Sakamoto, Masahito Tachibana, Nobuo Yaegashi *Tohoku University*

Objective *Basonuclin1* (*Bnc1*)- knock down oocytes appear morphologically abnormal, and fertilized *Basonuclin*- deficient eggs failed to develop beyond the two-cell stage. *Bnc1*- knock out mice decrease number of follicles at earlier age and show infertility phenotype. Identifing the novel Bnc1-binding proteins and elucidating a part of molecular mechanism regulated by Bnc1 highly expressed in oocyte could possibly help treating some meiotic anomalies and follicle developmental failures. Therefore, we suggest the significance on identifing novel Bnc 1-binding proteins and their physiological functions. **Methods** HEK 293 cells and 10,000 of adult mouse oocytes were collected and immunoprecipitated with the anti-Bnc1 antibody respectively. Novel Bnc1-binding proteins were identified by mass spectrometry. **Results** One of the novel Bnc1-binding proteins, SUMO E3 ligase Pias4 (Protein inhibitor of activated STAT 4) was identified. Bnc1 was modified with both SUMO-1 and SUMO-2/3, and Pias4 enhanced the both sumoylation of Bnc1. **Conclusion** Pias4 enhanced sumoylation of Bnc1, and this result suggests that sumoylation regulates the molecular function of Bnc1.

IS-WS-18-1

Loss of BRCA1 in the cells of origin of ovarian cancer induces glycolysis : identifying the strategy for ovarian cancer metabolic chemoprevention Tatsuyuki Chiyoda[1], Fumio Kataoka[1], Hiroyuki Nomura[1], Tomoko Yoshihama[1], Naoki Nakadaira[1], Yoshiko Nanki[1], Akira Hirasawa[1], Sakura Nakada[2], Ernst Lengyel[3], Iris L. Romero[3], Mamoru Tanaka[1], Daisuke Aoki[1] *Keio University[1], Kawasaki Municipal Hospital[2], The University of Chicago, USA[3]*

Objective Mutations in *BRCA1* increase the risk of developing ovarian cancer. However, beyond the role of BRCA1 in DNA repair, little is known about other mechanisms by which BRCA1 impairment promotes carcinogenesis. Given that aerobic glycolysis, also referred to as Warburg effect, is now recognized as important in the initiation and progression of cancer, we analyzed whether loss of BRCA1 changes metabolism in the cells of origin of ovarian cancer. **Methods** The effect of BRCA1 knockdown or overexpression of BRCA1 which harbors deleterious mutation (5382insC or P1749R) on several metabolic pathway was quantified using ovarian surface epithelial and fallopian tube cells. BRCA1's effect on enzymes which configure the major metabolic pathway altered by BRCA1 was measured using western blot and quantitative PCR. Then the mechanisms BRCA1 controls the identified enzyme were investigated using chromatin immunoprecipitation (ChIP) and promoter luciferase assay. **Results** Silencing BRCA1 or overexpression of the BRCA 1 mutant proteins in ovarian surface epithelial and fallopian tube cells increased glycolysis. Among the glycolytic enzymes, hexokinase-2 (HK2) was increased by BRCA1 impairment. ChIP showed BRCA1 does not bind HK2 promoter, but BRCA1 knockdown increased HK2 promoter activity 2.7 fold. While the major HK2 transcription factor HIF1α was unchanged by BRCA1, MYC and the signal transducer and activator of transcription 3 (STAT3) were identified as HK2 transcription factors directly controlled by BRCA1. **Conclusion** BRCA1 impairment elevates glycolysis by HK2 upregulation which is mediated by MYC and STAT3. Suppressing glycolysis or HK2 may be promising strategy for metabolic chemoprevention of *BRCA1* mutation carriers.

IS-WS-18-2

Prognostic significance of pretreatment leukocyte alterations in patients with epithelial ovarian cancer Naoko Komura, Seiji Mabuchi, Eriko Yokoi, Katsumi Kozasa, Hiromasa Kuroda, Michiko Kodama, Kae Hashimoto, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective Leukocyte alterations including leukocytosis or elevated neutrophil to lymphocyte ratio (NLR) have been occasionally observed and been associated with disease severity and poor prognosis in human malignancies. However, the prognostic significance of leukocytosis or elevated NLR in ovarian cancer patients remains unclear. We conducted a retrospective study to investigate the prognostic significance of pretreatment leukocytosis and elevated NLR in patients with epithelial ovarian cancer. **Methods** Clinical data from 346 epithelial ovarian cancer patients treated with operation and/or chemotherapy from April 2007 to March 2016 were collected, and retrospectively reviewed. Leukocyte alterations were defined as leukocyte count exceeding 10,000/μl or NLR exceeding 4.0. Univariate or multivariate analysis was employed to evaluate the association between pretreatment leukocytosis or elevated NLR and extraovarian spread (including metastasis in the contralateral ovary, regional nodes, distant nodes, or distant organs), rate of optimal surgery and progression-free survival (PFS). **Results** Both pretreatment leukocytosis and increased NLR were found to be associated with high probability of extraovarian spread ($p < 0.05$) and decreased optimal surgery ratio ($p < 0.05$). Leukocytosis or increased NLR are also predictive of shorter PFS ($p < 0.05$), advanced clinical stage ($p < 0.05$) and treatment failure rate ($p < 0.05$). **Conclusion** Leukocyte alterations is a significant prognostic factor in epithelial ovarian cancer patients.

IS-WS-18-3

GSKJ4, a selective jumonji H3K27 demethylase inhibitor, targets ovarian cancer stem cells Hirotsugu Sakaki, Manabu Seino, Tsuyoshi Oota, Satoru Nagase *Yamagata University*

Objective Global increase in the trimethylation of histone H3 at lysine 27 (H3K27me3) has been associated with the differentiation of normal stem cells and cancer cells, however, the role of H

3K27me3 in the control of cancer stem cells (CSCs) remains poorly understood. We investigated the impact of increased H3 K27me3 on ovarian CSCs using GSKJ4, a selective jumonji H3K 27 demethylase inhibitor. **Methods** The effect of GSKJ4 on the viability as well as on the self-renewal and tumor-initiating capacity of CSCs derived from A2780 and TOV21G human ovarian cancer cell line, was examined. **Results** GSKJ4 induced cell death in A2780 CSC and TOV21G CSC at a concentration non-toxic to normal human fibroblasts. Furthermore, GSKJ4 induced differentiation and inhibited sphere formation as well as stem cell marker expression of A2780 CSC and TOV21G CSC that survived GSKJ4 treatment. **Conclusion** Using ovarian CSCs as a model, we have demonstrated for the first time that GSKJ4 can target CSCs, suggesting a critical role for H3K27 methylation in their maintenance and survival. Our findings thus provide an initial clue to explore the role of GSKJ4 as a potent CSC-targeting agent for ovarian cancer and other types of human cancer.

IS-WS-18-4

The resistance to anti-VEGF therapy in ovarian cancer is mediated through recruitment of hypoxia-induced MDSC Naoki Horikawa[1], Kaoru Abiko[1], Junzo Hamanishi[1], Tsukasa Baba[1], Ken Yamaguchi[1], Ikuo Konishi[2], Noriomi Matsumura[1] *Kyoto University[1], Kyoto Medical Center[2]*

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 (MDSC) 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 anti-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 protein array of tumor lysates was performed. Expression of MDSC chemoattractants in HM-1 cells cultured under hypoxic conditions was analyzed. **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. Protein array exhibited increased Gm-csf, a chemoattractant for MDSC, in a-VEGF abs-resistant tumors. The expression levels of Gm-csf and RelA, a component of NF-kB complex, were up-regulated in HM-1 cells cultured under hypoxic condition. Up-regulation of Gm-csf expression was abrogated by silencing RelA. The combination therapy with anti-GM-CSF abs significantly inhibited the tumor growth compared with a-VEGF abs only. Tumor-infiltrating MDSC were reduced by combination therapy. **Conclusion** Anti-VEGF therapy induced tumor hypoxia and up-regulated Gm-csf expression thorough NF-kB signal. Anti-GMCSF abs overcomes the evasive resistance to a-VEGF abs through blockade of MDSC influx into tumor.

IS-WS-18-5

Whole-exome sequencing, transcriptome and DNA methylation array in ovarian clear cell carcinomas identified a subgroup characterized by absence of mutations in ARID1A and PIK3CA Akira Nishijima[1], Katsutoshi Oda[1], Kayo Asada[1], Kosei Hasegawa[2], Akira Kurosaki[2], Takahiro Kouso[1], Aki Miyasaka[2], Yuji Ikeda[1], Kei Kawana[1], Keiichi Fujiwara[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Saitama Intenational Medical Center[2]*

Objective Although mutations in ARID1A and PIK3CA were frequent in ovarian clear cell carcinoma (OCCC), integrated genome-wide characterization of OCCC has not been well clarified. The aim of this study is to identify and characterize a subgroup, which may be independent from ARID1A and PIK3CA mutations. **Methods** We performed whole-exome sequencing in 75 clinical OCCC patients under informed consent and approval of our institutional ethics committee. Expression array was performed using Human Genome U133 Plus 2.0 Array, and genome-wide methylation was analyzed with Infinium HumanMethylation450K BeadChip. **Results** Top 2 non-synonymous mutations were ARID1A (57% : n=43) and PIK3CA (55% : n=42). ARID 1A mutations were significantly more common in PIK3CA mutated tumors (73% : n=30, $p<0.01$). OCCC subgroup with no mutations in ARID1A and PIK3CA (n=21, 28%, "Double-Negative") was significantly associated with advanced stage (43% with stage III/IV, $p<0.01$) and poor prognosis ($p=0.034$). All mutations in TP53, ATM, and KEAP1 (n=15 : TP53 related pathway genes) were exclusively identified in the Double-Negaive tumors ($p<0.01$). Nucleotide substitution patterns of each mutation identifies three mutational signatures in OCCC (1. APOBEC : Dysregulation of C-to-U editing enzymes, 2. Age : Endogenous mutational process of aging, and 3. Novel). Double-Negative tumors were significantly associated with the "Novel" mutational signature ($p<0.01$). Moreover, hierarchical clustering by either expression array or methylation array identified a specific cluster, which is significantly enriched with Double-Negative tumors. **Conclusion** Comprehensive genome-wide analysis identified a subgroup without mutations in ARID1A and PIK3CA, which is characterized by an unreported mutational signature and TP53-related alterations. Sub-classification by genetic and epigenetic analysis may serve personalized therapies against OCCC.

ISP-1-1

The significance of tumor-associated neutrophils in uterine cervical cancer treated with definitive radiotherapy Yuri Matsumoto, Seiji Mabuchi, Eriko Yokoi, Katsumi Kozasa, Hiromasa Kuroda, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective The aim of this study was to investigate the prognostic significance of tumor-associated neutrophils (TANs) in cervical cancer patients treated with definitive radiotherapy. **Methods** The baseline characteristics and oncological outcome data of early-stage cervical cancer patients who were treated with definitive radiotherapy between January 1996 and December 2011 were collected. Using biopsy samples obtained at the time of initial diagnosis, intratumoral TAN (CD66+neutrophils) was assessed by immunohistochemistry. Based on the density of intratumoral CD66b+TANs, the patients were divided into three groups ; low, medium, and high TANs. The univariate and multivariate analyses were performed to evaluate the relationship between the intratumoral TANs density and the clinicopathological features as well as progression-free survival (PFS) in these patients. **Results** The number of patients in low, medium, and high CD66b+TANs groups were 41 (16.4%), 156 (62.4%), and 53 (21.1%), respectively. In the univariate analysis, increased intratumoral TANs density was found to be associated with younger age (<50), advanced FIGO stage, low pretreatment hemoglobin level (<10mg/dl), lymph node metastasis, elevated peripheral WBC count (>10,000/μl), and elevated peripheral neutrophil count (>7,500/μl). The density of intratumoral TANs were significantly associated with shorter PFS. Multivariate analysis identified increased intratumoral TANs, advanced FIGO stage, non-SCC histology, and lymph node metastases as independent prognostic factors for shorter PFS. **Conclusion** Increased intratumoral TANs density is an independent prognostic factor for shorter PFS in cervical cancer treated with definitive radiotherapy. TANs may be a promissing therapeutic target in cervical cancer patients.

ISP-1-2

Extended-field radiotherapy with concurrent chemotherapy (extended-field CCRT) for cervical cancer with para-aortic or high common iliac lymph node involvement Akiko Abe, Masato Nishimura, Eri Takiguchi, Takako Kawakita, Minoru Irahara *Tokushima University*

Objective Lymph node metastasis in cervical cancer is a potentially important risk factor for recurrence. For cases of suspected para-aortic lymphadenopathy or high common iliac lymph node involvement, extended-field radiotherapy was applied. The present study aimed to retrospectively evaluate the efficacy of extended-field CCRT as primary treatment. **Methods** Between January 2010 and December 2014, 26 patients with cervical cancer positive for para-aortic and/or high common iliac lymphadenopathy were treated with extended-field CCRT at our Hospital. **Results** The median age was 56 years (range, 30-75), and the median size of the tumors was 55.5 mm (range, 27-106). The distribution of stage was as follows : Ib2, n=2 ; IIb, n=6 ; IIIa, n=2 ; IIIb, n=16, and MA, n=15. The 2- and 5-year OS rates were 86% and 52%, respectively. Eleven patients had a recurrence. Adjuvant therapy was administered to 12 patients (9 in MA), and TC therapy was administered monthly for 3 cycles after extended-field CCRT. Three patients had a recurrence (locoregional failure, n=2 ; distant recurrence, n=1). The other 14 patients were treated without adjuvant chemotherapy, of whom 8 had a recurrence (locoregional failure, n=4 ; distant recurrence, n=4). No significant differences were found in PFS or OS between the patients treated with and those treated without adjuvant chemotherapy (p=0.546 and p=0.895, respectively). **Conclusion** Extended-field CCRT appears effective as reported in previous studies. When followed by adjuvant chemotherapy, it decreased the incidence of distant recurrence. However, owing to the small number of cases in this study, the benefits of extended-field CCRT to PFS and OS could not be observed.

ISP-1-3

Investigation of factors of radio resistance for cervical cancer Masato Nishimura, Eri Takiguchi, Takako Kawakita, Akiko Abe, Minoru Irahara *Tokushima University*

Objective To investigate the factors of radio resistance for the patient of advanced cervical cancer and improve the treatment. **Methods** 100 cases who received radiotherapy and examined the effect of treatment during 2011-16. Concurrent chemoradiotherapy (CCRT) was done for patients under 80 years old. Weekly cisplatin (40mg/m^2) was given before August 2014, and weekly paxlitaxel (50mg/m^2) and cisplatin (30mg/m^2) was given for the patients with non-SCC after September 2014. Radiotherapy with 50Gy/25fr was given for the patient who has only pelvic region, and extended irradiation with 50.4Gy/28fr was given for the patient who has paraaortic lymphnode metastasis. **Results** Clinical stages are as follows, 1B 10, 2A 5, 2B 40, 3B 27, 4A 4, 4B 13. Histological subtypes are as follows, SCC 79, adeno and adenosquamous carcinoma (non-SCC) 16, others 5. Local recurrence rate are as follows : 1B 1/10 (10%), 2A 0/5 (0%), 2B SCC 3/32 (9%), 2B non-SCC 4/8 (50%), 3B SCC 3/18 (17%), 3B non-SCC 6/9 (67%). Local recurrence was significantly frequent in non-SCC than SCC at same stage ($p<0.01$). For the relation with tumor diameter, local recurrence was 4/62 (7%) in SCC (<7cm), 5/15 (33%) in SCC (>7cm), 0/1 in non-SCC (<4cm), 11/15 (73%) in non-SCC (>4cm). For the relation with treatment period, local recurrence was occurred 8/22 in patients who took 50days or more, but 11/78 in patients with completed within 49 days ($p<0.05$). **Conclusion** Improvement of treatment was necessary for large tumor patients (SCC with over 7cm and non-SCC with over 4cm). Management of adverse event is needed to complete the treatment within 49days.

ISP-1-4

The evaluation of radiation-induced fistula in cervical cancer after therapy Mihoko Kawaguchi, Tomoko Shima, Azusa Sameshima, Kyoko Ookita, Tomoko Tanaka, Kei Tsuda, Kumiko Inada, Akitoshi Nakashima, Osamu Yoshino, Shigeru Saito *University of Toyama*

Objective The purpose of this study was to investigate factors influencing the fistula formation of patients with cervical cancer who received radiation therapy (RT) or concurrent chemoradiotherapy (CCRT). **Methods** Patients with cervical cancer who had received RT or CCRT between 2006 and 2016 were retrospectively analyzed. In bladder or rectal fistula formation cases, we analyzed the MRI findings obtained before radiation therapy. **Results** A total of 86 were identified, and 18 cases (23%) of patients were T4 stage. Five cases in T4 formed a fistula after radiation therapy. Most fistula was formed within one year of irradiation therapy. There was no significant difference in fistula formation rate between RT and CCRT. Age, the presence or absence of the center block and of intracavitary irradiation were not associated with fistula formation rate. Direct invasion into the bladder or rectum was involved in fistula formation. The bladder fistula formation rate was significantly higher in the cases which had multiple invasion site (bladder invasion + vaginal wall or rectum) than in the cases which had only bladder invasion. For rectal fistula, distance from the tumor to the rectum was a factor influencing the fistula formation. **Conclusion** Evaluation before treatment by MRI might be useful to prediction of the fistula formation. Sufficient attention to fistula formation

was needed, and we require careful management.

ISP-1-5

Radiation therapy determined by various imaging modalities and prognosis for advanced uterine cervical cancer Kaho Suzuki, Yasuhiko Ebina, Yoshiya Miyahara, Kotaro Ichida, Senn Wakahashi, Hitomi Imafuku, Mizuki Uenaka, Takako Arai, Hideto Yamada *Kobe University*

Objective Various imaging modalities are used to define radiation field before primary therapy in Japan. If we detected metastasis to pelvic (PLN) in patients with advanced uterine cervical cancer, inadequate treatment leads to early recurrence. This study aimed to evaluate the association between radiation therapy determined by various imaging modalities and prognosis. **Methods** From Jan 2010 to Sep 2016, 105 patients were enrolled. Patients with stage IA2–IVB cervical cancer were retrospectively studied. All patients underwent various imaging modalities before therapy. Patients were divided into the groups A and B, according to diagnostic imaging. Group A ; negative PLN and PAN nodes, Group B ; positive PLN and negative PAN, For Group A and B, CCRT or RT (external and internal radiation therapy) was performed. For stage IVB and recurrence high-risk cases, chemotherapy was performed. **Results** The median age of all patients was 68 years (range 24–91). The median follow - up time for all patients was 508 days (range 15- 2007). Significant differences of prognosis were observed between Group A and B ($p<0.05$). Significant differences in rates of recurrence were observed between Group A and B ($p<0.05$). The most frequent of recurrence site was PAN in Group B. None of patients underwent PET-MRI before therapy had recurrence. **Conclusion** For patients in Group B, adjuvant chemotherapy should be considered, because of the risk for recurrence. As for detecting metastasis to PLN, PET-MRI may be more useful than other imaging modalities.

ISP-1-6

A retrospective analysis of five cases of cervical cancer treated with concurrent paclitaxel and carboplatin-based chemoradiotherapy Natsuko Kamiya, Yuichi Imai, Tatsuya Matsunaga, Yukihide Ota, Yukio Suzuki, Tae Mogami, Naho Ruiz Yokota, Mikiko Sato, Etsuko Miyagi *Yokohama City University Hospital*

Objective Cisplatin-based concurrent chemoradiotherapy (CCRT) is associated with a better prognosis for cervical cancer than radiotherapy alone. However, cisplatin administration is not safe for patients with renal dysfunction. Therefore, it is necessary to use an alternative chemotherapeutic regimen for such patients. We performed paclitaxel and carboplatin (TC)-based CCRT for cervical cancer in five cases with renal dysfunction and evaluated the safety and efficacy of the TC-based CCRT. **Methods** We retrospectively analyzed the safety and efficacy of TC-based CCRT used for the treatment of five patients with progressive and recurrent cervical cancer between December 2015 and June 2016 at our hospital. Chemotherapy with paclitaxel at 135 mg/m^2 followed by a dosage of carboplatin at area under the curve of 5 was performed every 3 weeks. Radiotherapy was also performed with external irradiation and brachytherapy for primary disease and with external irradiation for remote metastasis according to cervical cancer guidelines. **Results** Three and two cases were treated as primary treatments and recurrence treatments, respectively. TC chemotherapy was performed for 2.6 cycles on average. Three cases had neutropenia of grade 3 or higher, of whom two needed to stop radiotherapy temporarily (average : 6.0 days). No cases needed to decrease the radiation dose because of neutropenia. One, two, and two cases showed a complete response, partial response, and stable disease, respectively. **Conclusion** Although TC-based CCRT for cervical cancer with renal dysfunction may control disease progression, this combined chemotherapy and radiotherapy protocol should be improved because of its adverse events.

ISP-1-7

A case of necrotizing fasciitis that occurred during hospitalization for chemoradiotherapy for cervical cancer Takako Arai, Yasuhiko Ebina, Yuka Murata, Erika Tanaka, Hitomi Imafuku, Kaho Suzuki, Yoshiya Miyahara, Hideto Yamada *Kobe University*

Necrotizing fasciitis is a rare infectious disease which is rapidly progressive and potentially fatal in nature. A woman in her 50s completed concurrent chemoradiotherapy for cervical cancer stage IVB 4 days before planning to leave the hospital. In the morning of planned discharge, she developed a fever of 38℃ with shaking chills. Septic shock was diagnosed and an investigation for the cause and treatment were begun. However, on the evening of the same day, the patient developed swelling, a flare, and a feeling of heat in the left thigh. Computed tomography showed diffuse thickening and elevation of computed tomography values in the left thigh and the deep part of the fascia. Necrotizing fasciitis was diagnosed, and debridement and irrigation were urgently performed. Muscle and fascial color were poor, and the circumference had a large quantity of serous fluid. E. coli was detected in blood and muscular tissue cultures. General condition of the patient improved postoperatively. On day 3 after the operation, the patient was moved to the general ward. VAC therapy was started on day 15 after surgery. The femoral region was sutured on the 29th day. The patient left the hospital on the 34th day. We consider that advanced cervical cancer and chemoradiotherapy could be a risk factor of necrotizing fasciitis.

ISP-1-8

The effectiveness of radiotherapy on neurogenic symptoms in uterine cervical cancer patients with brain or skeletal metastasis Kyoko Okita, Tomoko Shima, Mihoko Kawaguchi, Tomoko Tanaka, Kei Tsuda, Azusa Sameshima, Kumiko Inada, Akitoshi Nakashima, Osamu Yoshino, Shigeru Saito *University of Toyama*

Objective The purpose of this study was to evaluate the effect of radiotherapy in cervical cancer patients with brain or skeletal metastasis. **Methods** The medical records of patients with cervical cancer between January 2006 and August 2016 were reviewed retrospectively. **Results** Eighteen patients with brain (N =7) or skeletal metastasis (N=14) from uterine cervical cancer were enrolled. Median patient age at initial diagnosis of metastasis was 53 years old (range 28–82 years). Eleven patients (61%) had squamous cell carcinoma, and 7 (39%) had non- squamous cell carcinoma. Fourteen of the 18 patients had lymph nodes metastasis at the same time. The median survival interval from diagnosis of brain metastasis to death was 27 days (range 19–62 days), and that of skeletal metastasis was 66 days (range 15–325 days). One patient with brain metastasis is alive 289 days after treatment. Five patients with brain metastasis received whole brain radiotherapy, and six patients with skeletal metastasis received radiotherapy. The radiotherapy was effective for reducing neurogenic symptoms such as headache and dizziness on 80% of patients with brain metastasis and 67% of patients with skeletal metastasis. Disease control rate on the locus in the radiation field was 44%. **Conclusion** The prognosis of patients with brain or skeletal metastasis is poor. Early palliative radiotherapy is useful to reduce pain or neurologic symptoms of them.

ISP-1-9

The effectiveness of neoadjuvant chemotherapy with uterine arterial infusion of cisplatin followed by weekly intravenous paclitaxel infusion for the stage IB to IIB cervical cancer
Takashi Suzuki, Hiroshi Adachi, Satoru Nakayama, Hiroharu Kobayashi, Takahiro Ito, Shohei Noguchi, Mieko Hanaoka, Ayumi Yasuda, Takeshi Murakoshi *Seirei Hamamatsu General Hospital*
Objective To elucidate the effectiveness of uterine artery infusion (UAI) of cisplatin followed by weekly intravenous paclitaxel infusion as a NAC (UAI-NAC). **Methods** Patients who diagnosed cervical cancer from April 2011 through August 2016 with informed consent were enrolled. Indications of UAI-NAC in our institution are ; Staging of IB2, IIA2 and IIB and histopathologies are squamous cell carcinoma (SCC) and adenocarcinoma (AD). As for adenosquamous carcinoma (ADS), it depends on the physician's decision. Considering patient's age, medical complications and understanding, radical hysterectomy is appropriate if the tumor size is reduced. In case radical hysterectomy could not be scheduled within 8 weeks, not only IB2, IIA2 and IIB patients but IB1 and IIA1 patients were enrolled. Intraarterial cisplatin ($60mg/m^2$) on day 1 conducted by interventional radiologists and weekly intravenous paclitaxel ($80mg/m^2$) on days 2, 9 and 16 of a 28-day cycle, maximum of 3 courses. The primary endpoint was the response rate (PR+CR). Response was evaluated with RECIST guidelines. **Results** Total of 22 cases were enrolled. Median age was 44.5 years. SCC in 16 patients, AD in 4, ADS in 2. FIGO staging (2008) : IB2 in 8 patients, IIA1 in 1, IIA2 in 1, IIB in 12. Administered courses : 1 in 0 patient, 2 in 11, 3 in 11. CR in 5 patients, PR in 16, SD in 1, PD in 0. (PR+CR) was 95.2%. No life-threatening adverse event except one case of severe lumbago was occurred during UAI. **Conclusion** UAI-NAC is safe and hopeful option for stage IB2 to IIB cervical cancer patients.

ISP-2-1

Key role of Notch-ASCL1 pathway for trans-differentiation in a mixed small cell carcinoma/adenocarcinoma of uterine cervix
Satoshi Kubota[1], Yumiko Kiyohara[1], Akiko Okazawa[2], Shinya Matsuzaki[2], Eiji Kobayashi[2], Yutaka Ueda[2], Kiyoshi Yoshino[2], Tadashi Kimura[2], Masahiro Inoue[1] *Osaka Medical Center for Cancer and Cardiovascular Diseases[1], Osaka University[2]*
Objective Approximately 30% of small cell carcinoma (SMC) of uterine cervix shows mixed histology. We aimed to reveal the clonality of these tumors and the key factor of trans-differentiation. **Methods** The Institutional Ethics Committee approved this research. Using CTOS (cancer tissue-originated spheroid) method, we established 9 primary spheroid cultures of cervical SMC, including 3 mixed SMC and adenocarcinoma (ADC). We analyzed one of the cases in this study. Clonality was determined by gene mutation analysis and single cell cloning. For gene mutation analysis, each component was laser-microdissected, and the DNA was subjected to the hot-spot panel of 50 cancer-associated genes. For single cell cloning, EGFP was transfected into CTOSs. A CTOS containing only single cell expressing EGFP was selected, and the xenograft tumor was generated. The CTOSs were cultured in hypoxia. **Results** An identical K-RAS mutation alone was detected in each component. The single cell-derived EGFP positive cells were distributed in both SMC and ADC in xenograft tumor. Expression level of CD 99, a marker of SMC, was repressed in hypoxia. ASCL1 is known to play a key role in neuronal commitment and be degraded by Notch. Notch was activated and ASCL1 suppressed in hypoxia in the CTOSs. Knock down of HIF1α by shRNA resulted in maintenance of ASCL1 expression in hypoxia, and the hypoxia-induced phenotype change was attenuated. **Conclusion** In mixed SMC/ADC of uterine cervix, both components were monoclonal, and Notch-ASCL1 pathway played a key role in the differentiation. This is the first report of showing mixed SMC/ADC has ability to reversibly change differentiation.

ISP-2-2

Growth inhibitory effect of Src inhibitor Dasatinib in cervical adenocarcinoma cells
Eri Takiguchi, Masato Nishimura, Takako Kawakita, Akiko Abe, Minoru Irahara *Tokushima University*
Objective Cervical adenocarcinoma has poor clinical prognosis compared with squamous cell carcinoma (SCC), so development of different treatment has been required. Src is proto-oncogene and involved in cell proliferation, invasion, and angiogenesis in cell signaling. Src plays an important role in cancer progression. We have reported that Src is overexpressed in 44 percent of cervical adenocarcinoma patients. So this time, we investigated the possibility of treatment of Src inhibitor (Dasatinib) in cervical adenocarcinoma. **Methods** We confirmed the expression of Src in cervical adenocarcinoma cells (HeLa cells, TCO-2 cells) by using Western blot analysis. Next, cells were seeded in 96-well plates (5000 cells/well) for 24 hours and then cultured for 48 hours with the addition of different concentration of anticancer drugs (paclitaxel or oxaliplatin), Viable cell count were measured with MTT assay. The concentration of anticancer agents was fixed from obtained results, and the same experiments were performed in the combination of Dasatinib at various concentration to determine the concentration leaving significant difference in the number of viable cells. Also the presence or absence of apoptosis was investigated by measuring the caspase 3/7 assay. **Results** Src was expressed in any cell lines, and cell proliferation was significantly suppressed in each anticancer drugs using 10μM Dasatinib. Caspase 3/7 activity was also increased in Dasatinib combination. **Conclusion** Src may become the target of a new treatment of cervical adenocarcinoma. Src inhibitor Dasatinib was considered to be causing apoptosis.

ISP-2-3

STAT1 (Signal Transducers and Activator of Transcription 1) is activated in sphere-forming cells from SiHa and decreases the sensitivity to anti-cancer drug.
Akira Kawata[1], Katsuyuki Adachi[1], Ayumi Taguchi[1], Juri Ogishima[1], Masakazu Sato[1], Mitsuyo Yoshida[1], Takeshi Nagamatsu[1], Takahide Arimoto[1], Katsutoshi Oda[1], Kei Kawana[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Nihon University[2]*
Objective STAT1 is known as a transcription factor, and enhances either tumor-progressive or tumor-suppressive effect depending on context. In this study, our objective is to investigate the role of STAT1 in the sphere-forming cells, which possess stem cell-like property. **Methods** SiHa which is established from cervical cancer cell, was cultured in ultra-low attachment plates to form spheroids. Western blot was performed to analyze STAT1 and phosphorylated STAT1 (pSTAT1) expression on day2-SiHa cells both in spheroids culture (3D culture) and standard culture (2D culture). To evaluate drug-resistance, we compared cell numbers with combination of cisplatin and fludarabine phosphate, which is known to inhibit STAT1 activation and without them. **Results** Total-STAT1 expression was almost the same between sphere-forming cells and normal cells. In contrast, pSTAT1 was remarkably increased in sphere-forming cells. In drug-resistance assay, we observed additive effect with fludarabine phosphate. Live cells were decreased by 59% when they were treated with both fludarabine phosphate and cisplatin, compared to when they were treated with cisplatin alone. **Conclusion** We revealed that STAT1 is activated in sphere-

forming cells. STAT1 activation is associated with drug resistance. In other words, STAT1 signaling is important for sphere forming cells to have ability to proliferation. Therefore STAT1 inhibitor can be a good candidate of anti-cancer drug for cisplatin resistant cervical cancer.

ISP-2-4

Blockade of aurora kinase induces addiction to the EGFR pathway and enhances the sensitivity of an EGFR inhibitor in cervical squamous cell carcinoma Kanako Nakamura[1], Masayuki Komatsu[2], Fumiko Chiwaki[2], Yusuke Kobayashi[1], Kouji Banno[1], Moito Iijima[1], Takashi Takeda[1], Eiichiro Tominaga[1], Hiroki Sasaki[2], Mamoru Tanaka[1], Daisuke Aoki[1] *Keio University School of Medicine[1], National Cancer Center Research Institute[2]*

Objective Development of chemotherapy for cancers with few druggable gene alteration is a challenging task. In this study, we examined the synergistic effect of a combination of an aurora kinase A/B inhibitor and an EGFR inhibitor in cervical squamous cell carcinoma (CvSCC). **Methods** Gene expression and clinical outcomes were analyzed using the GEO and TCGA databases. MTT and apoptosis assays in the presence of an aurora kinase A/B inhibitor (PF-03814735) and/or an EGFR inhibitor (erlotinib) were performed in 5 CvSCC cell lines (SKG-I, SKG-IIIa, BOKU, HCS-2, and CaSki) and tumor progression was evaluated in a mouse model. EGFR expression were investigated by flow cytometry after knockdown of *AURKA/B* and *Rab11* which is required for recycling endocytosis. **Results** In the database analysis, expression levels of *AURKA/B* were significantly higher in CvSCC than in normal tissue ($p<0.0001$), while patients with high *EGFR* expression had significantly reduced survival compared to those with low *EGFR* expression ($p=0.0006$). A combination of PF-03814735 and erlotinib synergistically suppressed cell growth and induced apoptosis in vitro, and tumor growth was also suppressed in the mouse model ($p=0.03$). Expression of EGFR on the cell surface was increased after knockdown of *AURKA/B*, and was decreased by knockdown of *Rab11*. **Conclusion** These results indicate that aurora kinase inhibition induces addiction to the EGFR signaling pathway via acceleration of recycling endocytosis of EGFR in CvSCC. This intentional induction to other pathway is a new concept of dual pathway inhibition and can be adapted to other cancers that are difficult to treat with single-agent targeted therapy.

ISP-2-5

Analysis of human papillomavirus oncogene E6/E7 spliced transcripts in Liquid-Based Cytology samples from patients with cervical neoplastic diseases Shuling Liu[1], Takeo Minaguchi[1], Bouchra Lachkar[1], Yuri Tenjimbayashi[1], Ayumi Shikama[1], Nobutaka Tasaka[1], Azusa Akiyama[1], Manabu Sakurai[1], Sari Nakao[1], Hiroyuki Ochi[1], Toyomi Satoh[1], Hiroyuki Yoshikawa[2] *Tsukuba University[1], Ibaraki Prefectural Central Hospital[2]*

Objective A few studies previously implicated that human papillomavirus (HPV) E6 transcript exists uniformly in all grades of cervical intraepithelial neoplasia (CIN), whereas the detection rate of E7 transcripts (E6 spliced variants) may increase with disease progression from low-grade CIN to invasive carcinoma. The aim of this study was to investigate the different significances of E6 and E7 transcripts in the pathogenesis of cervical cancer. **Methods** The presence of E6 and E7 transcripts was analyzed in Liquid-Based Cytology samples from 83 patients with CIN or cervical carcinoma. We utilized the RT-PCR assay which could detect E6 and E7 transcripts separately for HPV types 16, 18, 31, 33, 35, 51, 52, 56, 58 and 59. Study protocol was approved by the ethical committe of our institution. All patients provided written informed consent. **Results** E7 transcript was detected in 7% of CIN1-2, 30% of CIN3, and 61% of cervical carcinoma. Positive E7 transcripts were significantly associated with progression from low-grade CIN to invasive carcinoma in contrast with positive E6 transcript or high-risk HPV DNA showing no such trends ($p=0.0002$, 0.92 and 0.77, respectively). E7 transcripts showed higher specificity and lower sensitivity for detecting CIN2+ as compared with high-risk HPV DNA (100% and 35% vs. 38% and 91%). **Conclusion** Our findings suggest the distinct functions of E6 and E7 transcripts in cervical carcinogenesis. Furthermore, it may be useful to combine E7 transcripts analysis following high-risk HPV testing for detecting CIN2+ more precisely and predicting progression from CIN to invasive cancer.

ISP-2-6

HPV E6 siRNA restores adenovirus-mediated transfer of p53 gene linked with estrogen response element into HPV 16 gene integrated immortalized cervical cells NCE16 and cervical cancer derived cells CaSki Kenichi Honda[1], Koji Kajitani[3], Hiroyuki Terada[1], Aki Takase[2], Tomoyo Yasui[2], Toshiyuki Sumi[2], Masayasu Koyama[2], Osamu Ishiko[2], Tomoko Nakagawa[1], Yasushi Kurihara[1], Tetsuji Ando[1] *Kashiwara Municipal Hospital[1], Osaka City University[2], Osaka City General Hospital[3]*

Objective To study the effects of HPV E6 siRNA and estrogen response element linked to p53 gene on adenovirus-mediated transfer into HPV16 gene integrated immortalized cervical cells NCE16 and cervical cancer derived cells CaSki. **Methods** After treatment with HPV E6 siRNA, p53 gene, linked to estrogen response element or not, and with the codon 72 of proline or arginine, were transferred into cells, cultured for 80 h and the cells were harvested. p53 gene transduction and p53 gene mRNA expression were measured with real time PCR, and annexin V binding rates of the cells were measured as a marker of apoptosis induction by flow cytometry. **Results** p53 gene transduction, p53 mRNA expression and annexin V binding rates of NCE 16 cells were higher after HPV E6 siRNA treatments, especially when the p53 gene with the codon 72 of proline is linked with estrogen response element. p53 gene transduction and p53 mRNA expression in CaSki cells were also restored after HPV E 6 siRNA treatments, and annexin V binding rates of CaSki cells were higher when the p53 gene with the codon 72 of proline is linked with estrogen response element. **Conclusion** In the cells integrated with HPV16 gene, knockdown of HPV E6 gene with siRNA restores p53 gene transduction and p53 mRNA expression. Furthermore, transduction of p53 gene with the codon 72 of proline is promoted by estrogen response element linked to the p53 gene.

ISP-2-7

HPV11 (low-risk) E6 directs p53 degradation in confluent keratinocytes and acts to sustain episomal copy number Isao Murakami, Masaru Nakamura, Tohru Morisada, Takashi Iwata, Kyoko Tanaka, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective Low and high-risk HPVs are thought to have different life cycle requirements and protein functions. To understand how low and high-risk HPVs persist and cause epithelial disease, we have used an isogenic keratinocyte cell line to establish whether these viruses have common and different requirements for genome maintenance and amplification in basal epithelial cells, and during differentiation. **Methods** Normal immortal keratinocytes (NIKS) transfected wild-type HPV11/16 genomes were cultured pre or post-confluence. Genome copy number, viral gene expression and protein function were subse-

quently analyzed using qPCR, immune staining (K10/MCM/p53) or Western blotting. **Results** HPV16 genomes were stably maintained during cell division, with genome copy number and the rate of cell division rising dramatically post-confluence. By contrast, HPV11 genome did not affect cell proliferation. Moreover, although HPV11 genomes were stably maintained pre-confluence, HPV11 genomes declined post-confluence. The deficiency in HPV11 genome maintenance post-confluence was rescued by exogenous expression of either low or high-risk E6 proteins, or by siRNA-mediated p53 loss. Surprisingly, not only high-risk but also low-risk HPV could mediate the efficient proteosomal degradation of p53 post-confluence by immune staining and Western blotting. **Conclusion** Our results suggest that the different abilities of low and high-risk HPVs to be maintained on tissue culture models arises post-confluence. Our current work suggests that both low and high-risk E6 proteins can mediate the proteosomal degradation of p53. Moreover, E6 and the decrease of p53 levels are required for both low and high-risk HPVs replication upon differentiation.

ISP-2-8

CDX2 expression in cervical cancer Suguru Nosaka, Iemasa Koh, Hiroshi Miyoshi, Yoshiki Kudo *Hiroshima University*

Objective The transcription factor caudal type homeobox 2 (CDX2) influences the degree of differentiation, malignancy, drug resistance, and cancer progression in the colon and stomach. Overexpression in the gastric mucosa induces gastric intestinal metaplasia, and long-term intestinal metaplasia induces intestinal-type gastric adenocarcinoma. We previously reported that in ovarian mucinous adenocarcinoma, CDX2 expression is observed and CDX2 transcriptionally regulates multidrug resistance 1 (MDR1) expression, leading to drug resistance. In cervical adenocarcinoma, detection at the stage of precancerous lesions is difficult, and invasion or metastasis is frequently detected even at the early stage. Generally, 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. Therefore, in this study, we examined CDX2 expression in uterine cervix. **Methods** We applied immunohistochemistry staining to clinical specimens in cervical cancer and non-cancer tissues, and examined the correlation between histopathological subtype and the degree of CDX2 expression. **Results** CDX2 expression was observed in eight of the 10 cases of adenocarcinoma in situ (AIS). All cases were positive in intestinal-type AIS. In invasive carcinoma cases, expression of CDX2 was observed in two of the four cases of intestinal-type mucinous adenocarcinoma. CDX2 expression was not observed in normal tissue and glandular dysplasia. **Conclusion** CDX2 expression was observed in AIS and intestinal-type mucinous adenocarcinoma. Our data suggested that CDX2 expression might influence cancer progression in intestinal-type mucinous cervical adenocarcinoma.

ISP-2-9

Expression of XPA predicts the efficacy of neoadjuvant chemotherapy for locally advanced uterine cervical cancer Takuma Wada, Takeshi Fukuda, Masaru Kawanishi, Reiko Tasaka, Kenji Imai, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

Objective We examined the correlation between XPA (xeroderma pigmentosum complementation group-A) expression and the efficacy of Neoadjuvant chemotherapy (NAC) for locally advanced uterine cervical cancer. **Methods** We reviewed 56 cases of locally advanced uterine cervical cancer stage IIIA-IIIB from 1995 to 2010. Cases were divided into two groups : one group in which NAC was effective, surgery was possible and radiotherapy was performed (group A ; n=31), and another group in which NAC was ineffective and radiation therapy was performed (group B ; n=25). XPA expression was examined immunohistochemically in paraffin-embedded sections using the avidin-biotin peroxidase complex method. This study was approved by the institutuional review board in our facility. **Results** The expression of XPA was significantly higher in the group B than in the group A (p=0.001). The overall survival of group A was significantly longer than of group B ($P<0.01$). Cases were divided into two groups : one group in which XPA expression was low level (weighted score$\leq$3, n=17), and another group in which XPA expression was high level (weighted score$\geq$4, n=39). Low XPA 2 expression group might be responsive to NAC than high expression group (p=0.001). **Conclusion** It is suggested that the expression of XPA may predict the efficacy of NAC as a treatment for locally advanced uterine cervical cancer.

ISP-2-10

17β-estradiol promotes cervical cancer progression by stimulating the production of myeloid derived suppressor cells Katsumi Kozasa, Seiji Mabuchi, Naoko Komura, Eriko Yokoi, Hiromasa Kuroda, Yasuto Kinose, Yuri Matsumoto, Michiko Kodama, Kae Hashimoto, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective We previously reported that cervical cancer (CC) patients displaying tumor related leukocytosis (TRL) had poor prognosis and that myeloid derived suppressor cells (MDSC) were involved in the mechanismL. As younger age is known to be associated with poorer prognosis in CC, and TRL is more frequently observed in younger CC patients, we speculated estrogen (E2) might play roles in the induction of TRL and MDSC. **Methods** 1. Ovariectomized BALB/c nude mice were subcutaneously inoculated with HeLa cells (known estrogen-receptor negative CC), treated with E2, and their tumor growth were examined. 2. Ovariectomized ICR mice were treated with or without E2, and the number of MDSC in bone marrow and peripheral blood was examined by flow cytometry. 3. MDSC were incubated with or without E2. Then, pro-angiogenic activity of E2 was examined by RT-qPCR and tube-formation assay. 4. Ovariectomized BALB/c nude mice were subcutaneously inoculated with HeLa cells and were treated with or without E2. Then, the number of tumor-infiltrating MDSC and micro-vessel density (MVD) in tumor were examined. 5. Finally, we examined the effects of MDSC-inhibition on the effects of E2 in mice. **Results** 1. E2 promoted tumor growth in mice. 2. Treatment mice with E2 increased the number of MDSC in mice. 3. E2 increased the production of pro-angogenic factor by MDSC in vitro. 4. E2 promoted the production of MDSC, increased the number of tumor-infiltrating MDSC, stimulate tumor-angiogenesis in mice. 5. MDSC-inhibition cancelled the pro-angiogenic and tumorigenic activity of E2 in mice. **Conclusion** E2 promote CC progression by stimulating MDSC-mediated tumor-angiogenesis.

ISP-2-11

The study of HPVE6, E7 protain and HPV E6/E7mRNA expression in cervical erosion between Han and Uyghur Mayinuer Niyazi, Gulan Tuohetimulati *The People's Hospital of Xinjiang Uighur Autonomous Region, China*

Objective To evaluate HPVsixteen DNA Esix Eseven and HPV Esix/Eseven mRNA in cervical erosion. To explore the distinct causes of cervical erosion between Han and Uyghur. **Methods** The data gathered at our hospital during tow years , the type and infection of cervical erosion was determined by HC -two, HPV - DNA. Patients were severed into cervicitis, CIN -one , CINtwo -three and cervical carcinoma groups. Immunocyto-

chemical and IHCA were applied to inspect cervical exfoliated cells and tissues towards two hundred specimens with positive HPV, **Results** The proteins of HPV sixteen Esix and Eseven in cervical tissues raised with the growth of ervical lesions , which indicated statistical significance (P<zero point zero five), the levels of HPV Esix/Eseven mRNA in cervical tissues upgraded with the severity of cervical lesions , which has statistical significance (P<zero point zero five). HPV Esix/Eseven mRNA was associated with the expression results of Eseven and Esix, which could be implied that the discrepancy had showed statistical significance. About the distinct grades no difference between HPV Esix/Eseven mRNA. the inspection of HPV sixteen Esix/Eseven mRNA had a diagnostic value upon high-grade cervical lesions, PPV equaled to senenty two% while NPV equaled to eighty one%, the AP was senenty six %. There is no statistical significance on the load of HPV E7DNA between Han and Uyghur. **Conclusion** The HPV sixteenEsix/Eseven mRNA expected to be an important marker for predicting the severity of cervical lesions in Uygur. Key Words, HPV, HPV Esix/Eseven mRNA, Esix/Eseven.

ISP-2-12

Dynamin 2 inhibitors as novel therapeutic agents in cervical cancer cells Hyeyeon Yi, Ji Hye Kim, Kyung-A Son, E Sun Paik, Ju Young Park, Chel Hun Choi, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Aim This study was performed to investigate the possibility of dynamin 2 as a potential treatment target in cervical cancer cells using various dynamin 2 inhibitors. **Materials and methods** Tissue microarray for the expression of dynamin 2 was performed in 208 early cervical cancer patients and analyzed the association between expression of dynamin 2 and primary tumor characteristics such as tumor size and depth of invasion. Then we performed in vitro using dynamin 2 inhibitors including MiTMAB, OcTMAB, Dynasore, and DD-6 on HeLa cells with proliferation, apoptosis, and migration assay. **Results** When we compare the expression level of Dynamin 2 based on the pathological findings, tumor size more than 2 cm and tumor invasion more than half of the entire cervix were associated with higher proportion of any dynamin 2 expression compared with no expression (+1, +2, and +3 vs. 0, P=0.013, P=0.045). All of dynamin 2 inhibitors including MiTMAB, OcTMAB, Dynasore, and DD-6 significantly decreased proliferation and increased apoptotic activity in HeLa cells. And also these all inhibitors significantly decreased MMP-9 expression compared with control in HeLa cells. In migration assay, dynasore and DD-6 decreased migration in in HeLa cells coated by laminin 1. However, DD-6 most strongly decreased migration performance in fibronectin-coated wells. **Conclusion** Targeting dynamin 2 with various specific inhibitors may be a promising new approach for the treatment of cervical cancer in the future.

ISP-3-1

Clinicopathological significance of claudin-6 expression in uterine endometrial cancer Manabu Kojima, Shu Soeda, Shinji Nomura, Hideki Chiba, Takafumi Watanabe, Toshifumi Takahashi, Hideki Mizunuma, Keiya Fujimori *Fukushima Medical University*

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** All experiments were approved by the Ethical Committee of our university. The Cldn6 expression was evaluated by immunohistochemistry in paraffin-embedded cancer tissues resected from 141 UEC cases, which are proved outcomes, and semi-quantitatively scored Cldn6 expression by the immunoreactive scoring method (score 0, 1+, 2+, 3+) with slight modification. We next determined whether Cldn6 expression score was correlated with 5-year overall survival (OS), disease free survival (DFS), and clinicopathological factors. **Results** Of 141 UEC cases, 105, 14, 12, 10 cases exhibited Cldn6 score 0, 1+, 2+, 3+, respectively. 5-year OS and DFS 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 ; DFS, 30.0% vs 87.0%, P<0.001). The frequencies of clinical stage III/IV, non-endometrioid adenocarcinoma, histological grade 3, LVSI, lymphnode metastasis, distant metastasis, peritoneal dissemination were significantly higher in Cldn6 score 3+ group than those in score 0/1+/2+ groups. **Conclusion** In UEC, high Cldn6 expression is a very poor prognostic factor.

ISP-3-2

Identification of biomarkers to diagnose lymphatic metastasis based on gene expression patterns in the primary lesion in endometrial carcinoma Emiko Yoshida, Yasuhisa Terao, Yosuke Ito, Kazunari Fujino, Takafumi Ujihira, Tsuyoshi Oota, Atsuo Itakura, Satoru Takeda *Juntendo University*

Objective Lymphadenectomy in endometrial carcinoma should be performed based on individualized considerations of the risk of lymphatic metastasis. Here, we attempted to identify biomarkers to diagnose lymphatic metastasis based on gene expression patterns in the primary lesion in patients with endometrial carcinoma. **Methods** We collected endometrial carcinoma tissue from 115 patients between April 2009 and August 2015. Genome-wide gene expression was analyzed using cap analysis gene expression (CAGE) in 10 lymphatic metastasis-negative (LN-) and five lymphatic metastasis-positive (LN+) cases with G1 endometrial carcinomas with invasion less than or equal to 1/2 myometrial depth. Candidate genes used to distinguish between LN-/LN+ were identified and verified by quantitative real-time reverse transcription polymerase chain reaction. We investigated the candidate gene expression patterns in metastatic lymph nodes. **Results** Semaphorin 3D (SEMA3D) and a TACC2 isoform with a novel transcription start site (novel TACC2) were identified as biomarkers with the highest diagnostic accuracy. SEMA3D was highly expressed in the LN- group (p<0.001), while novel TACC2 was highly expressed in the LN+ group (p<0.05). Combined analysis of the expression of these two genes had higher accuracy than analysis of any one gene alone, with area under the curve (AUC) values of 0.929. The two gene expression patterns were uncorrelated between primary lesion and metastatic lymph nodes. **Conclusion** SEMA3D and a novel TACC2 were identified as biomarkers to evaluate lymphatic metastasis in endometrial carcinoma. These findings pave the way for pre-operative lymphatic metastasis diagnoses and the realization of individualized surgical methods.

ISP-3-3

Anti-tumor effect of inhibition of DNA damage response pathway in endometrial cancer cells Makoto Takeuchi, Michihiro Tanikawa, Katsutoshi Oda, Osamu Hiraike, Yoshiko Kawata, Shinya Oki, Chinami Makii, Kenbun Sone, Kazunori Nagasaka, Takahide Arimoto, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Advanced and recurrent endometrial cancer is poor

prognostic disease due to limited therapeutic choice and treatment resistance. In various malignancies, activated DNA damage response (DDR) pathways are one of major causes of chemo- and radio-resistance, and supposed to be the promising molecular target. ATM-Chk2 and ATR-Chk1 are two major DDR pathways with mutual crosstalk. To explore the efficacy of molecular therapy of DDR for endometrial cancer, we evaluated the anti-tumor effects of inhibitors for ATM-Chk2 and ATR-Chk1 pathway. **Methods** Endometrial cancer cells were treated with canonical genotoxic agents, doxorubicin (DXR), cisplatin, and irradiation (RT), with or without inhibitors for DDR pathway (ATM inhibitor ; KU55933, ATR inhibitor ; VE822, Chk1 inhibitor ; AZD7762). Combination effects of these inhibitors were also analyzed. Anti-tumor effects were evaluated by colony formation and MTT assay. Synergistic effects were evaluated by combination index. The effects for DDR pathways were analyzed by immunofluorescence of DDR proteins. **Results** DXR, cisplatin and RT exposure activated two major DDR pathways, ATM-Chk2 and ATR-Chk1. The inhibitors suppressed this activation and enhanced the cytotoxicity of these agents for endometrial cancer cells. Combination treatment of ATR inhibitor and Chk1 inhibitor induced severe DNA damage, and showed synergistic (combination index=0.28) and significant cytotoxicity for endometrial cancer cells. **Conclusion** Our results showed the efficacy of inhibitors for DDR pathway in endometrial cancer cells. Molecular therapy of DDR will offer promising therapeutic options for endometrial cancer.

ISP-3-4

PD-0332991, the cyclin-dependent kinase 4/6 inhibitor palbociclib, in endometrial cancer Tomohito Tanaka, Yoshito Terai, Syun Sasaki, Akihiko Touji, Keisuke Ashihara, Satoe Fujiwara, Yoshimichi Tanaka, Satoshi Tsunetoh, Hiroshi Sasaki, Masahide Ohmichi *Osaka Medical College*

Objective PD-0332991, the selective cyclin-dependent kinase 4/6 inhibitor palbociclib, causes cell cycle arrest by inhibiting phosphorylation of retinoblastoma protein (Rb). The aim of this study was to evaluate the therapeutic potential of PD-0332991 in endometrial cancer. **Methods** After the Institutional Review Board approval, an immunohistochemical analysis was performed in 337 endometrial cancer specimens. In vitro, four human endometrial cancer cell lines, ECC, HEC1A, HEC108 and TEN, were treated with PD-0332991 to determine the IC50. Western blotting and flow cytometry analyses were used to evaluate the function. In vivo, therapeutic efficacy was evaluated in subcutaneous endometrial cancer model mice. **Results** Immunohistochemical analyses revealed that the positive rate of Rb, phospho-Rb, p16 and cyclin D1 were 67.7%, 32.6%, 84.0% and 52.5%, respectively. There was no significant relationship between the expression levels of Rb and the tumor grade. Two of the 4 cell lines expressed Rb and phospho-Rb. Phosphorylation of Rb was suppressed by the treatment of PD-0332991 in a time- and concentration-dependent manner. These cell lines were sensitive for PD-0332991 according to a proliferation assay with an IC50 of 0.65 μM (HEC1A) and 0.58 μM (HEC108), respectively. Both cell lines had G0/G1 cell cycle arrest after treatment with PD-0332991 according to flow cytometry. In vivo, PD-0332991 had antitumoral efficacy with decline the activity of Ki67 and phosphorylation of Rb. **Conclusion** PD-0332991 had a therapeutic potential in endometrial cancer cell lines expressing Rb. An immunohistochemical analysis revealed that approximately 70% patients with endometrial cancer might have therapeutic indications for PD-0332991, however, the tumor grade had no impact on the indication for treatment.

ISP-3-5

The 17β-hydroxysteroid dehydrogenase type 2 expression induced by the androgen signal in endometrial cancer Chiaki Hashimoto[1], Keita Tsuji[2], Sota Tanaka[3], Bin Li[1], Hitoshi Niikura[1], Kiyoshi Ito[4], Nobuo Yaegashi[1] *Tohoku University Hospital[1], Japanese Red Cross Ishinomaki Hospital[2], Kesen-numa City Hospital[3], International Research Institute of Disaster Science (IRIDeS), Tohoku University[4]*

Objective Endometrial cancer, one of the most common female pelvic cancer, has been considered an androgen-related tumor. Several studies demonstrated the anti-cell proliferative effect of androgen on endometrial cancer cells. However, the mechanisms of anti-cancer effect of androgen are still largely unclear. 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2), which catalyzes the conversions of E2 to E1, is known to be up-regulated by androgen treatment in breast cancer cells. Therefore, in this study, we focused on the role of androgen on estrogen dependence of endometrial cancer. **Methods** In nineteen endometrioid endometrial adenocarcinoma (EEA) tissues, we measured intratumoral DHT concentration by liquid chromatography/electrospray tandem mass spectrometry. We examined the correlation between intratumoral DHT concentration and 17β-HSD2 immunohistochemical status. We further examined the correlations between 17β-HSD2 immunoreactivity and clinicopathological parameters in 53 EEA tissues. **Results** Dihydrotestosterone (DHT) could induce 17β-HSD2 mRNA and protein in endometrial cancer HEC-1B cells. DHT could also inhibit cell proliferation of HEC-1B induced by estradiol treatment. The 17β-HSD2 status was inversely associated with the histological grade, clinical stage, and cell proliferation marker, Ki-67 and positively correlated with the progesterone receptor expression. 17β-HSD2 status tended to be positively associated with androgen receptor status. In 53 EEA cases, 17β-HSD2-positive group tended to have better prognosis than those negative group with respect to progression-free survival and endometrial cancer-specific survival. **Conclusion** These findings suggest that androgen suppresses the estrogen dependence of endometrial cancer through the induction of 17β-HSD2.

ISP-3-6

Angiogenesis factors in Patients with endometrial malignancies Mayu Yunokawa *Department of Breast and Medical Oncology, National Cancer Center Hospital*

Objective Endometrial malignancy is the most common in gynecologic malignancy and increasing year by year in developed country. Proliferation of endometrial epithelial and stromal cells was correlated with angiogenesis factors and angiogenesis was important factor to growth and metastasis of endometrial malignancies. **Methods** The Bio-Plex Pro™ Human Cancer Biomarker Panel 1 includes 16 magnetic bead-based assays were performed using plasma with patients with endometrial malignancies. We compared the clinical features and pathologic characteristics with plasma levels of relevant angiogenic factors, such as angiopoietin-2, VEGFR-1 and VEGFR-2. **Results** The median age of the patients was 55 years (range, 40-73). Histological diagnosis was atypical hyperplasia complex in 1, endometrial adenocarcinoma in 11, serous adenocarcinoma in 3 and carcinosarcoma in 3 patients. The clinical stage was 0 in 1 patient, I in 11, II in 2, III in 3 and IV in 1. There were relationship between stage and plasma leptin level, myometrial invasion and plasma angiopoetin 2 and G-CSF levels and lypmph-vascular invasion and plasma angiopoetin 2 level. Plasma HER2 level was significantly higher in patients with grade 3 endmetrial cancer, serous carcinoma and carcinosarcoma. **Conclusion** These results suggests that anti angiopoietin 2 therapy will be target therapy for uterine malignancies. Further investigation will be needed.

ISP-3-7

Reactivation of epigenetically silenced miR-124 reverses the epithelial-to-mesenchymal transition and inhibits invasion in endometrial cancer cells via the direct repression of IQGAP1 expression Kei Ihira[1], Peixin Dong[2], Yosuke Konno[1], Tatsuya Kato[1], Noriko Kobayashi[1], Mahito Takeda[1], Hidemichi Watari[1], Masataka Kudo[1], Noriaki Sakuragi[1] *Hokkaido University[1], Hokkaido University Womens Health Educational System[2]*

Objective Overexpression of IQGAP1 and microRNA (miRNA) dysregulation are frequent in human tumors, but little is known about the role of IQGAP1 and its relationship to miRNA in endometrial carcinogenesis. **Methods** By using microarray analysis, we identified 29 miRNAs that are significantly down-regulated in invasive HEC-50-HI (HI) cells compared to HEC-50 cells. Of these miRNAs, we chose to focus on miR-124. We further investigated the functional roles of miR-124 and the interaction between miR-124 and *IQGAP1* mRNA in EC cells. **Results** We demonstrate that IQGAP1 activates the epithelial to mesenchymal transition (EMT) program and that miR-124 directly represses IQGAP1 expression in EC cells. The overexpression of IQGAP1 stimulates EMT features and enhances migration, invasion and proliferation of EC cells, whereas knocking down IQGAP1 expression reverses EMT and inhibits these malignant properties. **Conclusion** Our data suggest that IQGAP1 promotes EMT, migration and invasion of EC cells. MiR-124, a novel tumor suppressor miRNA that is epigenetically silenced in EC, can reverse EMT and the invasive properties, by attenuating the expression of the *IQGAP1* oncogene.

ISP-3-8

Investigation of the antineoplastic effect of lovastatin on endometrial cancer Yusuke Kobayashi, Kouji Banno, Haruko Kunitomi, Moito Iijima, Takashi Takeda, Masataka Adachi, Miho Iida, Kanako Nakamura, Kiyoko Umene, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective Drug repositioning is an emerging strategy for finding new therapeutic indications for existing drugs. This approach has recently focused on certain cancers for which conventional drug development is limited. We have previously shown an antitumor effect of statins, which are antidyslipidemic drugs, on ovarian cancer in vitro and in vivo. In this study, we investigated the antineoplastic effect of lovastatin on endometrial cancer to examine whether drug repositioning of statins can be applied to another gynecologic cancer. **Methods** Ishikawa, HEC-IB and HEC-50B cells were used as endometrial cancer cell lines. Cell counts after lovastatin administration were performed to examine inhibitory ability. Apoptosis, autophagy and cell cycle status were evaluated by qRT-PCR, western blot and flow cytometry, respectively. **Results** Growth of all the endometrial cancer cell lines was significantly reduced by lovastatin, with IC50 values of 0.73 to 1.28 μM. Lovastatin-treated cells had characteristic morphological features suggestive of apoptosis and autophagy. Lovastatin treatment significantly increased expression of autophagy marker LC3A/B and apoptosis markers cleaved caspase-3 and PARP. Lovastatin also increased expression of p16, p21 and p27, and decreased expression of CDK2, cyclin D1 and cyclin E1. Flow cytometry showed that lovastatin increased the fraction of cells in G0/G1 phase and decreased the fraction in G2/M phase. **Conclusion** Lovastatin has an inhibitory effect on endometrial cancer cell growth, similar to that for ovarian cancer. This effect is probably due to apoptosis, autophagy and cell cycle dysregulation.

ISP-3-9

Development of a novel biomarker for neoplasms through analysis of copy number variations in cell-free DNA of the blood of patients Makoto Nakabayashi, Akihiro Kawashima, Akihiko Sekizawa *Showa University*

Objective Patients with some malignant tumors reportedly have the abnormal copy number variations (CNV) in their cell-free DNA. Reports about the CNV in the cell-free DNA of the patients with gynecological malignancies is limited. We analyzed the CNV of the cell-free DNA of the patients with gynecological malignancies in order to clear the correlations between the CNV of cell-free DNA and gynecological tumors. **Methods** Cell-free DNA was extracted from the plasma of patients with gynecological malignancies after informed consent. CNV were analyzed by Maternity21 PLUS consisting of whole genome massively parallel sequence and bioinformatic analysis used for prenatal genetic testing. **Results** The samples were obtained from 64 patients with a gynecological tumors (4 cervical cancer cases, 23 endometrial cancer cases and 37 ovarian cancer cases). CNV in all chromosomes were detected in 4 cases ; 2 patients were ovarian cancer in stage III, a patient was endometrial cancer in stage III, and a patient was endometrial cancer in stage IV. In 19 patients, CNV were detected in some parts of chromosomes (9 patients were endometrial cancer and 10 patients were ovarian cancer). **Conclusion** It is revealed CNV can be detected in cell-free DNA of patients with gynecological neoplasms. Although the sensitivity was not high enough to detect the alteration of CNV, we think that analysis of cell-free DNA in the patients with tumors might lead to the detection of the malignancy.

ISP-3-10

Differential gene expression profile of lymphovascular space invasion in endometrial cancer Takafumi Watanabe, Shinji Nomura, Manabu Kojima, Shu Soeda, Keiya Fujimori *Fukushima Medical University*

Objectives Lymphovascular space invasion (LVSI) is a poor prognostic factor in endometrial cancer (EC) patients. Recently, LVSI has been described as an independent risk factor for lymph node metastasis in EC. We examined the characteristic of the gene expression profiles for EC associated with LVSI. **Material and Methods** Total RNA was extracted from a total of 91 primary EC samples and analyzed by cDNA microarray. Data analysis was done using the Student's t-test, hierarchical clustering and gene ontology. **Result** When differences of gene expression level between LVSI-positive (28) and LVSI-negative (63) samples, the genes were detected by the calculation of the Student's t-test ($p < 5 \times 10^{-3}$). The EC samples were segregated to each LVSI-positive cluster (EC positive sample rate : 25/49, 51%) and negative cluster (EC positive sample rate : 3/42, 7%) using the set of genes. The majority of EC samples of lymph node positive and poor prognosis were included in the LVSI-positive cluster. These genes were classified into oncogene, apoptosis, cell cycle, drug metabolism, and so on. **Conclusion** Gene expression profiling of the primary tumors in patients with EC seems promising for identifying genes associated with LVSI. Our findings suggest that gene expression profiling can potentially contribute to clinical classification and management of recurrence of EC. In the future, molecular mechanisms between LVSI and lymph node metastasis may be elucidated.

ISP-3-11

Dysadherin might be an independent prognostic factor for in uterine endometrial cancer Kyoko Akashi, Taisuke Mori, Shiori Umemura, Kaori Sasamoto, Tetsuya Kokabu, Hiroshi Matsushima, Hiroshi Tatsumi, Haruo Kuroboshi, Jo Kitawaki

Kyoto Prefectural University of Medicine
Objective Dysadherin is a membrane glycoprotein, which is negatively correlated with the expression of E-cadherin, however, the significance of dysadherin in uterine endometrial cancer still remains unexamined. The aim of this study is to examine the association of expression of dysadherin with clinico-pathological factors and prognosis in patients with uterine endometrial cancer and the role of dysadherin in vitro using endometrial cancer cell lines. **Methods** Specimens from patients with endometrial cancer were immunochemically stained and evaluated according to the H-score. The association of dysadherin and E-cadherin expression with clinic-pathological factors and prognosis was statistically examined. The role of dysadherin in endometrial cancer in vito, realtime PCR, invasion/migration assay, scratch assay with gain or loss of function of dysadherin were performed. **Results** 85 specimens were examined. Dysadherin was highly expressed in 22.3% (19/85), while E-cadhrein was in 97.8%. The inverse association of the expression between dysadherin and E-cadherin was not seen. Dysadherin expression was clinically related to lymphatic metastasis and lymphatic vascular invasion. Kaplan-Meier analysis revealed dysadherin was significantly associated with poor prognostic-free. In vitro experiment, dysadherin stimulated cell motility and invasive reaction in Ishikawa and KLE cell lines. **Conclusion** Dysadherin might be one of prognostic factors to promote invasiveness in uterine endometrial cancer.

ISP-4-1

Clinical implication of cervical cytology in serous carcinoma of the endometrium Satoko Matsuzaki, Kiyoshi Yoshino, Aiko Kakigano, Michiko Kodama, Kae Hashimoto, Eiji Kobayashi, Seiji Mabuchi, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Tadashi Kimura *Osaka University*
Objective Serous carcinoma of uterine corpus (SCU) shows poor prognosis because of it's aggressive behavior. Therefore, early diagnosis and subsequent timely start of therapy is desired. We aimed to evaluate whether cervical cytology helps for the diagnosis of SCU. We also reveal the association between the pathological feature of cervical cytology and the clinical data. **Methods** We retrospectively reviewed the medical records of 32 SCU for patient's background, surgical staging and histological diagnosis. Patients were treated from 2005 to 2013. For control, 98 endometrioid adenocarcinomas (EC) were also analyzed. In addition, we re-evaluated slides to find out features of SCU cells in cervical cytology. **Results** Among all 130 endometrial cancers, the abnormal cervical cytology was significantly more frequently observed in patients over the age of 65. Abnormal cervical cytology was more frequently observed in SCU than in EC (23/28 (82%) and 34/90 (37%), respectively ($p<0.01$)). In addition, the positive cytology of ascites was significantly correlated with the abnormal cervical cytology. For cytological features, larger cell clumps, large naked-like nucleus, eosinophilic cytoplasm and diverse cytological phenotypes indicated SCU histology. **Conclusion** Abnormal cervical cytology may predict SCU histology of endometrial cancer.

ISP-4-2

Laparoscopic Lymph Node Sampling other than Initial Treatment for Endometrial Cancer : A Retrospective Single-institution Study Tsukasa Baba, Akihito Horie, Kaoru Abiko, Ken Yamaguchi, Miyuki Ito, Ryusuke Murakami, Taito Miyamoto, Noriomi Matsumura *Kyoto University*
Objective The aim of this study is to investigate the feasibility and outcomes of laparoscopic node excision of para-aortic lesion with/without pelvic lesion as a complementary staging surgery (Lap-staging) or a secondary debulking surgery (Lap-SDS) which are not operated as an initial treatment for endometrial cancer. **Methods** Between April 2014 and September 2016, 14 patients with gynecologic cancer who underwent Lap-staging or Lap-SDS in our departmen were enrolled and retrospectively reviewed. As short-term surgical outcomes, operating time, blood loss, postoperative date of discharge or adjuvant treatment (PDD/AT), and perioperative adverse events were evaluated. **Results** Lap-staging was performed prior to primary concurrent chemo-radiation therapy for 5 patients who bore advanced cervical or vaginal cancers without any FDG-uptake in para-aortic lesion on PET-CT imaging, and to complete surgical staging for 4 endometrial or ovarian cancer patients without primarily undergoing para-aortic node dissection. Lap-SDS was performed for 5 patients who had relapse at lymph nodes. Median operation time and PDD/AT were 239.5min and 5.5 days, respectively. There is no case with the amount of blood loss more than 100g or to be converted in the laparotomy. The median number of dissected nodes was 25 in the Lap-staging group and 6 in the Lap-SDS group. There are 2 Lap-staging cases who were dead of disease without node recurrence, and transient lymphocele was observed in 2 cases, while there is no case with persistent lymph edema or bowel obstruction. **Conclusion** Lap-staging and Lap-SDS did not compromise the short-term outcome, and might be safe alternatives in the treatment of gynecologic cancer.

ISP-4-3

The significance of sentinel lymph node (SLN) biopsy for performing safely minimal invasive surgery in patients with endometrial cancer Kei Kudo, Tomoyuki Nagai, Hitoshi Niikura, Shoko Sakurada, Yusuke Shibuya, Chiaki Hashimoto, Ai Otsuki, Michiko Kaiho, Masafumi Toyoshima, Hideki Tokunaga, Muneaki Shimada, Nobuo Yaegashi *Tohoku University*
Objective In Stage 1A endometrial cancer patients with endometrioid G1 or G2 histopathological types (low-risk EC), the risk of lymph node metastasis is low. So that, pelvic and/or para-aortic lymphadenectomy may be omitted in some institutions. However, low-risk EC patients could not be always selected precisely. Our purposes were to analyze the discrepancy between pre and post-operative diagnosis in low-risk EC and to evaluate the necessity of SLN biopsy. **Methods** A) The present study A included all women who were diagnosed as pre-operative low-risk EC and underwent hysterectomy (N=140) from 2011 to 2015. We evaluated the diagnostic accuracy about depth of myometrial invasion and histopathological diagnosis. B) The present study B Data included all women who were diagnosed as post-operative low-risk EC and underwent pelvic and para-aortic lymph node dissection (N=138) from 2004 to 2014. We evaluated the rate of lymph node metastasis. **Results** A) The concordance rate of pre and post diagnosis was 111/140 (79.3%). Under-diagnosed patients, EC had progressed more deeply and/or growed more poorly differentiated, were 29/140 (20.7%). B) In post-operative low-risk EC, lymph node metastases were detected in 6/138 (4.3%). Of the 6 patients with lymph node metastases, 3/25 (12.0%) underwent SLN biopsy and 3/113 (2.7%) didn't. **Conclusion** The frequency of under-diagnosis was larger than we had expected. On the other hand, lymph node metastases existed in post-operative low-risk EC. These findings demonstrated that it is dangerous to omit lymph node dissection for pre-operative low-risk EC patients. Furthermore, SLN biopsy might be effective to perform minimal invasive surgery safely and improve the detection rate of micrometastases without under-diagnosis.

ISP-4-4

A retrospective study of the efficiency of adjuvant chemo-

therapy for subdivided endometrial carcinoma with intermediate risk group Naoki Matsuoka, Yasuko Yamamoto, Iemasa Koh, Eiji Hirata, Hiroshi Miyoshi, Yoshiki Kudo *Hiroshima University*

Objective For postoperative therapy of endometrial carcinoma with intermediate risk, we performed a retrospective analysis by comparing intermediate risk cases after subdividing patients into the low-intermediate risk (LIR) group and high-intermediate risk (HIR) group. We used the FIGO 2008 system. **Methods** For postoperative endometrial carcinoma cases in our hospital from January 2004 to September 2013, we subdivided the intermediate risk group into the HIR and LIR groups and retrospectively evaluated the degree of tumor differentiation, venous or lymphatic invasion, the degree of myometrial invasion, and age. **Results** The total number of postoperative cases was 158 ; 17 cases (10.7%) were categorized as having intermediate risk, for which the histological type was endometrioid adenocarcinoma (G1-3). The median follow-up was 89 months (36-129 months). The numbers of cases in the HIR and LIR groups were 6 (3.8%) and 11 (7.0%), respectively. In the HIR group, 4 patients were treated with adjuvant chemotherapy (TC or AP therapy, 2-5 cycles), and 2 patients were not treated. There was only one recurrent case without chemotherapy. In the LIR group, 8 patients were treated with adjuvant chemotherapy (TC therapy, 3 cycles), and 3 patients were not treated. All 11 patients did not show recurrence. **Conclusion** Since the number of cases in this study was small, it was impossible to perform statistical analysis. However, our findings suggested that the efficiency of adjuvant chemotherapy may be increased in the HIR group, but that this therapy may be optional in the LIR group.

ISP-4-5

A study of endometrial serous carcinoma in a super-aging society Shinya Kusumoto, Hisaya Fujiwara, Keisuke Okabe, Maiko Sagawa, Takahiro Nobuzane, Yasuhiro Katsube *Chugoku Rosai Hospital*

Objective In Japan, with the aging, the ratio of endometrial serous carcinoma (ESC) has been increasing to 5% of endometrial cancers. This study was analyzed and evaluated the clinical findings of ESC in a super-aging society. **Methods** A retrospective study was performed to evaluate the age, clinical stage, treatments and prognosis in 15 patients who were diagnosed as ESC in our hospital from 2007 to 2016. **Results** Ratio of ESC was 18.1% (15/83). Median age of the patients was 71 years (range 43-84). Using the surgical staging system, 5 patients were classified as stage1, 2 were stage2, 5 were stage3, 3 were stage4. Surgery was performed in 13 patients, and post-operative chemotherapy was carried out in 11 patients. 2 patients were shifted to palliative care. Median progression-free survival time and overall survival time were 5 months (range 1-72 months) and 16 months (range 3-72 months). Of the 15 patients, 9 were dead of disease, 2 were alive with disease, and 4 had no evidence of disease. Five-year survival rate of ESC (24.7%) by the Kaplan-Meier method was significantly lower than endometrioid adenocarcinoma (96.5%). **Conclusion** There is a possibility that super-aging society is associated with the high frequency of ESC in our hospital. It is suggested that ratio of highly malignant ESC may be increasing more in the future.

ISP-4-6

A case of endometrioid adenocarcinoma arising from adenomyosis Azusa Wada[1], Naho Umezawa[1], Soonna Yun[1], Hiroko Fukuoka[1], Chifumi Ooyagi[1], Hiroaki Tsubouchi[1], Aya Fukuda[1], Eiji Kobayashi[2], Yutaka Ueda[2], Tateki Tsutsui[1] *Japan Community Healthcare Organization Osaka Hospital[1], Osaka University[2]*

Endometrioid cancer in the uterine endometrium is rare, but there are a few reports on endometrioid adenocarcinoma arising from adenomyosis. We report a case of endometrioid adenocarcinoma occurring in the uterine myometrium that was difficult to diagnose. A 64-year-old postmenopausal woman, gravida 0, para 0, was referred to our hospital. The patient had rheumatism for over 40 years. She underwent myomectomy at the age of 36, and had been diagnosed with adenomyosis by magnetic resonance imaging (MRI) at the age of 57. She did not have any symptoms. However, computed tomography revealed many nodules in her lungs when the serum level of sialylated carbohydrate antigen KL-6 increased during methotrexate therapy for rheumatism. Her orthopedist suspected interstitial lung disease, and ordered imaging tests. Positron emission tomography computed tomography showed uptake of 18F-2-fluoro-2-deoxyglucose in the uterine corpus and para-aortic lymph nodes. MRI showed an 8-cm solid mass in the posterior wall of the uterine corpus, which we suspected was a uterine sarcoma. We performed total abdominal hysterectomy and bilateral salpingo-oophorectomy. The surgical specimen revealed solid poorly marginated tumor in the posterior wall of the uterine corpus without evidence of any tumor in the uterine endometrium. Histopathological evaluation revealed endometrioid adenocarcinoma, Grade II. We strongly suspected that this tumor arose from adenomyosis. Paclitaxel and carboplatin are now being administered as postoperative chemotherapy.

ISP-4-7

A case of multi-focal endometrioid adenocarcinoma grade1 that was thought to originate independently of endometrial hyperplasia Yukiyo Shimada, Eisuke Kaneki, Kazuo Asanoma, Keisuke Kodama, Akifumi Yasunaga, Yoshiaki Kawano, Tatsuhiro Ohgami, Yushi Yagi, Kaoru Okugawa, Hideaki Yahata, Kenzo Sonoda, Kiyoko Kato *Kyusyu Medical University*

Endometrial cancer (EMCA) is usually divided into 2 types. Endometrioid adenocarcinoma grade1 and 2 were classified as type1 which is thought to arise from endometrial hyperplasia under hyperestrogenism. We here report a case of multi-focal endometrioid adenocarcinoma grade1 that was thought to originate independently of endometrial hyperplasia. A case was a 34-years-old female, gravida 0. Her body mass index was 18kg/m^2 and her menstrual cycle was regular. She visited a gynecologist because of infertility. The cervical polyp was found and it was resected. The pathological diagnosis was adenocarcinoma, thus she was referred to our hospital for further examination and treatment. We performed cervical conization for the differential diagnosis of cervical cancer or EMCA. The pathological examination revealed invasive endometrioid adenocarcinoma, depth 1 mm and width 1 mm, existed with atypical endometrial glands in endometrial curettage. The immunohistochemistry showed positive estrogen and progesterone receptors and focally positive p16. The pelvic MRI did not detect any lesion in the uterus. We diagnosed her as EMCA with cervical interstitial infiltration that originated from the inferior region of uterine corpus by accumulating all data including hysteroscopy findings in the previous doctor. Her diagnosis was EMCA stage II and we performed semi-radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, para-aortic lymph node dissection, partial omentectomy, and appendectomy. The pathological findings indicated that multi-focal endometrioid adenocarcinoma grade1 originated independently of endometrial hyperplasia. There were no lesions outside the uterus and no findings of polycystic ovary. We will discuss carcinogenic mechanisms of this case with bibliographic consideration.

ISP-5-1

Characteristics of endometrial cancer accompanied with endometriosis Marie Sato[1], Ayumi Taguchi[1], Katsuyuki Adachi[1], Yamato Fukui[1], Akira Kawata[3], Kazunori Nagasaka[1], Takahide Arimoto[1], Kaori Koga[3], Katsutoshi Oda[3], Kei Kawana[2], Yutaka Osuga[3], Tomoyuki Fujii[3] *Faculty of Medicine, The University of Tokyo[1], Nihon University School of Medicine[2], Graduate School of Medicine, The University of Tokyo[3]*

Objective Endometrial cancer (EC) is sometimes accompanied with endometriosis, however, little is known about its relationship. We investigated clinicopathological features of EC with endometriosis. **Methods** Totally, 240 patients with EC between 20 and 60 years old who underwent hysterectomy in our hospital from 2007 to 2015 were retrospectively evaluated under approval of our institutional ethics committee. Forty patients (16.7%) were accompanied with endometriosis at their initial surgery for cancer. Chi-square tests and logistic regression models were conducted in endometriosis-positive and -negative groups, using their clinicopathological features. **Results** Age, body mass index (BMI), histological grade, myometrial invasion, and vascular or lymphatic invasion were not significantly different between endometriosis-positive and -negative groups. Coexistence of ovarian cancer was significantly higher in the endometriosis-positive group (p=0.0037). Five of six (83%) coexistent ovarian cancer were endometrioid, and one of six (16.7%) was clear cell carcinoma. The proportion of EC patients with endometriosis tended to increase over 50 years old (p=0.091). EC patients with endometriosis under 50 years old showed significantly higher ratio of well differentiation (93% vs 72%) and lower ratio of lymphatic invasion (0% vs 22%), compared to those over 50 years old (p=0.04 and p=0.046, respectively). **Conclusion** EC with endometriosis may be a risk factor for coexistence of ovarian cancer. Our results suggest that characteristics of EC with endometriosis may be influenced by age. Long time exposure of chronic inflammation or other complicated factors might be correlated with unfavorable clinicopathological characteristics in patients over 50 years old.

ISP-5-2

Evaluation of laparoscopic surgery for early-stage endometrial cancer in our Hospital Keisuke Kodama, Hironori Kenjyou, Yoshiaki Kawano, Eisuke Kaneki, Hiroshi Yagi, Masafumi Yasunaga, Tatsuhiro Ohgami, Ichiro Onoyama, Kaoru Okugawa, Hideaki Yahata, Kenzo Sonoda, Kiyoko Kato *Kyushu University*

Objective Laparoscopic surgery has been increasingly performed in gynecologic field and this technique started to be adapted for early-stage endometrial cancer by national health insurance since 2014. We here evaluated oncological outcome and perioperative complications in our hospital. **Methods** Patients with endometrial cancer who underwent laparoscopic surgery were retrospectively examined. Perioperative data, complications, disease recurrence, and long-term survival were reviewed from medical records. All patients provided written informed consent before treatment. **Results** The study included 56 patients [mean age (±standard deviation), 54±11.2 years; mean body mass index, 23.2±6.2kg/m^2] with a follow-up ranging from 1 to 35 months. One patient was converted to laparotomy by referring intraoperative findings. The mean operative time was 428±101.5 minutes and the mean blood loss was 282.5±336.8 mL. The mean number of removed pelvic lymph nodes was 17±5.3 per patient. The overall complication rate was 8.9% including common iliac vein injury, obturator nerve injury, vaginal cuff bleeding, crush syndrome, and compartment syndrome (1 case each). One patient, who had no adjuvant treatment because of diagnosis as low risk of recurrence, experienced para-aortic lymph node recurrence 12 months after surgery. This patient received para-aortic lymphadenectomy followed by chemotherapy. **Conclusion** Patients treated by laparoscopic surgery in our hospital had compatible oncological outcome and less complications in comparison with the previously published data. When minimally invasive characteristics were considered, laparoscopic surgery might be the important treatment of choice for early-stage endometrial cancer.

ISP-5-3

Short term outcomes of laparoscopic surgery for early-stage endometrial cancer Emiko Niiro, Yasuhito Tanase, Sumire Sugimoto, Kana Iwai, Sachiko Morioka, Yuki Yamada, Fuminori Ito, Natsuki Koike, Hiroshi Shigetomi, Ryuji Kawaguchi, Toshiyuki Sado, Hiroshi Kobayashi *Nara Medical University*

Objective We began laparoscopic surgery (hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy) for early-stage endometrial cancer (EC) at July 2013 in our institute. Until now, we have experienced 39 cases for about three years. This time we evaluated the short term prognosis and the feasibility of our laparoscopic management for early-stage EC. **Methods** The surgical indication was FIGO stage IA and grade 1 or 2 of endometrioid adenocarcinoma. Clinical dates of the patients who underwent laparoscopic treatment including pelvic lymphadenectomy from July 2013 to September 2016 were collected retrospectively. We analyzed the dates mainly associated with the short-term prognosis, lymphatic metastasis, recurrence rate, and so on. **Results** In this period, 39 women were enrolled. Their median age was 55 years (range: 23-75) and body mass index was 23.1 kg/m^2 (range: 17.3-43.3). Eight cases (20%) were upstaged to FIGO stage IB and II after surgery, and associated with histology, 2 cases (5%) were upgraded to carcinosarcoma. The median number of resected lymph nodes detected by pathological examination was 38 (range: 20-72). No lymph node metastasis was observed. We performed adjuvant chemotherapy in 13 cases after surgery considering the risk factors. No recurrence has been observed during follow-up periods; the median was 17 months (range: 1-38). **Conclusion** The feasibility and the prognosis of laparoscopic approach for early stage EC in our institute were good with short term periods. Larger scale and longer-term studies are needed.

ISP-5-4

Non-obesity and non-polycystic ovary are risk factors for recurrence in fertility-sparing treatment with medroxyprogesterone acetate for endometrial cancer Yamato Fukui[1], Ayumi Taguchi[1], Katsuyuki Adachi[1], Marie Sato[1], Akira Kawata[2], Mayuyo Mori[1], Kazunori Nagasaka[1], Takahide Arimoto[1], Katsutoshi Oda[2], Kei Kawana[3], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2], School of Medicine, Nihon University[3]*

Objective Nearly ten percent of endometrial cancer (EC) is diagnosed under 40 years old. Medroxyprogesterone acetate (MPA) is the most common strategy for fertility-sparing therapy for EC of stage IA and grade1. Although complete response (CR) rate is 60-80%, recurrence rate is high. The objective of this study is to clarify risk factors for the recurrence of EC after MPA therapy. **Methods** We retrospectively analyzed 35 EC patients treated with MPA for fertility preservation in our hospital between 2000 and 2016 under approval of our institutional ethics committee. Correlation between recurrence and various clinical characteristics, including age, body mass index (BMI), absence of polycystic ovaries (PCO), and parity, was analyzed by univariate analysis. **Results** In 35 patients, 25 patients (71%) achieved complete response (CR), while 10 patients (29%)

underwent hysterectomy because of failure of MPA therapy. Twelve out of 25 (48%) with CR successfully gave births after MPA therapy, however, 8 out of 25 (32%) got relapsed. Relapse of EC was significantly associated with non-obesity (BMI<25 : p=0.016) and non-PCO (p=0.001), but not with age (<35) and parity. All the 13 patients with either high BMI (>=25) or presence of PCO did not get relapsed. **Conclusion** Absence of obesity and PCO may be a poor prognostic marker for relapse after MPA therapy in EC. These results suggest that hormone-independent carcinogenesis may exist in EC patients with these factors.

ISP-5-5

Comparison between laparoscopy and laparotomy for the incidence of postoperative lymphocyst following pelvic lymphadenectomy for uterine cancer Reisa Kakubari[1], Eiji Kobayashi[1], Takeshi Yokoi[2], Mamoru Kakuda[1], Michiko Kodama[1], Aiko Kakigano[1], Seiji Mabuchi[1], Yutaka Ueda[1], Kenjiro Sawada[1], Takuji Tomimatsu[1], Kiyoshi Yoshino[1], Tadashi Kimura[1] *Osaka University[1], Kaizuka Municipal Hospital[2]*

Object Our goal was to compare the incidence of lymphocyst formation following two types of pelvic lymphadenectomy surgery for uterine cancer : laparoscopy versus laparotomy. **Method** We reviewed retrospectively the medical records of all patients who underwent a pelvic lymphadenectomy for stage I uterine cancer from March 2010 to March 2016. Patients who underwent a para-aortic lymphadenectomy were excluded. We defined lymphocysts as accumulation of fluid of 2 or more cm in cross-section diagnosed with ultrasound or computed tomography imaging. **Result** 198 patients with stage I uterine cancer underwent a pelvic lymphadenectomy. Following surgery, there was no significant difference in post-operative lymphocyst formation between two surgery groups : a lymphocyst formed in 13.3% (12/90) and 13.9% (15/108) of the laparoscopy and laparotomy cases, respectively (p=1.00). The median follow-up time was different, 19 and 41 months, respectively (p<0.001). The number of dissected lymph nodes was not statistically different (p=0.536). The rate of lymphocyst infection was not statistically different (p=0.353), it occurred in 7 (7.8%) of the laparoscopy cases and in 13 (12.4%) of the laparotomy cases. Six of the seven cases of symptomatic infection following laparoscopy were treated with antibiotics alone, one case needed drainage under IVR (interventional radiology). **Conclusion** The reported incidence of lymphocyst formation following pelvic lymphadenectomy has varied 16-49%, but laparoscopy has had a tendency having a lower rate in lymphocyst formation. In our study of 198 cases, we found that there was no difference between laparoscopy and open laparotomy surgery groups in terms of lymphocyst incidence.

ISP-5-6

Research on early warning factors of cervical carcinomas and precancerous lesions Gulan Tuohetimulati, Mayinuer Niyazi *The People's Hospital of Xinjiang Uighur Autonomous Region., China*

Objective To test the IL-two, IL-six, IL-ten, IFN-γ and (HPV) Lone in serum from Han and Uyghur screened with HPV (positive). **Methods** The data gathered Uyghur at our hospital of these two years, the type and infection of cervical erosion was determined by HC-two, HPV- DNA, and HPV typing technique. the factors analyzed by means of Logistic Regression Analysis, which were severed into several groups of cervicitis, CIN one, CINtwo-three and cervical carcinoma. the levels of IL-two, IL-six, IL-ten and IFN-γ in serums and cervical tissues was measured. ELISA and Immunocytochemical and IHCA were applied to inspect one hundred and ninety-seven specimens with positive HPV. **Results** The IFN-γ in cervical tissues was inversely proportional to the severity of cervical lesions while the IL-ten 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<zero point zero five). The IL-two and IFN-γ with different grades of cervical lesions declined with an increase of the severity of cervical lesions while the IL-six and IL-ten was opposite, which went up with the severity of cervical lesions, showed statistical significance (P<zero point zero five). The comparison between Han and Uyghur no statistical differences (P>zero point zero five). **Conclusion** The IL-two and IFN-γ with different grades of cervical lesions declined with an increase of the severity of cervical.

ISP-5-7

Learning curve for laparoscopic staging of early and locally advanced cervical and endometrial cancer Morva Tahmasbi Rad[1], Markus Wallwiener[2], Michael Eichbaum[2], Sven Becker[1] *University of Frankfurt, Germany[1], University of Heidelberg-Germany[2]*

Background Laparoscopic staging is rapidly evolving as an important surgical approach. However, the specific learning curve associated with this approach remains poorly investigated. **Methods** A series of 28 consecutive laparoscopic hysterectomies with without pelvic and or paraaorticlymph node sampling for the treatment of early and locally advanced endometrial or cervical cancer were performed. The analyses of the learning curves of the institution were performed for 20 patients who had undergone pelvic lymphadenectomy and or paraaortal lymph node sampling. The learning curve period has also been compared with the last 26 patients who received laparotomy staging (open group) due to the same diagnosis and by the same surgical team. To assess the short and Longterm outcomes, we used validated questionnaires. The learning curve was evaluated using the cumulative sum (CUSUM) method. **Results** The CUSUM learning curve consisted of two distinct phases : phase 1 (the initial 9 cases) and phase 2 (the subsequent cases) which presented the mastery phase (p 0.0001). The significance of the difference between the two phases and open group changed in terms of number of lymph nodes retrieved, intraoperative blood loss and hospital stay. **Conclusions** The data reported suggest that after a learning curve of 9patients, a relevant improvement at least regarding the duration of the operation can be achieved for experienced surgeons who start performing laparoscopic staging. However, due to the limited number of patients as well as number of para-aortic lymph node sampling procedures, further studies are required for firm conclusions to be drawn.

ISP-6-1

FOXL2 copy number is predictive of early recurrent adult type granulosa cell tumor of the ovary Satoshi Yanagida, Momoko Inoue, Yasushi Iida, Aikou Okamoto *The Jikei University School of Medicine*

Objective Adult-type granulosa cell tumor of the ovary (aGCTs) is rare ovarian tumor with low malignant potential, but this tumor is characterized by late recurrence. The mean time for the first recurrence is about 5 years, and no effective treatments but surgery were established for the recurrent tumor. Since the landmark study by Shah showed the majority of this tumor express somatic heterozygous 402C>G FOXL2 mutation, this mutation was investigated as a promising driver. However, the role of this mutation in the mechanisms of recurrence is unknown. **Methods** We collected the DNA of the matched primary and recurrent FFPE samples from the aGCT patients (5 patients, 7 recurrences, 19 sites, median follow up time 33 months

(range 21–172 months)). We compared the FOXL2 status of the primary and recurrent tumor from the same patient by TaqMan allelic discrimination assay, TaqMan copy number assay. We also performed immunohistochemical staining and compared the expression of FOXL2, p53, GATA4, and HER2 using the same samples. **Results** All the samples showed the heterozygous 402C>G FOXL2 mutation (longest time until recurrence was 172 months) and the FOXL2 protein expression. FOXL2 and p53 protein expression didn't correlate with the recurrence. FOXL2 copy number of all the primary tumors were 2. The mean time until recurrence of the recurrent samples with copy number 3 or 4 was significantly shorter than that with copy number 2 (29.25 months, 122.3 months, $p<0.01$). **Conclusion** The heterozygous 402C>G FOXL2 mutation is critical for maintaining the tumorigenesis of aGCTs. FOXL2 copy number is predictive of early recurrent aGCTs.

ISP-6-2

FBXW7 is involved in the acquisition of the malignant phenotype in epithelial ovarian tumors Shoko Kitade[1], Ichiro Onoyama[1], Hiroshi Yagi[1], Sachiko Yoshida[1], Masaya Kato[1], Ryosuke Tsunematsu[1], Kazuo Asanoma[1], Kenzo Sonoda[1], Hiroaki Kobayashi[2], Kenichiro Hata[3], Kiyoko Kato[1] *Kyushu University[1], Kagoshima University[2], National Research Institute for Child Health and Development[3]*

Objective FBXW7 is a ubiquitin ligase that mediates ubiquitylation of oncoproteins, such as c-Myc, cyclin E, Notch, and c-Jun. *FBXW7* is a tumor-suppressor gene, and mutations in *FBXW7* have been reported in various human malignancies. Moreover, it is well known that mutation of both *FBXW7* and *p53* drives oncogenesis actively. In this study, we analyzed the mechanism that FBXW7 contributed to the acquisition of the malignant phenotype in ovarian tumors. **Methods** We examined sequences of the *FBXW7* and *p53* genes, and *FBXW7* expression levels in epithelial ovarian tumor samples to search the correlation between *FBXW7* expression and *p53* mutation status. We also performed DNA methylation array and bisulfite PCR analysis of *FBXW7* promotor regions in ovarian cancers. **Results** We found no *FBXW7* mutations associated with amino acid changes. *FBXW7* expression levels in ovarian cancers were significantly lower than those in borderline and benign tumors ($p<0.01$). *FBXW7* expression levels in serous carcinomas were the lowest among four major histological subtypes. In addition, *p53*-mutated ovarian cancer showed significantly lower levels of *FBXW7* expression compared with *p53* wild-type cancer ($p<0.001$). DNA methylation array and bisulfite PCR sequencing revealed that 5'-upstream regions of *FBXW7* gene in *p53*-mutated samples were significantly more methylated compared with those in *p53* wild-type samples ($p<0.01$). **Conclusion** *FBXW7* expression was downregulated in ovarian cancers, and was associated with *p53* mutations and the DNA methylation status of the 5'-upstream regions of *FBXW7*. This data indicates that *p53* mutations might suppress *FBXW7* expression through DNA hypermethylation of *FBXW7* 5'-upstream regions.

ISP-6-3

PRKRA/PACT expression promotes chemoresistance in mucinous ovarian cancer Takeshi Hisamatsu *Osaka Police Hospital/Anderson Cancer Center, USA*

Objective To investigate the mechanism of resistance and developing strategies to overcome resistance in mucinous ovarian cancer (MOC). **Methods** We carried out a kinome-based siRNA synthetic lethality screen using human MOC cell lines. We next examined the combined efficacy of siPRKRA plus oxaliplatin for MOC using 2 intraperitoneal mouse xenograft models. We investigated the role of PRKRA in MOC. Finally, we examined the impact of PACT, which is a protein encoded by PRKRA, on chemoresistance in MOC. **Results** Among the 939 genes, we focused on PRKRA because in the siRNA screen, it was 1 of the top 5 downregulated genes in the target gene-siRNA plus oxaliplatin group relative to the target gene-siRNA group. The combination of oxaliplatin plus siPRKRA treatment reduced cell viability compared with oxaliplatin plus control siRNA in MOC cells, while knockdown of PRKRA did not result in a significant change in cell viability compared with the control. We also observed a significant increase in cell apoptosis after treatment with oxaliplatin plus siPRKRA. Using orthotopic mouse models, we observed a significant reduction in tumor weight and the number of tumor nodules in the siPRKRA plus oxaliplatin group compared with the oxaliplatin plus control siRNA group. In addition, we found that the PRKRA expression in MOCs was higher than was that in serous ovarian tumors. The PACT assay revealed that the expression of mature-miR-515-3p was regulated by the PACT-Dicer interaction, and miR-515-3p promotes chemosensitivity in MOC. Mechanistically, miR-515-3p regulates chemosensitivity by targeting AXL. **Conclusion** PRKRA/PACT expression promotes chemoresistance in MOC by regulating miR-515-3p expression.

ISP-6-4

Identification of somatic genetic alterations in ovarian clear cell carcinomas 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 cancers. OCCC arises from endometriosis and is more prevalent in Japanese than Caucasians (25% and 5% of all ovarian cancer, respectively). Frequent somatic mutations in the *ARID1A* (60%) and *PIK3CA* (40%) are reported for OCCC, but these mutations seem to be insufficient for explaining the characteristics of OCCC. The aim of this study is to discover the novel genomic alterations causing OCCC. **Methods** With institutional approval, paired genomic DNAs of 48 OCCC tumors and corresponding non-cancerous tissue were extracted from the formalin-fixed, paraffin embedded specimen collected between 2007 and 2015. All specimens underwent genotyping by exome sequencing and SNP arrays. Exome library was prepared with Sure Select Human All Exon V6. Copy number analysis was performed with Japonica array (SNP array optimized for Japanese population). **Results** The 48 OCCCs are divided into 5 clusters based on the mutation spectra and the each cluster shows significant similarity to the distinct COSMIC mutation signature. Frameshift or stop gain changes in the *ARID1A* (66.7%) and nonsynonymous and hot-spot mutations in the *PIK3CA* (50%) are found. Copy number analysis discloses partial trisomy of long arm of chromosome 8. Some oncogenic genes were significantly amplified. **Conclusion** We found several somatic genetic alterations, either novel or reported, in OCCC. We are comparing between clinical features and investigating gene ontology analyses of those genes. Next step is to characterize the biological properties of those genes by the experiments using cultured OCCC cells.

ISP-6-5

Saikosaponin-d sensitizes chemoresistant ovarian cancer cells to cisplatin-induced apoptosis by facilitating mitochondrial fission and G2/M arrest Hideaki Tsuyoshi, Makoto Orisaka, Yoshio Yoshida *Fukui University*

Objective The objective of this investigation is to examine the hypothesis that Saikosaponin-d (Ssd), a triterpenoid saponin derived from Bupleurum falcatum L., sensitizes chemoresistant

ovarian cancer (OVCA) cells to cisplatin (CDDP)-induced apoptosis by facilitating mitochondrial fission and G2/M cell cycle arrest. **Methods** Chemosensitive (A2780s) and chemoresistant cells with different p53 status [A2780cp (p53-mutant), Hey (p53-wild type) and SKOV3 (p53-null)] were incubated with CDDP in the absence and presence of Ssd. Apoptosis, mitochondrial membrane potential and mitochondrial phenotypes were assessed by Immunofluorescence. The expression of protein was examined by western blot analysis. The protein interaction was assessed by in Situ Proximity Ligation Assay. Cell cycle progression was examined by flow cytometry. **Results** In chemosensitive cells, CDDP treatment results in the phosphorylation and activation of p53 and activation of Oma1, leading to Opa1 processing, mitochondrial fission and apoptosis. CDDP also activates Chk1, which phosphorylates p53, leading to G1/S arrest and apoptosis. In chemoresistant cells which often exhibit high incidence of p53 mutation and increased PPM1D stability, which inhibits Chk1 activity, CDDP fails to induce G1/S arrest and Opa1 processing. However, Ssd inhibits phospho-Ser637-Drp1, increases cytosolic calcium concentration and, in the presence of CDDP, decreases mitochondrial membrane potential and increases CaMKI phosphorylation. These actions of Ssd lead to mitochondrial fission and subsequent apoptosis. Moreover, in the presence of CDDP, Ssd decreases PPM1D level, activates Chk1 and increases phosphor-Cdc25c content, resulting in G2/M arrest and apoptosis. **Conclusion** These Ssd-induced biochemical changes are consistent with the notion that Ssd may potentially be important in overcoming the chemoresistance in OVCA.

ISP-6-6

The presence and consumption of anti-PEG IgM in ovarian cancer patients under treatment with PLD Yoko Matsumoto, Asaha Fujimoto, Kenbun Sone, Michihiro Tanigawa, Mayuyo Mori, Katsuyuki Adachi, Kazunori Nagasaka, Takahide Arimoto, Katsutoshi Oda, Kei Kawana, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

Objective Polyethylene glycol (PEG) is widely used for modification of drug carriers. PEGylated liposomal doxorubicin (PLD) is approved for treatment with ovarian cancers. Although PEG was supposed to have low immunogenicity, accelerated blood clearance of the PEGylated reagent through production of anti-PEG IgM was reported in animals. This study aimed to assess the significance of anti-PEG IgM in treatments with PLD. **Methods** Clinical data and blood serum samples of 17 ovarian cancer patients who underwent PLD treatment were obtained under approval of our institutional ethics committee. Quantities of anti-PEG IgM and doxorubicin in blood serum were analyzed before and during treatments. **Results** Among 17 patients, five had anti-PEG IgM prior to PLD injections. The initial production of anti-PEG IgM induced by PLD treatment was not detected. In IgM positive patients, anti-PEG IgM was consumed by injection of PLD and significantly decreased ($p=0.001$), but recovered by next treatment. The concentrations of PLD in blood serum 20 hours after injections and quantities of anti-PEG IgM had no correlations. Disease control rates at 16 weeks and non-hematological grade 3/4 adverse events in IgM positive and negative groups were not significantly distinct ($p=1.00$ and $p=0.62$, respectively). **Conclusion** Our study showed the presence of anti-PEG IgM and its decrease after injection of PLD for the first time in human patients. Our results indicated that anti-PEG IgM might not significantly affect pharmacokinetics of PLD by itself. However, further study would be needed to figure out the effect of anti-PEG IgM under treatment with other PEGylated drugs.

ISP-6-7

Impact of CXCL10 and plasmacytoid dendritic cells for tumor microenvironment in KRAS-driven ovarian cancer mouse model Juri Ogishima[1], Ayumi Taguchi[1], Kei Kawana[2], Mitsuyo Yoshida[1], Akira Kawata[1], Hiroe Nakamura[1], Masakazu Sato[1], Katsuyuki Adachi[1], Takeshi Nagamatsu[1], Katsutoshi Oda[1], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Nihon University[2]*

Objective Oncogene KRAS is known to modulate tumor microenvironment (TME) with severe inflammation in ovarian cancer model mice. CXCL10, which is associated with inflammation, is a central chemokine for recruitment of plasmacytoid dendritic cells (pDCs). We herein focused on the mechanism of T cell dysfunction by alteration of DC population in the KRAS-induced TME. **Methods** Mice were intraperitoneally injected with murine ovarian cancer cell line, ID8, or mutant KRAS-transduced ID8 (ID8-KRAS). DC subset and CD8+ exhausted T cells were assessed by flow cytometry. Concentration of CXCL10 and cytokines was assessed using specific ELISA. Expression of IL-10 (in T cells from ascites) and of CXCL10 (in tumor cells) was analyzed by real-time PCR. **Results** pDC subset was more predominant in ascites from ID8-KRAS, compared with that from ID8. Concentration of CXCL10 was significantly higher in ascites of ID8-KRAS, compared with that of ID8 ($p<0.05$), accompanied with increased expression of CXCL10 in ID8-KRAS tumor. In addition, IL-10 concentration was significantly increased in ID8-KRAS mice in both serum and ascites, compared with ID8 mice ($p<0.05$). IL10 in ID8-KRAS ascites was predominantly expressed in T cells. The ratio of CD8+ exhausted T cells was highly observed in ID8-KRAS mice, compared with ID8 mice. **Conclusion** Suppressed anti-tumor immunity in ID8-KRAS TME is represented by the increased expression of IL10 in T cells. Increased level of CXCL10 followed by pDC recruitment might be associated with T cell dysfunction in ID8-KRAS TME.

ISP-6-8

Snail inhibits anti-tumor immunity through upregulation of CXCR2 ligands in ovarian cancer Mana Taki, Kaoru Abiko, Tsukasa Baba, Junzo Hamanishi, Ken Yamaguchi, Ryusuke Murakami, Naoki Horikawa, Noriomi Matsumura *Kyoto University*

Objective Epithelial-mesenchymal transition (EMT) is a key process in tumor invasion and metastasis. Recently, several studies have investigated the role of EMT on tumor immunity. The aim of this study is to explore the functional relationship between EMT and tumor immunity in ovarian cancer. **Methods** The expression of EMT-related gene Snail was analyzed using The Cancer Genome Atlas (TCGA) dataset. From mouse ovarian cancer cell line HM-1, a Snail-silenced cell line, HM1-sh-Snail was established. Using these cell lines, EMT, peritoneal dissemination, survival, local immunity, and NF-kB pathway activity were analyzed. CXCR2 ligands was analyzed in serum of ovarian cancer patients. **Results** High Snail expression was correlated with short overall survival in TCGA ($p<0.05$). In the immunocompetent mouse model, HM1-sh-Snail demonstrated longer survival and smaller tumor volume than control ($p<0.05$), but in immunosuppressive mouse model, there was no difference between the two groups. Intratumoral CD8+ T cells increased, and myeloid-derived suppressor cells (MDSCs) decreased in number by Snail knockdown ($p<0.05$). Snail increased CXCR2 ligands via NF-kB pathway. CXCR2 ligands promoted MDSC chemotaxis and the addition of CXCR2 antagonist suppressed it, indicating that CXCR2 ligands promote MDSC migration to tumors via CXCR2. CXCR2 antagonists inhibited infiltration of MDSCs and mice tumor growth. Serum

levels of CXCR2 ligands were elevated in ovarian cancer patients and the levels were associated with poor prognosis ($p<0.05$). **Conclusion** Snail suppresses anti-tumor immunity by recruitment of MDSCs through expression of NF-kB and CXCR2 ligands in ovarian cancer cells.

ISP-7-1

The pivotal role of LATS1 in ovarian cancer progression
Hiroshi Yagi, Keisuke Kodama, Masafumi Yasunaga, Tatsuhiro Ohgami, Ichiro Onoyama, Kazuo Asanoma, Kenzo Sonoda, Kiyoko Kato *Kyushu University*
Objective $G\alpha_{12/13}$, heterotrimeric G-proteins, encoded by GEP oncogene, have been implicated in the progression of several human cancers. In the previous study, we demonstrated that GEP oncogene promotes ovarian cancer progression through YAP activation. We herein evaluated the underlying mechanisms by which GEP oncogene activates YAP in ovarian cancer cells. **Methods** To examine the signaling pathways regulated exclusively by $G\alpha_{13}$, we employed a synthetic biology approach using a GPCR activated solely by artificial ligands (RASSLs). The activation and protein stability of LATS1 were evaluated by Western blot after cycloheximide treatment. Migration properties were also examined by using LATS1 shRNA-infected cells. **Results** $G\alpha_{13}$ induced not only phosphorylation of LATS1 at serine 909, but also dephosphorylation of LATS1 at threonine 1079. Intriguingly, LATS1 protein level decreased markedly, though LATS1 mRNA level did not change. In the presence of proteasome inhibitor, MG132, $G\alpha_{13}$-mediated LATS1 protein degradation was suppressed. Knock down of LATS1 using shRNA resulted in decreased migratory properties in ovarian cancer cells. **Conclusion** Proteasome-dependent LATS1 degradation induced by $G\alpha_{13}$ might contribute to the progression of ovarian cancer.

ISP-7-2

Differential requirement of amino acids on cell survival of ovarian cancer cells
Akiko Furusawa, Jun Inoue, Naoyuki Miyasaka, Johji Inazawa *Tokyo Medical and Dental University*
Objective It has been known that amino acids (AAs) play an important role for cell survival of cancer cells as a metabolic source. However, it is unclear whether the AAs requirement for cell survival of cancer cells are almost same or cell-type specific. In this study, we examined the differential requirement of AAs on cell survival in ovarian cancer (OVC) cell lines. **Methods** Single amino acid-depleted medium was prepared by adding other 19 amino acids into amino acid-free DMEM medium. Seeded 17 OVC cell lines on 96 well plates and cultured them for 48 hours. Survival cells were measured by crystal violet staining method. More than 30% reduction in cell survival rate, compared with the cultivation in standard medium, were assessed as effective. **Results** The requirement of extracellular AAs on cell survival is cell-type dependent manner. Extracellular essential amino acids (EAA) is not required for cell survival of a part of OVC cells, nevertheless EAA cannot be synthesized endogenously. Non-EAA (NEAA) required cells showed dependency on the requirement of at least one AA among 5 NEAAs on cell survival. While NEAAs are endogenously synthesized by each enzyme, the expression level of glutamine synthetase (GS) was significantly down-regulated in OVC cell lines with the sensitivity to depletion of glutamine. **Conclusion** GS down-regulated OVC cell lines showed dependency on extracellular glutamine for cell survival. Inhibiting uptake of extracellular glutamine or being decreased amount extracellular glutamine level may be therapeutically useful strategy for patients with ovarian cancer with GS down-regulation.

ISP-7-3

Investigation of the utility of IL-18 to develop new adoptive cellular immunotherapy for ovarian cancer patients with malignant ascites
Yuki Abe[1], Yoshika Akizawa[1], Ken Ishitani[2], Kazunori Hashimoto[1], Hideo Matsui[1] *Tokyo Women's Medical University[1], Kitasato University Kitasato Institute Hospital[2]*
Objective We recently investigated Vdelta2+ T cells of gamma delta T cells as effector cells for adoptive cellular immunotherapy. The ability of cells to proliferate in culture is reduced in cancer patients. It is necessary to establish effective cultures. IL-18 promotes proliferative Vdelta2+ T cells and enhances CD 56 expression and cytotoxic activity. We conducted a clinical trial wherein gamma delta T cells were intraperitoneally injected in ovarian cancer patients with malignant ascites. IL-18 promotes proliferative Vdelta2+ T cells during culture of the patient's peripheral blood mononuclear cells (PBM). We aimed to clarify the IL-18 function for CD56-Vdelta2+ T cells. **Methods** We centrifuged healthy donor blood and isolated cells using magnetic cell separation or cell sorter. PBM cultures were performed for gamma delta T cell expansion. Total PBM were stimulated using 2-methyl-3-butenyl-1-pyrophosphate, and IL-2 was added with/without IL-18. PBM were incubated for 14 days and analyzed using flow cytometry and cytotoxic assay. **Results** 1. When we added IL-2 with/without IL-18 to purified CD56+Vdelta2+ T cells, CD56+Vdelta2+ T cells proliferation and CD56-Vdelta2+ T cells induction were indicated. 2. When we added IL-2 in isolation to purified CD56-Vdelta2+ T cells, less CD56 expression was indicated. If CD56 expression was revealed, it did not indicate proliferative Vdelta2+ T cells. When we added IL-2 with IL-18 to purified CD56-Vdelta2+ T cells, CD56 expression and proliferative CD56+Vdelta2+ T cells were indicated. 3. Cytotoxicity-dependent pyrophosphoric acid was present on CD56-Vdelta2+ T cells cultured with IL-2 and IL-18 from purified CD56-Vdelta2+ T cells. **Conclusion** IL-18 induces cytotoxicity in CD56-Vdelta2+ T cells.

ISP-7-4

Alpha-chain of Complement 4-Binding Protein with Fully-Sialylated Glycans (FS-C4BP) : Diagnostic utility for early stage ovarian clear cell carcinoma and endometrioma
Masaru Hayashi[1], Tetsuji Iida[1], Masae Ikeda[1], Masako Shida[1], Takeshi Hirasawa[1], Toshinari Muramatsu[2], Hitoshi Ishimoto[1], Shunichiro Izumi[1], Mikio Mikami[1] *Tokai University Hospital[1], Tokai University Hachioji Hospital[2]*
Objective While certain fraction of endometrioma (EM) can develop de nove epithelial ovarian cancer (EOC) such as ovarian clear cell carcinoma (OCCC), we developed the new marker for early stage OCCC (FS-C4BP ; this compound has been applied for patents (PCT/JP2015/068390)), which can be potentially applied for the monitoring of EM patients (Gynecol Oncol. 2015 ; 139 : 520-8). To upgrade the diagnostic utility of FS-C4BP between EM and early stage OCCC, we tried to examine the combination assay of FS-C4BP and C4BP with all types of glycans (ALL-C4BP). **Methods** Serum FS-C4BP and ALL-C4BP values were measured from 77 pretreatment EOC patients (including 36 OCCCs) and 10 EM patients by ELISA and mass spectrum approach, respectively. Diagnostic accuracy of the combination of FS-C4BP and ALL-C4BP (COMB) was compared to one of CA125 and FS-C4BP by comparing PPV and NPV. **Results** The mean value of serum ALL-C4BP in early stages of OCCC patients was significantly lower than in EM patients ($p<0.01$). And the mean value of serum FS-C4BP was significantly higher in early stages of OCCCs than in EMs ($p=0.001$). Diagnostic accuracy of COMB to distinguish early stage OCCC from EM is significantly higher than that of CA-125 or FS-C4BP only : PPV for CA125, FS-C4BP only versus COMB, 64, 95 versus

95% ; NPV, 58, 85 versus 92%. This COMB can increase the diagnostic utility for early stage OCCC and EM (NPV ; 85% to 95%). **Conclusion** This diagnostic system can be potentially applied for the monitoring of EM patients, which could make the early diagnosis of OCCC possible.

ISP-7-5

In vivo loss-of-function screen with pooled shRNA library identifies KPNB1 as a new drug target for epithelial ovarian cancer Michiko Kodama[1], Kosuke Yoshihara[2], Aya Nakae[1], Kae Hashimoto[1], Seiji Mabuchi[1], Kenjiro Sawada[1], Tadashi Kimura[1] *Osaka University Graduate School of Medicine[1], Niigata University Graduate School of Medical and Dental Sciences[2]*

Objective Epithelial ovarian cancer (EOC) is most lethal gynecological cancer, mostly diagnosed at advanced stage with peritoneal carcinomatosis (PC). To seek its new therapeutic targets, we performed in vivo loss of function screen. **Methods** Human EOC cell line, SKOV3, was transduced with pooled druggable shRNA library containing 42450 shRNAs targeting 7490 genes. Transduced cells were intraperitoneally injected into 12 female nude mice and monitored for PC tumor formation. Genomic DNA of 12 biggest PC tumors were sequenced to identify shRNAs depleted in these tumors. **Results** Ten potential drug targets were identified, including 2 known oncogenes, ERBB2 and RAF1. Individual validation showed that siRNAs targeting 9 genes decreased cell proliferation in SKOV3 cells. Knockdown of 2nd ranked gene, KPNB1 significantly decreased in vitro cell proliferation in multiple EOC cell lines and in vivo tumor formation through inducing apoptosis and multi-phase cell cycle arrest. There was positive correlation between KPNB1 mRNA levels and poor survival of EOC patients, suggesting the oncogenic role of KPNB1 in EOC. Comprehensive mass spectrometric study identified that KPNB1 positively regulated several members of anaphase promoting complex/cyclosome. Lastly, we found that ivermectin, a well-known ant-parasitic drug, exerted an anti-proliferative effect on EOC cell lines via KPNB1 inhibition, and its combination with paclitaxel synergistically suppressed cell proliferation and inhibited tumor formation in vivo. **Conclusion** In vivo pooled shRNA library screen identified KPNB1 as a new drug target for EOC. Ivermectin can be a new therapeutics for EOC especially combined with paclitaxel.

ISP-7-6

Novel implications of La-Related Protein 4, an RNA chaperon, in ovarian cancer metastasis suppression Mahy Egiz[1], Kazuyuki Kitatani[2], Masafumi Toyoshima[1], Masumi Ishibashi[1], Shogo Shigeta[1], Junko Minato[1], Nobuo Yaegashi[1] *Tohoku University[1], Tohoku Medical Megabank Organization, Tohoku University[2]*

Background The lethality of ovarian carcinoma primarily stems from silent metastasis and targeting metastasis is a vital clue to improve patient survival. In ovarian cancer, an enhanced cell motility is a key regulator for metastasis. La-related protein (LARP) 4 is one of the LARP family members that act as RNA chaperons stabilizing multiple mRNA transcripts and are involved in many cellular processes as proliferation, cytoskeletal organization and migration. Here, we investigated LARP4 role for ovarian cancer metastasis. **Methods** Cell motility was assessed by lamellipodia formation, and transwell migration assay. Ovarian cancer xenograft model was established with SKOV3 cells inoculation into the peritoneal cavity of nude mice. Mice were sacrificed 4 weeks later for counting metastatic nodules number in the peritoneum. **Results** LARP4 silencing by small interfering RNA in ovarian cancer SKOV3 cells significantly upregulated lamellipodia formation by approximately 2 folds. Reciprocally LARP4 overexpression downregulated lamellipodia formation with 0.4 fold. The migratory activity of SKOV3 cells increased by 1.85 folds with LARP4 silencing. Furthermore, in the xenograft model 50% increase in metastatic nodules number was observed in LARP4 silenced group compared with control group. These findings suggested that LARP4 suppresses the metastatic potential by limiting the cell motility in ovarian cancer. **Conclusion** LARP4 is proposed to serve as a metastasis-suppressor protein in ovarian cancer, therefore RNA chaperon can act as a future cancer therapeutic target.

ISP-7-7

POSTTREATMENT TWO YEARS FOUR MONTHS CANCER FREE SURVIVAL FROM FIGO STAGE 4 INVASIVE CERVICAL CANCER (BY CLINICAL EXAMINATION, PET CT SCAN & HISTOPATHOLOGICAL CRITERIA) IN MALAYSIA Eugene Leong Weng Kong[1,2] *Taylors University, Malaysia[1], BP HEALTHCARE, Malaysia[2]*

Objective To report on cancer free survival from FIGO Stage 4 Cervical Cancer. Methodology ; Madam X, a 50 year old lady presented with irregular per vaginal bleeding in May 2014. A full evaluation revealed a fungating cervical cancer, invasive squamous cell carcinoma. Examination under anaesthesia, cystoscopy revealed bladder involvement. PET CT Scan evaluation showed serosal and pelvic nodal metastases. Consultant Radiotherapy (DrTho LMBeacon) opinion the patient agreed for adjuvant chemotherapy carboplatin/paclitaxel iv (3 cycles by author) followed by concurrent chemoradiotherapy (full dose including brachytherapy). There was followed another 3 cycles of adjuvant chemotherapy (by author). In 2016 vault smears showed inflammation, ASCUS, LGSIL, LGSIL with a hard roughened cervix with enlarged shotty inguinal lymph nodes. After repeat counselling, CT Scan, PET CT scan evaluation which were negative ; patient requested for histological confirmation. (2016) full thickness severe dysplasia on cervix. Patient requested for inguinal lymph node open biopsies versus leave alone. Resection of the remnant cervix and nodes no malignancy. **Results** Despite being on treatment still works except rest breaks whilst on treatment (completed 2014). **Conclusion** It is possible to obtain negative clinical, PET CT Scan and histopathology for cervical cancer FIGO Stage 4 after treatment in Malaysia. Written consent obtained.

ISP-8-1

Establishment of primary cell culturing method to study ovarian cancer heterogeneity Kyoso Ishida, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective Tumor heterogeneity is one of the distinctive characteristics of ovarian cancer, which would have crucial roles in response to chemotherapy. Recent advances in next generation sequencer (NGS) and its application make it possible to analyze single-cell gene expression, which might reveal tumor heterogeneity. Cancer cell lines are essential to validate the roles of candidate genes found by NGS analyses, but recent studies revealed many of them failed to retain the original phenotype. To make optimal tumor models, we are trying to establish ovarian cancer cell lines from primary tumor. **Methods** Both ascites fluid and solid tumors are collected from ovarian cancer patients. To isolate cells from solid tumor, the samples are placed in collagenase-containing PBS. After removing dead cells and erythrocytes using Ficoll, the cells are cultured in the mixture of M199 and F-12 medium with 31 ingredients. The cells are also analyzed using a flow cytometry (FCM). **Results** Cells derived from both ascites fluid and solid tumors could be cultured in the medium. As fibroblasts grew faster than epithelial cells, serial trypsinization method was helpful to remove fibroblasts. Some cultured cells had cobble stone-like appearance and could

be subcultured in several passages. FCM analysis revealed that most of the obtained cells were lymphocytes after administration of anticancer agents. **Conclusion** To establish new ovarian cancer cell lines which retains the original phenotype, primary cells has been collected and been analyzed by FCM. We could obtain a couple of cancer cell lines resembling commonly used cell lines by optimal medium.

ISP-8-2

Anti-tumor activities of ceramide nanoliposomes in ovarian cancer Xuewei Zhang[1], Kazuyuki Kitatani[2], Masafumi Toyoshima[1], Masumi Ishibashi[1], Shogo Shigeta[1], Junko Minato[1], Nobuo Yaegashi[1] *Tohoku University[1], Tohoku Medical Megabank Organization[2]*

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 that have been preclinically studied. However, the effect of ceramide naniliposomes in ovarian cancer still remains an open question. Thus, we tested the potential of ceramide nanoliposomes as therapeutic reagents in ovarian cancer. **Methods** Cell viability was measured by Cell-Titer Glo Kit. Cell death was determined by Annexin-V/7-amino-actiomycin D assay. The proteins involved in apoptosis and necroptosis were detected by immunostaining. **Results** Treatment of ovarian cancer cells with ceramide nanoliposomes decreased the number of living cells. Importantly, ceramide nanoliposomes-treated ovarian cancer cells died with necrosis, but not apoptosis. Necrosis is also executed in a regulated manner like apoptosis, representing necroptosis and ferroptosis. Necroptosis, the most well-studied form of regulated necrosis, is biochemically characterized by activation of protein kinase receptor-interacting protein kinase 1 (RIPK1) and pseudokinase mixed lineage kinase domain-like (MLKL). Treatment with ceramide nanoliposomes increased phosphorylation of RIPK1 and oligomerization of MLKL. In addition, inhibition of MLKL by siRNA significantly abolished ceramide nanoliposomes-induced cell death. **Conclusion** Ceramide nanoliposomes exhibited a cytotoxic effect by inducing MLKL-dependent necroptosis in ovarian cancer. Therefore, we concluded that ceramide nanoliposomes are suggested to serve as a new type of therapeutic reagent in ovarian cancer.

ISP-8-3

Tyrosine kinase receptor TIE-1 mediates platinum resistance by promoting nucleotide excision repair in ovarian cancer Masumi Ishibashi[1], Masafumi Toyoshima[1], Xuewei Zhang[1], Junko Minato[1], Shogo Shigeta[1], Kazuyuki Kitatani[2], Nobuo Yaegashi[1] *Tohoku University[1], Tohoku Medical Megabank Organization[2]*

Objective Platinum resistance is one of most challenging problem in the treatment of ovarian cancer patients. We investigated target molecules which can conquer platinum resistance in ovarian cancer cells utilizing a functional genomics approach. **Methods** We used high-throughput functional RNA interference screening to target 6550 genes in cisplatin-resistant A2780 CP human ovarian cancer cells. We validated the screening results and examined the detailed mechanisms how candidate gene was involved in cisplatin-resistance. **Results** *TIE1*, encoding tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE-1), was identified as a top candidate out of 6550 genes. TIE-1 is completely new as anticancer resistance-associated molecules. We found inhibition or over-expression of TIE-1 regulated cisplatin sensitivity in ovarian cancer cells without affecting cisplatin uptake and excretion. Over-expression of TIE-1 in tumor tissues was significantly correlated with poor prognosis in patients with ovarian cancer. DNA damage induced by cisplatin was significantly suppressed in TIE-1 over-expressing cells, suggesting that TIE-1 was involved in the nucleotide excision repair system that removes chemical adducts from DNA. We found TIE-1 regulated the expression of xeroderma pigmentosum complementation group C (XPC), a key component of nucleotide excision repair through re-localization of transcription factor Kruppel-like factor 5 (KLF-5). **Conclusion** TIE-1 contributed to cisplatin resistance by promoting KLF-5-XPC-dependent DNA repair system. We identified novel type of gene as molecular therapeutic target for cisplatin-resistant ovarian cancer through functional genomics approach. These findings could further the development of novel treatments for cisplatin-resistant ovarian cancer.

ISP-8-4

Regulation of Reg IV by CDX2 in ovarian mucinous adenocarcinoma Iemasa Koh, Eiji Hirata, Suguru Nosaka, Hiroshi Miyoshi, Yoshiki Kudo *Hiroshima University*

Objective Ovarian mucinous adenocarcinoma is a disease with a poor prognosis and a low response rate to chemotherapy. *REG4*, which encodes Reg IV protein, is a potent activator of the epidermal growth factor receptor (EGFR) /AKT/activator protein 1 (AP-1) signaling pathway. Reg IV has been shown to be overexpressed in several human cancers, and is reportedly involved in apoptosis inhibition, carcinogenesis, and cancer differentiation. Ovarian mucinous adenocarcinoma has also been found to be associated with overexpression of Reg IV. Therefore, we examined the regulation of Reg IV expression by CDX2. **Methods** The expression of CDX2 and Reg IV was confirmed by immunohistochemical staining of clinical specimens. Furthermore, we applied RNA interference and performed CDX2 overexpression with retroviral expression constructs in ovarian mucinous adenocarcinoma cell lines. **Results** We found that endogenous Reg IV expression was positively associated with CDX2 expression in ovarian mucinous adenocarcinoma. We also observed decreased Reg IV expression following inhibition of CDX2 by RNA interference in OMC-1 cells. CDX2 overexpression in OMC-3 cells, which display low endogenous CDX2, resulted in upregulation of Reg IV expression. **Conclusion** Our findings showed that Reg IV expression was regulated by CDX2 in ovarian mucinous adenocarcinoma. In addition, CDX2 is known to regulate the expression of MDR1, which is involved in drug resistance. Our study suggests that the kinetics of the expression of these molecules may allow for estimation of the responsiveness to chemotherapy.

ISP-8-5

Evaluation of neo-antigen specific $CD8^+$ T cells in ascites of gynecologic cancer patients and identification of their T cell receptors using next generation sequencer Yuji Ikeda[1], Kosei Hasegawa[2], Sho Sato[2], Keiichi Fujiwara[2], Yusuke Nakamura[1] *The University of Chicago, USA[1], Saitama Medical University International Medical Center[2]*

Objective In recent years there has been increased attention to neo-antigen as a novel target for immunotherapy ; hence, we aimed to prove the existence of neo-antigen specific $CD8^+$ T cells in gynecologic cancer patients. **Methods** Five gynecologic cancer patients with ascites were analyzed in this study under patients' consent and approval of IRB in each institution. Integrated molecular analysis and bioinformatics were employed to predict neo-antigens : whole exome sequencing (WES), RNA sequencing, HLA typing by OptiType, and neo-epitopes prediction by NetMHC. Ascites cells were cultured, and neo-antigen specific $CD8^+$ T cells were analyzed by flow cytometry. In addition, T-cell receptor (TCR) sequencing was performed by a

MiSeq based platform. **Results** WES and RNA sequencing identified 4 to 36 (meidan：27) non-synonymous mutations with RNA expression for each patient. Four out of five patients had HLA-A*24：02 allele：2 heterozygous and 2 homozygous. NetMHC method predicted 2 to 38 neo-epitopes per patient when each biding affinity was calculated as less than 500nM. Using 18 synthesized multimers, **we found a subset of neo-antigen specific CD8$^+$ T cells, which recognized L114F mutation in *SURF4* gene,** in 0.24% of total CD8$^+$ T cells in the ascites. Those cells were isolated and the TCR sequences of them were identified. **Conclusion** We successfully found a subset of **neo-antigen specific CD8$^+$ T cells in the ascites from the ovarian cancer patient**, and **identified its TCR sequences.** Our data suggest neo-antigen would be a promising target of immune therapeutics for gynecologic cancer patients. We are currently working on the engineered T cells expressing neo-antigen targeted TCRs.

ISP-8-6

Ovarian cancer-associated neutrophils have anti-cancer property through CD8 T cell activation Mitsuyo Yoshida[1], Ayumi Taguchi[3], Kei Kawana[2], Katsuyuki Adachi[3], Juri Ogishima[1], Hiroe Nakamura[1], Takeshi Nagamatsu[3], Takahide Arimoto[3], Kaori Koga[3], Yutaka Osuga[3], Tomoyuki Fujii[3] *Graduate School of Medicine, Tokyo University[1], Nihon University[2], Faculty of Medicine, Tokyo University[3]*

Objective Elevated number of neutrophils is known to be associated with poor prognosis in various types of cancer, however, little is known about functions of neutrophils. It has been reported that mutant KRAS accelerates cancer progression with increased number of neutrophils in peritoneal cancer mice model. We herein investigated the function of neutrophils in ovarian cancer progression. **Methods** Mice were intraperitoneally injected with murine ovarian cancer cell line, ID8, or KRAS-transduced ID8 (ID8-KRAS). Neutrophils were depleted with neutrophil-specific antibody in ID8-KRAS mice, and cytokine levels were assessed with specific ELISA. T cell subsets and co-stimulatory molecules on neutrophils were assessed by flow cytometry. In vitro CD8 T cell proliferation was assessed using standard CFSE dilution methods. **Results** Depletion of neutrophils tended to accelerate cancer progression of ID8-KRAS mice. The level of IL-6 in blood was 11 times higher in the neutrophil-depleted group than in the isotype-control group ($p< 0.05$). CD8/CD4 ratio in ID8-KRAS-induced ascites was significantly decreased in the neutrophil-depleted group, compared with the isotype-control group ($p<0.05$). In vitro assessment of T cell proliferation revealed that neutrophils from ID8-KRAS-induced ascites significantly stimulated CD8 T cell proliferation, compared with neutrophils from ID8-induced ascites or ID8-KRAS blood. T cell costimulatory molecules, especially OX40L and 4-1BBL, were highly expressed on neutrophils from ID8-KRAS-induced ascites, compared with those on neutrophils from ID8-induced ascites or ID8-KRAS blood. **Conclusion** Neutrophils from ID8-KRAS-induced ascites have anti-tumor property with the function of CD8 T cell activation. Number of neutrophils together with their function could give us better understanding about ovarian cancer progression.

ISP-8-7

Establishment and utility assessment of patient-derived models for ovarian clear cell carcinoma with ARID1A deficiency Kazuaki Takahashi[1], Mitsuya Ishikawa[2], Aikou Okamoto[1], Tomoyasu Kato[2] *Jikei University School of Medicine[1], National Cancer Center Hospital[2]*

Objective The purpose of this study is to develop a therapeutic strategy against ovarian clear cell carcinoma (OCCC) with ARID1A deficiency. Here, patient-derived model (PDM) was established and its utility was assessed by examining its sensitivity to molecular targeting drugs. **Methods** Tumor samples were obtained from three OCCC patients by surgery, and were cultured in vitro under approval of the institutional review board and informed consent from the patients. Western blot analysis and immune-histochemical staining were performed using a few anti-ARID1A antibodies. Mutations in the ARID1A gene were examined by targeted sequencing of genomic DNA using the Illumina MiSeq sequencer. The effect of drugs on survival of ARID1A-deficient and proficient OCCC cells was evaluated by a clonogenic survival assay. **Results** Three cases of PDM for OCCC were established from three Japanese patients. Loss of ARID1A protein was observed in two of the three cases both by western-blot and immunostaining analyses. Deleterious ARID1A mutations were detected in the two PDMs lacking ARID1A expression；they had two frameshift mutations (E1783 fs and A1517fs) and one nonsynonymous mutation- S241C. A few drugs showed differential sensitivity according to deficiency/proficiency of ARID1A in PDMs. **Conclusion** The present shows the utility of PDM in examining drug efficacy in OCCC in vitro. This study was done in collaboration with Drs. Hideaki Ogiwara, Ghani Farhana Ishrat, Reiko Watanabe, Hiroshi Yoshida, Tohru Kiyono and Takashi Kohno of National Cancer Center.

ISP-8-8

Expression of N-acetylgalactosaminyltransferase-6 (GalNAc-T6) in ovarian carcinomas Midori Murakami, Seiji Kagami, Chiho Koui, Rie Urabe, Taeko Ueda, Tomoko Kurita, Toshinori Kawagoe, Hiroto Izumi, Yusuke Matsuura, Toru Hachisuka *University of Occupational and Enviromental Health*

Objective The polypeptide N-acetylgalactosaminyltransferase (GalNAc-Ts) family of enzymes regulates the initial steps of mucin-type O-glycosylation. GalNAc-Ts influence cancer biology like invasion, metastasis. A recent study showed that GalNAc-T6 expression associated with progression and a poor prognosis in Breast and Pancreas cancer. In this study, we evaluated the expression of GalNAc-T6 in ovarian carcinomas. **Methods** The subjects of the present study are 150 patients with ovarian carcinoma who received treatment in our department between January 1995 and July 2008. Immunohistochemial expression of GalNAc-T6 were analysed immunohistochemically in paraffinembedded tumour samples. Data analyses were performed using SPSS version18.0. $P<0.05$ was regarded as statistical significant. **Results** The positive expression of GalNAc-T6 were 57.6% (34/59) in serous carcinoma, 85.3% (29/34) in mucinous carcinoma, 15.6% (5/27) in clear cell carcinoma, 44.0% (11/25) in endometrioid carcinoma. In Kaplan-Meier analysis, the 10-years overall survival rate of patient with serous ovarian carcinoma were 26.9% in positive of GalNac-T6 group compared with 24.5% in negative group ($p=0.493$). **Conclusion** The expression of GalNAc-T6 may be different from pathological sub type. There was no significant association between expression of GalNAc-T6 and prognosis of serous ovarian carcinoma.

ISP-9-1

Expression of UCP2 is associated with sensitivity to platinum-based chemotherapy for ovarian serous carcinoma Masaru Kawanishi, Takeshi Fukuda, Takuma Wada, Reiko Tasaka, Kenji Imai, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

Objective We examined the correlation between UCP2 (uncoupling protein 2) expression and the sensitivity to platinum-based chemotherapy for ovarian serous carcinoma. **Methods** We reviewed 51 cases of ovarian serous carcinoma stage III-IV

from 2005 to 2012. Cases were divided into two groups：one group in which maximum debulking surgery followed by platinum-based chemotherapy was performed and did not recur within 6 months after initialization of chemotherapy (group A；n=26), and another group in which maximum debulking surgery followed by platinum-based chemotherapy was performed and recur within 6 months (group B；n=25). UCP2 expression was examined immunohistochemically in paraffin-embedded sections using the avidin-biotin peroxidase complex method. This study was approved by the institutional review board in our facility. **Results** The expression of UCP2 was significantly higher in the group B than in the group A (p=0.027). Cases were divided into two groups：one group in which UCP2 expression was low level (weighted score≦6, n=24), and another group in which UCP2 expression was high level (weighted score≧8, n=27). Low UCP2 expression group might be sensitive to platinum-based chemotherapy than high expression group (p=0.07). The overall survival of Low UCP2 expression group was significantly longer than High UCP2 expression group (p=0.006). **Conclusion** It is suggested that the expression of UCP2 might be associated with sensitivity to platinum-based chemotherapy and predictor of prognosis of advanced ovarian serous carcinoma.

ISP-9-2

Expression of TBX2 is associated with sensitivity to platinum-based chemotherapy for ovarian serous carcinoma
Reiko Tasaka, Takeshi Fukuda, Takuma Wada, Masaru Kawanishi, Kenji Imai, Tomoyo Yasui, Toshiyuki Sumi *Osaka City University*

Objective We examined the correlation between TBX2 (T-box 2) expression and the sensitivity to platinum-based chemotherapy for ovarian serous carcinoma. **Methods** We reviewed 54 cases of ovarian serous carcinoma stage III-IV from 2005 to 2012. Cases were divided into two groups：one group in which maximum debulking surgery followed by platinum-based chemotherapy was performed and did not recur within 6 months after initialization of chemotherapy (group A；n=29), and another group in which maximum debulking surgery followed by platinum-based chemotherapy was performed and recur within 6 months (group B；n=25). TBX2 expression was examined immunohistochemically in paraffin-embedded sections using the avidin-biotin peroxidase complex method. This study was approved by the institutional review board in our facility. **Results** The expression of TBX2 was significantly higher in the group B than in the group A (p=0.004). Cases were divided into two groups：one group in which TBX2 expression was low level (weighted score ≦6, n=44), and another group in which TBX2 expression was high level (weighted score ≧8, n=10). Low TBX 2 expression group might be sensitive to platinum-based chemotherapy than high expression group (p=0.02). The overall survival of Low TBX2 expression group was significantly longer than High TBX2 expression group (p=0.023). **Conclusion** It is suggested that the expression of TBX2 might be associated with sensitivity to platinum-based chemotherapy and predictor of prognosis of advanced ovarian serous carcinoma.

ISP-9-3

2',4'-bridged nucleic acid antisense for Annexin A4 Improve platinum drug resistance of ovarian clear cell carcinoma
Satoshi Nakagawa[1], Kiyoshi Yoshino[2], Reisa Kakubari[2], Satoko Matsuzaki[2], Akiko Okazawa[2], Shinya Matsuzaki[2], Eiji Kobayashi[2], Yutaka Ueda[2], Tetsuji Naka[3], Tadashi Kimura[2] *Sakai City Medical Center[1], Osaka University[2], NIBIOHN[3]*

Objective We previously reported Annexin A4 plays an important role in innate platinum resistance of ovarian clear cell carcinoma (OCCC). However it is hard to regulate Annexin A4 by existing drugs or antibodies. The aim of this research is to improve platinum drug resistance of OCCC by using antisense oligonucleotides (ASOs) of Annexin A4 containing 2',4'- bridged nucleic acid (2,4-BNA/LNA). **Methods** ASOs containnig 2',4'-BNA/LNA targeting Annexin A4 mRNA were designed in silico and synthesized by Gene Design (Osaka, JAPAN). Real-time reverse transcription-PCR and western blotting analyses were done to evaluate the effect of ASOs. RMG-1 (human CCC cell line) was used in the all experiments. The IC50 of carboplatin and cisplatin were measured by WST assay. Female ICR nu/nu mice xenograft were treated twice a week with intratumoral BNA9 (1.0mg/kg) or control injection and intraperitoneal cisplatin (3mg/kg) administration. **Results** Two of 20 ASOs, BNA7 and BNA9, improved IC50 of cisplatin (3.3μM and 1.8μM, respectively) compared with negative control (5.2 mM) ASOs BNA7 and BNA9 also improved IC50 of carboplatin (35.5μM and 34.5μM, respectively) compared with control (52.0 μM). BNA9 and cisplatin treatment significantly inhibited tumor growth compared with control ASO and cisplatin treatment (42.5±6.3%). **Conclusion** ASOs containing 2',4'-BNA can be synthesized artificially and homogeneously. Down-regulating Annexin A4 with ASOs containing 2',4'-BNA is promising therapeutics for OCCC.

ISP-9-4

EpCAM expression affects resistance to chemotherapy and survival in epithelial ovarian cancer patients
Takeshi Motohara, Fumitaka Saitou, Kiyomi Takaishi, Isao Sakaguchi, Hironori Tashiro, Hidetaka Katabuchi *Kumamoto University*

Objective Emerging evidence suggests that cancer stem cells are responsible for tumor resistance to chemotherapy. We evaluated the molecular mechanisms of cancer stem cell marker EpCAM in the resistance to platinum-based chemotherapy and the potential relevance of EpCAM to the clinical outcomes in patients with epithelial ovarian cancer. **Methods** The clinical significance of EpCAM was investigated by immunohistochemical analysis using primary ovarian cancer specimens from 168 patients. Multivariate analysis was performed to estimate the influence of various clinicopathological factors on resistance to chemotherapy. Additionally, we studied the molecular functions of EpCAM in the resistance to platinum agents in in vitro assays and in an in vivo mouse model. This study was approved by the institutional review board. **Results** Increased expression of EpCAM was observed in ovarian cancer tissues obtained from patients treated with platinum-based chemotherapy compared with patients without chemotherapy. Multivariate analysis demonstrated that EpCAM expression was an independent risk factor for chemoresistance. Consistent with clinical findings, in in vitro assays, the subpopulation of EpCAM-positive cells showed significantly higher viability in comparison with EpCAM-negative cells in response to platinum agents. In an in vivo mouse model, platinum agents preferentially eliminated EpCAM-negative cells and induced enrichment of the EpCAM-positive cancer cells. Finally, Kaplan-Meier analysis showed that increased EpCAM expression contributed to shortened overall and progression-free survival. **Conclusion** We demonstrated that EpCAM expression is a predictive biomarker of chemotherapeutic response and unfavorable prognosis in ovarian cancer patients. Given that the subpopulation of EpCAM-positive cells affects chemoresistance, EpCAM represent a prospective molecular therapeutic target for eradicating ovarian cancer stem cells.

ISP-9-5

Ceramide synthase 2-ceramide synthesis pathway modulates the metastatic potential of ovarian cancer
Kazuyuki Kitatani, Xuewei Zhang, Masafumi Toyoshima, Egiz Mahy, Minato

Junko, Masumi Ishibashi, Shogo Shigeta, Nobuo Yaegashi *Tohoku University*

Objective Targeting cell motility, which is required for dissemination and metastasis, has a therapeutic potential for treating ovarian cancer. Our previous studies revealed that a bioactive lipid ceramide suppresses cell motility and serves as a metastasis suppressor in ovarian cancer. Ceramide is formed through catalytic action of ceramide synthases (CerSs), sphingomyelinases and cerebrosidases and we very recently found potential of CerS2 as an enzyme predominantly responsible for ceramide synthesis in ovarian cancer cells. In this study, we investigated roles for CerS2 in ovarian cancer metastasis. **Methods** SKOV3 ovarian cancer cells were inoculated into peritoneal of nude mice, generating metastatic nodules in mesentery. Highly metastatic SKOV3 ovarian cancer cells (M1-1, M1-2, M1-3, M1-4) were reestablished from metastatic nodules. To identify characteristics of highly metastatic cells, ceramide mass spec analysis and transcriptome analysis with RNAseq were performed. SKOV3 cells spontaneously form protrusions, such as lamellipodia, required for generating locomotive force in cell motility. Cell motility was determined by lamellipodia formation. **Results** CerS2 expression and ceramide contents were significantly decreased in highly metastatic SKOV3 ovarian cancer cells (M1-1, M1-2, M1-3, M1-4) as compared to parental cells. Down-regulation of CerS2-dependent synthesis of ceramide might be characteristic of metastasis-prone cells. Most importantly, inhibition of CerS2 by siRNA significantly up-regulated the formation of lamellipodia (cell motility) and the metastatic potential in a xenograft model. Those results suggest that CerS2-ceramide pathway suppresses cell motility accounting for metastasis. **Conclusion** CerS2 is suggested to serve as a key enzyme that limits ovarian cancer metastasis.

ISP-9-6

Pretreatment Multiplication of Neutrophil and Monocyte counts as a Prognostic Factor in Epithelial ovarian cancer Sooyoung Jeong, Wonkyo Shin, E Sun Paik, Minji Kim, Ju Young Park, Ji Hye Kim, Chel Hun Choi, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Objective The aim of this study was to investigate the prognostic value of the multiplication of neutrophil and monocyte counts (MNM) in epithelial ovarian cancer (EOC). **Methods** A retrospective review of the medical records was performed on EOC patients who were treated at the Samsung Medical Center between January 2002 and December 2013. **Results** We enrolled 674 patients with EOC. Because pretreatment neutrophil and monocyte counts showed the potential as a biomarker, these parameters were combined to be designated as MNM. The median MNM was 182.3, with a range of 16.0~4449.5). When cohort was divided according to the median MNM, poorer survival outcomes were observed in the group with higher MNM than in the lower MNM group. Higher MNM was associated with advanced stage and presence of residual disease after primary debulking surgery. In multivariate analysis, higher pre-treatment NLR was identified as being an independent poor prognostic factor for survival. **Conclusions** Pretreatment MNM may be a useful biomarker to stratify risk of recurrence and death in patients with EOC.

ISP-9-7

Nomograms predicting Platinum-sensitivity using pre-treatment White Blood Cell differential Count in Epithelial Ovarian Cancer Kyung-A Son, E Sun Paik, Hyejoo Lee, Minjeong Yun, Ju Young Park, Ji Hye Kim, Chel Hun Choi, Jeong-Won Lee, Byoung-Gie Kim, Duk-Soo Bae *Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Objective To evaluate the prognostic significance of pre-treatment white blood cell (WBC) differential count in epithelial ovarian cancer (EOC) patients and develop nomograms for platinum-sensitivity. **Methods** We retrospectively reviewed 757 EOC patients with primary treatment consist of surgical debulking and chemotherapy in Samsung Medical Center from 2002 to 2012. Nomogram for platinum-sensitivity were created as visualizations of prediction models for prognostic variables including age, stage, grade, CA-125 level, residual disease after primary debulking surgery (PDS), and pre-treatment CBC. The models were validated by 10-fold cross-validation (CV) procedure. Additionally, nomograms for 3-year progression-free survival (PFS) and 5-year overall survival (OS) were created in same manner. **Results** In addition to stage and residual disease after PDS, lymphocyte and monocyte count for platinum-sensitivity, platelet for PFS, and neutrophil count for OS were identified as significant prognostic factors in multivariate analysis. AUCs of platinum-sensitivity, 3-year PFS, and 5-year OS calculated by 10-fold CV procedure were 0.8159, 0.815, and 0.7405, respectively. **Conclusions** Prognostic factors including pre-treatment WBC differential counts were used to develop nomograms for platinum-sensitivity, 3-year PFS, and 5-year OS for EOC patients. These nomograms can be used to better estimate individual and collective outcomes.

ISP-10-1

Hypoxia induced cell proliferation and apoptosis in uterine leiomyoma and myometrial cells Hiroshi Ishikawa[1], Tetsuji Nishiwaki[2], Makio Shozu[1] *Chiba University[1], Chiba Aoba Municipal Hospital[2]*

Objective Although uterine leiomyoma enlarges in hypoxia, hypoxic responses have not been elucidated in this tumor. We recently elucidated hypoxia significantly induced hypoxia inducible factor-1 in both uterine leiomyoma and myometrial cells. To further evaluate hypoxic responses, we clarified whether hypoxia induces cell proliferation and apoptosis in both cells. **Methods** IRB at our facility approved all experimental protocols. We obtained consents from participants. We cultured primary leiomyoma and myometrial cells obtained from surgical specimens under hypoxia (1% oxygen) or normoxia for 2, 6, 12, and 24 hours (n=5), and then measured cell proliferation using Cell Counting Kit-8. We also measured caspase activity using Caspase-Glo 3/7 Assay kit. We performed all experiments according to the manufacture's protocols. **Results** Cell proliferation was not induced by hypoxia in both leiomyoma and myometrial cells up to 24 hours. Caspase 3 and 7 activity was not induced by hypoxia in myometrial cells up to 24 hours, but was significantly induced in leiomyoma cells at 24 hours. **Conclusion** Hypoxia significantly induces caspase 3 and 7 activities in uterine leiomyoma cells. This hypoxic response may affect hypoxia induced apoptosis in uterine leiomyoma.

ISP-10-2

Tissue remodeling by renin-angiotensin system is uncontrolled in the endometriotic lesion and eutopic endometrium of endometriosis cases Takahiro Nakajima, Fumihisa Chishima, Takehiro Nakao, Erina Kato, Hiromitsu Azuma, Chuyu Hayashi, Go Ichikawa, Kenji Sugita, Shinichi Takada, Tatsuo Yamamoto, Kei Kawana *Nihon University School of Medicine*

Objective Tissue renin-angiotensin (RA) system plays important roles in the tissue remodeling including tissue thickening and sclerosis. We have demonstrated AT1 and AT2, receptors of angiotensin II, are expressed in the endometriotic lesions suggesting RA system modulates pathogenesis of endometriosis.

Here we addressed the significance of MAS1, one of the angiotensin1–7–related components competing with AT1, in the endometriotic lesions. **Methods** Written informed consents were obtained from all the patients participating in this study. Ovarian endometriotic tissues (Ov) and eutopic endometrial tissues (endo–Em) were obtained from patients of endometrial cyst. As control, normal endometrial tissues (cont–Em) were obtained from patients undergoing hysterectomy for benign gynecological diseases with no endometriotic lesion in the abdominal cavity. mRNA levels of MAS1, AT1, and AT2 in these tissues were examined by RT–quantitative PCR. **Results** AT1, AT2 and MAS1 were expressed in Ov, endo–Em, and cont–Em. Both MAS1 and AT1 expressions in Ov and endo–Em were higher than those in cont–Em. However, mRNA level of MAS1 did not parallel that of AT1 in Ov and endo–Em, although mRNA level of MAS1 correlated strongly with that of AT1 in cont–Em. **Conclusion** The competitive effects of MAS1 and AT1 seems to balance on the endometrium of non–endometriosis cases. The balance was abrogated in the endometriotic lesion and eutopic endometrium of endometriosis cases, suggesting tissue remodeling by RA system may be uncontrolled in the endometriosis patients.

ISP-10-3

Molecular background of estrogen receptor–dependent gene expression in endometriotic cells Fuminori Taniguchi, Masao Izawa, Tasuku Harada *Tottori University*

Objective Endometriosis is an estrogen–dependent, inflammatory disease. To explain the pathophysiology of this disease, the distinct profile of estrogen receptor (ER) expression, a higher ERβ and a lower ERα expression, has been proposed as a major background of estrogen action. We evaluated the molecular background of ER–dependent gene expression in endometriotic cells. **Methods** We obtained the informed consent from all patients. The chocolate cyst lining of ovaries from patients with endometriosis was the source of endometriotic tissue. As the control, the eutopic endometrial tissues were obtained from uteri of premenopausal women who had uterine leiomyoma. Stromal cells were prepared from endometriotic and endometrial tissues. ER gene expression was evaluated using RT–PCR. ER–dependent gene expression was estimated using PCR array. **Results** 1) Relative expression of ERα mRNA in endometriotic cells was estimated to be one tenth of that in endometrial cells. 2) A transcript of wild–type ERα was always expressed in endometriotic and endometrial cells. 3) A wild type ERβ1 mRNA was expressed in endometriotic cells, which is almost at a comparable level of the ERα. 4) A splice variant ERβ2 mRNA was expressed at a comparable level of the ERβ1. 5) In response to ER isoform–specific ligands, a distinct pattern of gene expression was observed. **Conclusion** We demonstrated the molecular background of ER–dependent gene expression in endometriotic cells. The finding that 3 ER isoforms, ERα, ERβ 1 and ERβ 2, are expressed at a comparable level provides a facet in understanding the estrogen–dependent pathophysiology in endometriosis.

ISP-10-4

The role of peritoneal macrophages in the pathogenesis of endometriosis Tomoko Makabe[1], Kaori Koga[1], Erina Satake[1], Alisa Takeuchi[1], Ayumi Taguchi[2], Fusako Sue[1], Mariko Miyashita[2], Miyuki Harada[2], Tetsuya Hirata[2], Yasushi Hirota[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Faculty of Medicine, The University of Tokyo[2]*

Objective Peritoneal macrophages (PM) in endometriosis are shown to be polarized to alternative activated macrophages (M2); however, the role of PM in the pathogenesis of endometriosis has not been well–determined. In order to elucidate the role of PM in endometriosis, we comprehensively examined their features. **Methods** Under informed consents, peritoneal fluids were collected from control and endometriosis patients. PM were isolated using CD14 MACS selection, and RNA was extracted. 1) Three samples of each group were pooled, and comprehensive comparison was made using Gene Chip analysis. 2) Validation analysis for up–regulated (IL–6, IL–8, CXCR4, CXCL 2 and CXCL3) and down–regulated (HLA–DRA, HLA–F, CXCL 9 and CXCL10) genes was performed using quantitative RT–PCR with newly collected samples (11 control and 6 endometriosis samples). **Results** 1) 288 genes were identified as >2–fold up–regulated, whereas 31 genes were found as >2–fold down–regulated in endometriosis. High–ranking genes in up–regulation in endometriosis included IL–6, IL–8, CXCL2 and CXCL3. High–ranking genes in down–regulation in endometriosis were HLA–DRA, HLA–F, B2M, GZMA, CXCL9 and CXCL10. 2) mRNA expressions of IL–6, IL–8, CXCR4, CXCL2 and CXCL3 in PM of validation samples were significantly higher ($p<0.05$), whereas those of HLA–DRA and CXCL10 were significantly lower ($p<0.05$). **Conclusion** PM of endometriosis are not just M2 macrophages, but have a specific profile showing angiogenic, pro–inflammatory, and neutrophil–attractive properties, and less ability to present antigens and to induce Th1 cells. These features of PM may contribute to the pathogenesis of endometriosis.

ISP-10-5

Exome sequencing of endometriosis identified recurrent somatic mutations in MAPK pathway Kazuaki Suda[1], Kosuke Yoshihara[1], Tatsuya Ishiguro[1], Ryo Tamura[1], Kaoru Yamawaki[1], Yutaro Mori[1], Hiroaki Kase[2], Itsuro Inoue[3] *Niigata University[1], Nagaoka Chuo General Hospital[2], National Institute of Genetics[3]*

Objective Endometriosis is a common complex disease caused by genetic and environmental factors. However, molecular characteristics of endometriosis remain still unclear. The aim of our study is to determine the genomic landscape of endometriosis, leading to clarification of the pathogenesis of endometriosis. **Methods** After ethical committee approval and written informed consents, we performed whole exome sequencing of DNAs from endometriotic glands derived from 13 ovarian endometriotic cysts, and histologically normal endometrial glands derived from 12 surgically removed uteri for benign conditions. Of those, both endometriotic glands and histologically normal endometrial glands are analyzed in 5 cases. We used laser microdissection to obtain genomic DNA from frozen sections of both endometriotic glands and endometrial glands. Genomic DNA from blood cells was used for reference. **Results** There was no significant difference in mutation frequency per sample between endometriotic and endometrial glands (168.8 ± 99.5 and 178.3 ± 71.2, $p=0.85$). Of nonsynonymous mutations, *KRAS* was identified as the most recurrent mutated gene in endometiotic glands (n=8/13 ; 62%), and that was more frequent than in endometrial glands (n=4/12 ; 33%). In addition, the average of mutant allele frequency of *KRAS* in endometriotic glands ($48 \pm 22\%$) was significantly higher than that in endometrial glands ($21 \pm 6.5\%$) ($p=0.033$), suggesting *KRAS* mutation may occur in expansion phase. **Conclusion** We clarified the existence of endometriosis–related mutation profile. Especially, *KRAS* mutation might be a driving force of clonal expansion of endometriotic cells.

ISP-10-6

Differential status of epithelial–mesenchymal transition in endometriosis and adenomyosis : ZEB1 as a potential indicator

of endometriotic invasiveness Hirotaka Masuda[1], Masataka Furuya[2], Hironori Asada[3], Tetsuo Maruyama[1], Hiroshi Uchida[1], Sayaka Uchida[1], Yasunori Yoshimura[1], Hidetaka Katabuchi[4], Hideyuki Saya[1], Mamoru Tanaka[1], Daisuke Aoki[1] *Keio University School of Medicine[1], Eiju General Hospital[2], Shin-yurigaoka General Hospital[3], Kumamoto University[4]*

Objective Although endometriosis is a benign disease, it shares some features with cancers, such as invasiveness and the potential to metastasize. These features are thought to be involved in epithelial-mesenchymal transition (EMT). This study sought to investigate the EMT status in each type of endometriosis and adenomyosis compared to normal endometrium. **Methods** Ten endometriosis patients, nine adenomyosis patients and twelve control women without endometriosis undergoing surgery for benign indications were recruited. We evaluated the expression of E-cadherin, N-cadherin, vimentin and EMT-related transcriptional factors (Snail and ZEB1) in epithelial cells of various endometriotic lesions, adenomyosis and normal endometrium by immunohistochemistry. The relationship between ZEB1 expression and serum level of CA125 was also investigated. **Results** Immunohistochemical scoring revealed that although E-cadherin, N-cadherin, Snail, and vimentin were expressed in epithelia of all types of samples, each marker expression differed significantly according to the type of samples. Notably, ZEB1 expression was only expressed in epithelia of endometriosis and adenomyosis. Additionally, ZEB1 was most frequently observed in epithelial cells of deep infiltrating endometriosis and adenomyosis. Furthermore, the patients with high serum CA125 level were more likely to have ZEB1-positive lesions. **Conclusion** The results of immunohistochemical scoring suggested that the EMT status was different according to the type of lesions, which is the first report showing the differential EMT status in each endometriotic lesion and adenomyosis. The expression pattern of ZEB1 indicated that ZEB1 can be a potential indicator of invasiveness or severity. This is also the first observation of ZEB1 expression in epithelial cells of a benign disease.

ISP-10-7

Investigate the Inhibitory Effect of SS5020-A Selective Estrogen Receptor Modulator on Uterine Leiomyomas in an Xenograft Mouse Model Bin Li[1], Takashi Takeda[2], Kenji Tsuiji[3], Nobuo Yaegashi[3] *Department of Tohoku Medical Megabank Organization, Tohoku University[1], Division of Women's Health, Research Institute of Traditional Asian Medicine, Kinki University School of Medicine[2], Tohoku University Graduate School of Medicine[3]*

Objective Uterine leiomyomas are the most common gynecological benign tumors and greatly affect reproductive health and wellbeing. Selective estrogen receptor modulators (SERMs) are estrogen receptor (ER) ligands that act as estrogens in some tissues while blocking estrogen activity in others. SS5020, a new benzopyran antiestrogen, has anti-breast cancer potential in rats and mice model. In this study, we investigated the inhibitory effect of SS5020 on uterine leiomyomas in vitro and in vivo. **Methods** In vitro study, ELT-3 cells were treated with various concentrations of Tamoxifen (TAM), SS1020 and SS5020. Cell proliferation was evaluated by MTS assay. In vivo study, human leiomyoma tumor tissues were collected from female Japanese patients at the time of hysterectomy and implanted into immunodeficient mouse. The features of uterine leiomyoma in xenografted tissues were maintained by adding estrogen or estrogen plus progesterone. Mice were administered orally with SS5020. Then tumors were evaluated by tissue morphology, steroid receptors, apoptosis and collagen components. **Results** SS5020 inhibited ELT-3 cells proliferation. Xenograft model study showed that SS5020 administration inhibited the enlargement of the tumor, caused the inhibitory effect of cellular proliferation and ER, PR expression levels. Furthermore, SS5020 increased TUNEL positive cells. However, the expression levels of smooth muscle actin (SMA) and collagen components exhibited no significant changed. **Conclusion** These experimental findings showed that SS5020 inhibited uterine leiomyoma cells proliferation both in vitro and in vivo. However, the inhibitory effect was not as strong as to affect the expression levels of SMA and collagen components.

ISP-10-8

Global gene profiling of primary endometriotic epithelial cells Akari Nakazawa, Tetsuya Hirata, Shinya Fukuda, Kazuaki Neriishi, Miyuki Harada, Yasushi Hirota, Kaori Koga, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *Faculty of Medicine, The University of Tokyo*

Objective Transcriptome comparison between ectopic and eutopic endometrium has been examined for endometriosis research. However, there is no report focusing on isolated epithelial cells. The aim of this study is to isolate endometriotic epithelial cells (EmoECs) and characterize the difference between EmoECs, endometrial epithelial cells (EECs) or endometriotic stromal cells (EmoSCs). **Methods** The experimental procedures were approved by the Institutional Review Board of a university. EmoECs were isolated from ovarian endometriomas, by our own methods. RNA-seq library was constructed for EmoECs (N=6), EmoSCs (N=4) and EECs (N=4), and analyzed by RNA-sequencing. Significant genes were defined by statistical significance (ANOVA, False Discovery Rate (FDR) <0.05). **Results** Firstly, isolated EmoECs were positive for cytokeratin and PAX 8, a Mullerian lineage marker, and negative for CD10, endometriotic stromal marker. Secondly, the gene profiling and principal components analysis showed that these three type of cells formed three distinct clusters, demonstrating that the gene profiles of EmoECs, EECs and EmoESc were clearly different from each other. Thirdly, the gene profiling analysis revealed that 42 genes (e.g. KRT7, PAX8) were overexpressed and 30 genes (e.g. ACTA2) were under-expressed significantly in EmoECs compared to EmoSCs. Furthermore, 100 genes were overexpressed and 48 genes were under-expressed significantly in EmoECs compared to EECs. Especially, EMT related genes were included in overexpressed gene list of EmoECs. **Conclusion** Our study demonstrated that EmoECs and EECs were distinct from each other in terms of gene expression profile. EmoECs specific gene signature included EMT related genes, which might characterize the pathophysiology of endometriosis.

ISP-10-9

Comparison of follicular density between ovaries with and without ovarian endometrioma Takashi Mimura[1], Koji Matsumoto[1], Miki Kushima[2], Shingo Miyamoto[1], Chiaki Iitsuka[1], Mamiko Onuki[1], Tetsuya Ishikawa[1], Akihiko Sekizawa[1] *Showa University School of Medicine[1], Showa University School of Medicine, department of pathology[2]*

Objective Ovarian endometriomas (OEs) often adhere to the uterus and induce local inflammation and extensive fibrosis in surrounding tissues, suggesting adverse effects of OEs on ovarian reserve. The aim of the present study was to evaluate follicular densities in the ovaries with and without OEs. **Methods** We analyzed follicular density count (number of follicles in cm^2) in ovaries from women with OEs (cases, n=26) and women that underwent laparoscopic risk-reducing salpingo-oophorectomy (RRSO) for hereditary breast and ovarian cancer (HBOC) (controls, n=20). They had regular menstruation cycles at the time of surgery. Follicular density was histologically measured and compared at two different sites of removed ovaries. Wilcoxon

signed-rank test was used for statistical analysis. **Results** The median age of the study subjects was 44 years (range, 35-52) in cases and 44 years (range, 36-50) in controls, respectively. In cases, all OEs adhered to the uterus, thus implying follicular loss at the uterus side of the ovaries. In women with OEs, the follicular density was significant lower in ovarian tissues adjacent to OEs (i.e., at the uterine side) than in tissues distant form OEs (i.e., at the fimbrial side) (1.0/cm^2 [range 0-6.8/cm^2] vs. 2.1/cm^2 [range 0-7.4/cm^2], p=0.02). In controls, the follicular density was similar between two sections close to and distant from the uterus (3.4/cm^2 [range 0.0 - 41.4] vs. 4.4/cm^2 [range 0.0 - 19.4], p=0.54). **Conclusion** Our findings suggested that OEs may induce follicular loss in normal-looking tissues surrounding OEs. Therefore, early intervention may be beneficial in young women with OEs to protect their ovarian function.

ISP-10-10

Serum CA125 during menstruation as a diagnostic marker to predict early-stage endometriosis Chiaki Kashino[1], Mikiya Nakatsuka[2], Toru Hasegawa[1], Hirofumi Matsuoka[1], Ai Sakamoto[1], Sayoko Kotani[1], Yasuhiko Kamada[1], Yuji Hiramatsu[1]
Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences[1], Graduate School of Health Sciences, Okayama University[2]

Objective Early-stage endometriosis, which is difficult to be diagnosed, is reported to be a significant cause of infertility. In this study, we studied a clinical role of serum CA125 during menstruation as an sensitive marker. **Methods** 131 women who have undergone laparoscopy and measurement of serum CA125 from 2005 to 2016, enrolled in this study after approval from the local ethics committee and informed consent. Endometriosis was diagnosed in 100 women (rASRM stage 1：n=27；stage 2：n=19；stage 3：n=34；and stage 4：n=20). Those without endometriosis (n=31) were defined as the control. **Results** There was a significant difference in CA125 levels except during menstruation between control women (11.9±2.2 U/ml, mean±S.D.) and women with endometriosis (39.7±5.2 U/ml). In addition, CA125 levels during menstruation in women with endometriosis (47.0±5.4 U/ml) were significantly higher than that of the control women (16.6±1.9 U/ml). The average CA125 levels during menstruation were 22.5 U/ml in stage 1, 44.3 U/ml in stage 2, 63.4 U/ml in stage 3, and 62.4 U/ml in stage 4. The ratio of women with a CA125 level over 25 U/ml during menstruation was 30.0%, 53.3%, 85.7%, and 92.3%, respectively, whereas there were no control women no women with a CA125 level over 25 U/ml. The ratio of the endometriosis that is presumable only from a serum CA125 level during menstruation is 22.2% in total and even higher (75.0%) in r-ASRM stage 2 endometriosis. **Conclusion** Measurement of serum CA125 during menstruation can be clinically used to predict endometriosis in the early stage.

ISP-10-11

Evaluation of deeply infiltrating endometriosis by preoperative MRI in patients with adenomyosis Kanako Yoshida, Yuri Kadota, Kana Kasai, Kaoru Keyama, Sumika Matsui, Takeshi Kato, Minoru Irahara *Tokushima University*

Objective The objective of this study is to retrospectively evaluate the accuracy of magnetic resonance (MR) imaging in predicting deeply infiltrating endometriosis (DIE) in patients with adenomyosis. **Methods** Institutional review board approval was not required for this retrospective study, but informed consent was obtained from all patients. Between 2008 and 2016, 44 patients with adenomyosis underwent total laparoscopic hysterectomy at Tokushima University Hospital. We retrospectively evaluated their Intraoperative findings and MR images. MR images were scored for the presence of the five findings：retroflexed uterus, elevated posterior vaginal fornix, intestinal tethering in direction of uterus, faint strands between uterus and intestine, and fibrotic nodule covering serosal surface of the uterus. **Results** Of the five findings, intestinal tethering and faint strands between uterus and intestine, the sensitivity is 65-76%, specificity is 93-100%, which is useful for the detection of deep endometriosis lesions. However, retroflexed uterus did not help in the detection of lesions. For elevated posterior fornix and fibrotic nodule covering surface of the uterus, the sensitivity is as low as 47-53%, specificity was as high as 85-96%. **Conclusion** For patients with intestinal tethering or faint strands between uterus and intestine in preperative MRI, appropriate informed consent and preoperative preparation are required.

ISP-10-12

The effect of ultrasound-guided high-intensity focused ultrasound treatment on uterine fibroid and adenomyosis Ki Hyon Kil, Eun-Ji Lim *HIFU center, St. Peter's Hospital, Korea*

Purpose To assess the outcomes after ultrasound-guided high-intensity focused ultrasound (HIFU) ablation in treatment of patients with uterine fibroid or adenomyosis at St. Peter's hospital, Seoul, Republic of Korea. **Methods** From January 2015 to August 2015, 591 patients which 147 suffered from uterine fibroid and 444 suffered from adenomyosis were treated as inpatients by US-guided HIFU ablation. An acoustic power of 400 W/cm2 were delivered with 150 m second interval at the target point. This process was repeated on a point by point basis. After one slice was treated, the target was shifted 4 mm laterally. If patient were complaining of pain, the procedures were stopped for a while. The patients were followed for 3 to 6 months to observe long-term therapeuticeffects. **Results** The distribution of age was 23~64years old, and of volume was 3.0 ~ 3610.0 cm3. Nobody gave up the procedure for pain or any other reason. The procedures took 68.0 to 2482.0 seconds. Nobody reported any clinically severe complications. Everybody returned to normal activities 1 day after the procedure. The average volume shrinkage at 3 and 6months was 37.60% and 42.36%, respectively. **Conclusion** Ultrasound imaging-guided HIFU treatment may be a safe and effective non-invasive alternative in treatment of uterien fibroid or adenomyosis.

ISP-11-1

Hypothalamic kisspeptin directly regulates prolactin synthesis in a pituitary lactotroph cell line Tomomi Hara, Haruhiko Kanasaki, Aki Oride, Satoru Kyo *Shimane University Faculty of Medicine*

Objective Prolactin released from pituitary lactotrophs plays a variety of roles in maintaining reproductive functions. Although prolactin is mainly under the inhibitory control of hypothalamic dopaminergic neurons, hypothalamic factors such as TRH and PACAP also participate in the regulation of prolactin as prolactin-releasing factors. Kisspeptin is a known hypothalamic neuropeptide that governs GnRH release within the hypothalamus. In addition, as kisspeptin was identified in the portal circulation, it may play a role as a pituitary hormone-releasing factor. We examined the possible role of kisspeptin in prolactin-producing cells. **Methods** The lactotroph cell line GH3 was used. Direct action of kisspeptin on prolactin gene expression was determined by promoter assay using a luciferase-expressing vector. Signal transduction induced by kisspeptin was assessed by reporter gene assays. Interactions between kisspeptin and TRH or PACAP were also examined. **Results** GH3 cells express the kisspeptin receptor. Stimulation of these cells with kisspeptin increased prolactin promoter activity in a dose-dependent manner. The kisspeptin-stimulated increase in prolactin promoter activity was similar to that stimulated by TRH, but combined

treatment with kisspeptin and TRH failed to potentiate their individual effects. However, combined stimulation with kisspeptin and PACAP increased prolactin promoter activity to a greater extent than that induced by kisspeptin and PACAP alone. Kisspeptin stimulated both extracellular signal-regulated kinase (ERK) and cAMP/protein kinase A (PKA) pathways. Kisspeptin-induced ERK and cAMP/PKA signaling activation were enhanced in the presence of PACAP, but not TRH. **Conclusion** We found that hypothalamic kisspeptin is a prolactin-stimulating factor. Kisspeptin may regulate prolactin expression alone or in cooperation with other prolactin-releasing factors.

ISP-11-2

What is preimplantation genetic diagnosis strategy for germline mosaicism? Junko Maki, Kou Sueoka, Suguru Sato, Kotaro Iino, Hiroshi Senba, Yuki Mizuguchi, Kenji Sato, Akira Nakabayashi, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective When healthy couples give birth more than two affected children and the mutation is not present in their DNA, we should consider the risk of germline mosaicism (GM). We attempted to establish preimplantation genetic diagnosis (PGD) strategy for GM. **Methods** Osteogenesis imperfecta (OI) is a dominant disorder caused by mutation in type I collagen genes and is often caused by GM. Somatic and seminal DNA was extracted from the parents and the proband of three families with OI seeking PGD. Whole genome amplification-allele specific PCR-capillary electrophoresis was performed to identify the high-risk haplotype consisting of mutations and short tandem repeats flanking those genes. Cases in which mutations are not detected are considered to be of pure GM of maternal origin. This study was approved by the ethics committee. **Results** Family 1 had affected fetuses harboring a mutation in COL1A1, and the husband had the same mosaic mutation. Selective transfer of embryos fertilized with low-risk haploid sperm was performed and an unaffected baby was born. In family 2, a mutation of COL 1A2 was transmitted maternally. Family 3 had two affected siblings, but no mutation from parental somatic DNA was identified. **Conclusion** Accurate PGD for GM can be performed by trio analysis of the somatic DNA and semen. To identify the high-risk allele in female mosaics, as in the cases of family 2 and 3, haplotype analysis must be done with oocyte and polar body. But it is challenging to carry out invasive procedures prior to the PGD cycle.

ISP-11-3

Global gene expression profile in the luminal epithelium of the mouse uterus during embryo attachment Shota Igaue, Yasushi Hirota, Tomoko Fujita, Hirofumi Haraguchi, Leona Matsumoto, Mitsunori Matsuo, Takehiro Hiraoka, Tomoki Tanaka, Shun Akaeda, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Implantation is a spatiotemporally limited event after a reciprocal interaction between embryo and uterine luminal epithelium. Endometrial gene expression at the site of implantation has been unclear due to the technical difficulty. In this study, we picked up mouse uterine luminal epithelium to which blastocysts attach by using laser microdissection system (LMD) and investigated global gene expression profile of the dissected luminal epithelium. **Methods** C57BL/6 wild-type mice on day 4 evening and day 5 morning were sacrificed (vaginal plug=day 1), and the uteri were obtained. Day 5 morning is the time when embryo attachment occurs. Uterine luminal epithelium was selectively dissected by LMD. The luminal epithelium at the site of blastocyst attachment and the distant area from blastocyst attachment were collected separately as samples. The extracted RNA was used for RNA-seq. As data analyses of RNA-seq, K-means and gene ontology (GO) analyses were performed. **Results** We identified 952 up/down-regulated genes in the luminal epithelium at the attachment site and 323 up/down-regulated genes in the luminal epithelium distant from embryo compared to gene expression profiles on day 4. In the luminal epithelium at the attachment site on day5, genes associated with regulation of secretion, protein binding, binding were up-regulated, and genes related to immune response, positive regulation of defense response, positive regulation of response to stimulus were down-regulated. **Conclusion** Our findings suggest that stimuli of embryo attachment induce unique gene expression in the luminal epithelium to support subsequent embryo implantation.

ISP-11-4

Uterine extracellular matrix is a useful material for normal uterine regeneration in a mouse model of decellularized matrix transplantation Chiaki Takehisa[1], Yasushi Hirota[2], Takehiro Hiraoka[2], Tomoko Fujita[2], Hirofumi Haraguchi[2], Leona Matsumoto[2], Mitsunori Matsuo[2], Shun Akaeda[2], Tomoki Tanaka[2], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2]*

Objective Decellularized matrix transplantation (DMT) can be a novel technique of infertility treatment by which we have achieved successful functional uterine regeneration in mice using decellularized uterine matrix. To investigate whether the use of uterine matrix instead of other organ matrices is important for successful uterine regeneration, we used the decellularized matrices derived from uterine and liver tissues (uterus- and liver-ECMs, respectively), and evaluated uterine regeneration by histological analyses. **Methods** Resected donor mouse livers or uteri were decellularized by SDS treatment, and transplanted into the artificial defects of recipient mouse uteri. The recipient uteri a month after transplantation were examined by H&E staining and immunohistochemistry using an epithelial marker CK8, a myometrial marker αSMA, estrogen receptor ERα, and progesterone receptor (PR). **Results** The decellularized uterus- and liver-ECMs were composed only of extracellular matrices without any cellular components. The regenerated uterus after uterus-ECM transplantation showed normal uterine structure with CK8/ERα/PR-positive luminal and glandular epithelium, ERα/PR-positive stroma and αSMA/ERα/PR-positive myometrium. The regenerated uterus after liver-ECM transplantation had very few glandular epithelium despite normal stromal and myometrial structure with ERα/PR-positive stroma and αSMA/ERα/PR-positive myometrium. Unlike normal uterus, apparent PR expression was not observed in the luminal and glandular epithelium regenerated after liver-ECM transplantation. **Conclusion** These findings indicate that the use of liver matrix induces the dysregulated uterine regeneration. Uterine matrix might be critical for uterine regeneration in the mouse model of DMT, although uterine matrix-specific role in this model remains to be elucidated.

ISP-11-5

STAT3 is crucial for the entire process of uterine regeneration in a mouse model of decellularized matrix transplantation Takehiro Hiraoka, Yasushi Hirota, Tomoko Fujita, Shun Akaeda, Tomoki Tanaka, Mitsunori Matsuo, Leona Matsumoto, Hirofumi Haraguchi, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Although a close relationship between uterine regeneration and successful pregnancy in both humans and mice has been consistently observed, its molecular basis remains unclear.

This study aims to clarify the process of uterine regeneration by establishing a mouse model of decellularized uterine matrix (DUM) transplantation. **Methods** Resected mouse uteri were processed with SDS to make DUMs composed of only extracellular matrix without intact cells. DUMs were transplanted into the mouse uteri at the site of artificially induced defects, and the transplantation sites were histologically examined. **Results** All the uterine structures were recovered at the transplantation sites within a month. In the regenerated uteri, not only normal hormone responsiveness was observed, but normal full term pregnancy was achieved, indicating the regeneration of functional uteri. Uterine epithelial cells rapidly formed a normal uterine luminal and glandular epithelial layer within a week followed by stromal and myometrial regeneration, indicating a remarkable regenerating capacity of the endometrial epithelium. In the ovariectomized mice, uterine regeneration was similarly observed, suggesting that ovarian hormones are not essential for uterine regeneration. Importantly, the epithelium around the DUM demonstrated heightened STAT3 activation and cell proliferation, which was suppressed in the uteri of Stat3 conditional knockout mice. Moreover, stromal and myometrial regeneration were significantly impaired in Stat3 conditional knockout mice compared to wild-type mice. **Conclusion** These data suggest a critical role of STAT3 in the whole uterine regeneration process. DUM transplantation model may provide new insight into the mechanism of uterine regeneration and the pathophysiology of endometriosis and adenomyosis.

ISP-11-6

Integrated epigenome profiling of histone modifications, DNA methylation and gene expression in human endometrial stromal cells during decidualization Noriko Kato[1], Keiji Kuroda[1], Rie Ozaki[1], Makoto Jinushi[1], Jun Kumakiri[1], Mari Kitade[1], Satoru Takeda[1], Kenichiro Hata[2] *Juntendo University[1], National Research Institute for Child Health and Development[2]*

Objective Decidualization, the transformation of endometrial stromal cells (ESC) into secretory decidual cells, is essential for pregnancy, and dependent on the postovulatory increase of progesterone and local cyclic AMP production levels in humans. Although the responsiveness of ESCs to the hormonal cues is considered to be potentiated by genome-wide chromatin remodeling followed by the coordinated action of decidua-specific transcriptional networks, information for such epigenetic alterations has been limited. To capture the epigenetic dynamics and to understand its roles during decidualization, we conducted epigenome profiling for ESCs and differentiated decidual cells. **Methods** Endometrial tissues from patients (without endometriosis and disease of endometrium) who underwent a surgery of hysterectomy were processed for primary ESC culture. The primary cells were untreated, or decidualized for 4 and 8 days in the presence of 8-bromo-cAMP and progesterone. The resultant cells were subjected to transcriptome and methylome profilings, and chromatin immunoprecipitation followed by sequencing (ChIPseq) for H3K27ac (an active mark), and for H3 K9me3 and H3K27me3 (repressive marks). **Results** Among 47,496 regions with H3K27ac signals detected by MACS, the regions with increased (>2 fold) and decreased (<0.5 fold) signals upon decidualization were 2,555 (5.4%) and 3,800 (8.0%), respectively. However, the ratios of the regions with altered signals of epigenetic modifications for gene silencing (DNA methylation, H3K9me3, and H3K27me3) were much lower (less than 0.5%). **Conclusion** We have successfully obtained epigenome profiles for an in vitro culture model for decidualization, and revealed the dynamic changes of H3K27ac upon cell differentiation.

ISP-11-7

Uterine dendritic cells in allogeneic mating mice are identified as tolerogenic dendritic cells Tomoko Shima, Akemi Ushijima, Sayaka Tsuda, Kumiko Inada, Akitoshi Nakashima, Osamu Yoshino, Shigeru Saito *University of Toyama*

Objective Tolerogenic dendritic cells (tDC) play central role for induction of immunological tolerance. We examined whether uterine DC has a tolerogenic character in pregnant mice. **Methods** (1) Female BALB/c mice were mated with male DBA/2 mice (allogeneic mating), and the surface markers of DCs were studied using the flow cytometry. To analyze the role of seminal fluid in DCs, we resected the seminal vesicle of male DBA/2 mice (SVX), then female BALB/c mice were mated with male SVX mice. (2) To analyze of DCs function, mixed lymphoid reaction (MLR) assay by thymidine uptake was performed. **Results** (1) CD86 and MHC class 2 are co-stimulation marker of DC, and B7-DC is immunosuppressive marker of DC. CD86 and MHC class 2 expressions on DCs were significantly decreased in uterus on day3.5 pc (before implantation) and day5.5 pc (after implantation) in allogeneic mating. On the other hand, B7-DC expression on DCs were significantly increased in uterus on day 3.5 pc and day5.5 pc in allogeneic mating. These molecules on DCs did not change in SVX allogeneic mating. (2) DCs derived from pregnant uterus in allogeneic mating suppressed the MLR reaction, but DCs derived from uterus in SVX allogeneic mating did not. (3) Uterine DCs expanded the regulatory T cells in vitro. **Conclusion** Seminal fluid priming induced tolerogenic DCs and induced paternal antigen specific tolerance by expanding of regulatory T cells.

ISP-11-8

Levonorgestrel prevents embryo implantation by suppressing uterine LIF expression Mitsunori Matsuo, Yasushi Hirota, Tomoko Fujita, Hirofumi Haraguchi, Shota Igaue, Leona Matsumoto, Takehiro Hiraoka, Shun Akaeda, Tomoki Tanaka, Yutaka Osuga, Tomoyuki Fujii *Faculty of Medicine, The University of Tokyo*

Objective Levonorgestrel (LNG) is a progestin used for contraceptive drug, and however, it remains unclear how LNG leads to contraception, especially prevention of embryo implantation. In this study, we investigated the effect of LNG on embryo implantation with a focus on leukemia inhibitory factor (LIF), a cytokine which is essential for implantation. **Methods** LNG (300μg/kg/day) or vehicle was given to C57BL/6 wild-type mature female mice (LNG or control mice) by oral gavage from day1 to day4 of pregnancy (vaginal plug=day1). Preimplantation blastocyst formation, progesterone (P4)-induced epithelial differentiation, estrogen (E2) /P4- responsive genes on day4 morning, LIF expression on day4 evening, number of implantation sites on day5 morning were examined. Day5 is the time of embryo attachment to the mouse luminal epithelium. Recombinant LIF (12μg, twice/day) was intraperitoneally injected to LNG mice on day4, and implantation was evaluated on day5 morning. **Results** In LNG mice, LIF expression was significantly reduced, but preimplantation blastocyst formation, P4-induced epithelial differentiation, expression of E2/P4- responsive genes were normal on day4. Importantly, eight out of nine LNG mice did not have any implantation sites on day5 (inhibition rate of implantation (IRI) =8/9, 89%), although all the control mice showed implantation sites (IRI=0/10, 0%). In addition, LIF injection significantly recovered from implantation failure of LNG mice (IRI=1/6, 17%). **Conclusion** These findings indicate that LNG has an effect of implantation inhibition through downregulation of uterine LIF expression.

ISP-11-9

The influence of early life psychological stress on sexual maturation in male and female rats Kiyohito Yano, Toshiya Matsuzaki, Takeshi Iwasa, Maira Iriasu, Minoru Irahara
Tokushima University

Objective Early-life stress is associated with depression, Breast cancer, Schizophrenia and metabolic abnormalities that increase the risk of cardiovascular disease and diabetes. The influence of early-life psychological stress induced by maternal separation (MS) on the sexual maturation was examined in male and female rats. **Methods** Male and female rats were divided into control (C) and maternal separation (MS) groups, respectively (n=20-24 per each group). Pups in MS groups were placed in isolated cages during 240min/day from postnatal day (PND) 2 to PND 11. On PND 28, male rats were randomly selected from C (n=10) and MS (n=11) groups, and killed by decapitation to measure serum testosterone levels. Onset of vaginal opening in females and preputal separation in males were monitored from PND 29 to PND40. Thereafter, estrous cycle in females were monitored from PND 62 to PND72. **Results** In males and females, body weights of MS group were significantly lower than those of C group at PND 21, 28 and at PND 14, respectively ($p<0.05$). Preputal separation in MS (34.83 ± 2.33day) group was significantly earlier than that of C group (36.60 ± 2.32 day) ($p<0.05$) in male rats. Serum testosterone level at PND 28 did not differ between MS group (0.70 ± 0.65ng/ml) and C group (0.27 ± 0.39ng/ml). Vaginal opening did not differ between MS group (33.05 ± 1.53) and C group (33.00 ± 1.95) in female rats. Estrous cycle also did not differ between groups. **Conclusion** Maternal separation-induced psychological stress advanced sexual maturation in male rats, whereas, such effects was not observed in female rats in this study.

ISP-11-10

Dynamic changes in mitochondrial distribution in human oocytes during meiotic maturation Yuki Takahashi[1], Keijiro Ito[2], Yoshiharu Nakaoka[2], Yoshiharu Morimoto[2], Nao Suzuki[1]
St. Marianna University School of Medicine[1], IVF Namba Clinic[2]

Objective Maturation of mammalian oocytes involves distinct events in the nucleus and the cytoplasm. Although nuclear maturation has been studied extensively, cytoplasmic maturation is less understood. The change of mitochondrial distribution in human oocytes during meiotic maturation was assessed. **Methods** Live cell images of fluorescence-labelled mitochondria in human oocytes were analyzed to investigate dynamic changes in mitochondrial distribution during meiotic maturation using a confocal microscope combined with an incubator in the presence or absence of colchicine and cytochalasin B, inhibitors for tubulin and actin filament, respectively. Subcellular distribution of mitochondria in human oocytes was also assessed at various stages using a transmission electron microscope. This study was approved by the local ethics IRB and JSOG. All donor patients provided the signed informed consent. **Results** Live cell imaging analysis revealed that the mitochondria-occupied cytoplasmic area decreased from 83 to 77% around 6h before germinal vesicle breakdown (GVBD) and that mitochondria accumulated preferentially close to the perinuclear region. The mitochondria-distributed area rapidly increased to 85% at the time of GVBD. In contrast, there was no significant change in mitochondrial distribution before and after polar body extrusion. Such changes in mitochondrial localization were affected by colchicine and cytochalasin B. Most of mitochondria in the cytoplasm formed cluster-like aggregates before GVBD while they distributed homogeneously after GVBD. **Conclusion** Most mitochondria localized predominantly in the non-cortical region of the cytoplasm of GV stage-oocytes, while the mitochondria-occupied area decreased before GVBD and increased to occupy the entire area of the cytoplasm at GVBD by some cytoskeleton-dependent mechanism.

ISP-11-11

Molecular detection of intrauterine microbial colonization in women with endometriosis Khaleque Khan[1], Akira Fujishita[2], Michio Kitajima[3], Hideaki Masuzaki[3], Jo Kitawaki[1]
Kyoto Prefectural Medical University[1], Saiseikai Nagasaki Hospital[2], Nagasaki University[3]

Objective Increased intrauterine microbial colonization by bacteria culture method has been reported in women with endometriosis. Here we investigated microbial colonization in intrauterine environment and cystic fluid of women with and without endometriosis by molecular approach. **Methods** This study was conducted under an approved protocol (No. 26011). With informed consent, a total of 32 women each with and without endometriosis were enrolled. Among them, 16 in each group received treatment with GnRHa. Pattern of microbial colonization in endometrial swabs and endometrioma/non-endometrioma cystic fluid was examined using broad-range polymerase-chain reaction (PCR) amplification of bacteria targeting 16S rRNA gene (rDNA). After quantification of index PCR product, 16S rDNA metagenome sequence analysis was done by Illumina Miseq system. **Results** A wide proportion (0.01-97.8%) of multiple bacteria was detected in both endometrial swabs and cystic fluid. 16S metagenome assay indicated that proportion of Lactobacillacae was significantly decreased ($p<0.01$) and of Streptococcaceae, Staphylococaceae, Enterobacteriaceae was significantly increased ($p<0.05$ for each) in GnRHa-treated women with endometriosis than in GnRHa-untreated women. While bacteria culture method failed to detect a single colony, 16S metagenome assay could detect significantly higher percentage of Streptococcaceae ($p<0.01$) and Staphylococaceae ($p<0.05$) in the cystic fluid derived from women with ovarian endometrioma comparing to that in cystic fluid collected from non-endometrioma cysts. **Conclusion** These findings indicate the occurrence of sub-clinical infection in intrauterine environment and in the cystic fluid of ovarian endometrioma. Additional side effect of GnRHa treatment in promoting silent intrauterine and/or ovarian infection should be considered.

ISP-11-12

Enhanced miR-132 expression promotes the pathogenesis of endometriosis through activation of AKT serine/threonine kinase 1 Yoko Aoyagi[1], Kaei Nasu[2], Kentaro Kai[1], Tomoko Hirakawa[2], Kanetoshi Takebayashi[2], Hisaishi Narahara[2]
Nakatsu Municipal Hospital[1], Oita University[2]

Objective Accumulating evidence indicates that microRNA aberrations are involved in the pathogenesis of endometriosis. We performed a microRNA microarray analysis to investigate the differences between normal endometrial stromal cells (NESCs) and endometriotic cyst stromal cells (ECSCs). We focused on the microRNA miR-132, which is overexpressed in ECSCs compared to NESCs. The purpose of this study was to evaluate the involvement of miR-132 in the pathogenesis of endometriosis. **Methods** NESCs and ECSCs were isolated from ovarian endometriotic tissues and eutopic endometrial tissues, respectively. The expression of miR-132 mRNA in ECSCs and NESCs was examined by real-time RT-PCR. We explored an existing database (TargetScan Release 7.1) for functional candidates of miR-132, and found AKT serine/threonine kinase 1 (Akt1). The expressions of Akt1 mRNA and protein in miR-132-transfected NESCs were examined by real-time RT-PCR and western blot, respectively. Migration capacity in miR-132-transfected NESCs was examined by wound healing assay. **Re-**

sults The expression of miR-132 mRNA was upregulated in ECSCs compared to that in NESCs. The expression of Akt1 mRNA in miR-132-transfected NESCs was attenuated. Conversely, that of phospho-Akt1 protein was upregulated. The compulsory expression of miR-132 in NESCs was found to enhance migration capacity. **Conclusion** Phospho-Akt1, the active form of Akt1, is involved in cell motility, proliferation and survival, and demonstrates high expression in most cancerous tissues. The compulsory expression of miR-132 in NESCs, which mimic ECSCs, induced high expression of phospho-Akt1 and enhanced cell migratory capacity, suggesting that miR-132 is involved in the acquisition of cancer hallmarks in endometriotic cells through Akt1 activation.

ISP-11-13

Effect of menopause on expression of progesterone receptor in ampulla of the fallopian tube Takayuki Uchimura, Rie Urabe, Taeko Ueda, Tomoko Kurita, Seiji Kagami, Toshinori Kawagoe, Toru Hachisuka *University of Occupational and Environmental Health*

Objective An age-related change of the expression of hormonal receptors has not been well examined in fallopian tube. We herein described effect of menopause on the progesterone receptor A (PRA) in ampulla of the fallopian tubes (AFTs), in comparison with cortical inclusion cyst (CICs) of the ovary. **Methods** A total of 84 AFTs, including 26 premenopausal and 58 postmenopausal women, and 27 postmenopausal CICs were immunohistochemically studied for progesterone receptor A (PRA) and Ki-67. Apoptotic cells were identified using a TUNEL assay. **Results** In the univariate analysis, the labeling index (LI) for apoptosis to inversely correlate with menopausal status (P=0.021), and it positively correlated with LI for PRA (P=0.005), while multivariate analyses showed no variable to correlate with apoptosis. No significant correlation of immunohistochemical makers was found in premenopausal AFTs, but LI for PRA was positively correlated with that for Ki-67 (P=0.004) in postmenopausal AFTs. Among postmenopausal cases, the expression of PRA in CICs were significantly higher than that of PRA in AFTs (P=0.001). **Conclusion** Low expression of PRA in postmenopausal AFTs has a similar feature as that of PRA of high-grade serous carcinoma, while almost cases of CIC showed high expression of PRA.

ISP-12-1

The vector synthesis high-resolution electrocardiography, ANP and NT-proBNP for estimation of cardiac load in the normal pregnancy Shino Tanaka, Rie Oyama, Hideyuki Chida, Gen Haba, Yuri Sasaki, Tomonobu Kanasugi, Chizuko Isurugi, Akihiko Kikuchi, Akimune Fukushima, Toru Sugiyama *Iwate Medical University*

Objective We analyzed the atrial natriuretic peptide (ANP), the N-terminal pro B-type natriuretic peptide (NT-pro BNP) and the vector synthesis high-resolution electrocardiography, to estimate cardiac load with the circulatory dynamic change through the postpartum from normal pregnancy. **Methods** The subjects were singleton pregnant women (n=19), who were divided three stages 1 (34~36 weeks of gestation), stage 2 (2~6 days postpartum), and stage3 (1~3 months) that was after delivery. We preformed the vector synthesis high-resolution electrocardiography and measured ANP and NTproBNP. **Results** The two-dimensional distribution map of the RTc dispersion markedly were comprised in I+II on all cases. The ANP levels in stages 1, 2, and 3 were 23.2±2.4 pg/mL, 58.4±14.0 pg/mL, and 23.8±4.4 pg/mL. Stage 2 was higher than stage 1 and 3 (p=0.001). The NT-proBNP levels in stages 1, 2, and 3 were 37.6±4.0pg/mL, 170.2±27.5 pg/mL, and 41.6±10.0pg/mL that stage 2 was significant higher than the standard in stage 1 and 3 ($P<0.0001$). The ANP and NT-proBNP levels in stages 2 were significant higher than stage 1 and 3. **Conclusion** This study shows that the use of ANP, NT-proBNP and the vector synthesis high-resolution electrocardiography may be effective as a screening test to prevent cardiomyopathy for pregnant and postpartum women. Particularly, the 2D-distribution map of RTc dispersion could display cardiac load regions in normal pregnant and postpartum women as color visualization images.

ISP-12-2

Transition of uterine luminal volume in early pregnancy Yumiko Nishimori, Atsushi Komatsu, Toshio Nakayama, Takayuki Iriyama, Takeshi Nagamatsu, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective According to technological evolution in volume measurement by 3D ultrasound, precise measurement of uterine luminal volume (ULV) in early pregnancy becomes available. However, the clinical significance of ULV in obstetrics is still unknown. This study aimed to determine the transition of ULV in early pregnancy and to make a standard curve of ULV. **Methods** This study was carried out under approval of the ethics committee of our facility. We recruited 77 women with uncomplicated pregnancies between 8 and 17 weeks of gestation. ULV was measured using Voluson E8/S8 (GE Healthcare) virtual organ computer-aided analysis (VOCAL) technique. The VOCAL method calculates volume by rotating a structure around its axis so that at each rotation, an area is traced. At the end of the process, the equipment automatically displays the volume of the structure. We can get 3D volume data easily in a short time (about 30seconds). Data were stored on HDD, we evaluated offline the luminal volume at a later date. **Results** During the early pregnancy, ULV increased with advancing gestational age along with quadratic approximation curve (Uterine luminal volume=$-462.74+6.36\times$gestational age (day)$+0.095$(gestational age (day)$-94.69)^2$ $R^2=0.89$ $P<0.001$). The individual variation was extremely small. **Conclusion** Our findings revealed that ULV in early pregnancy strongly depends on gestational week. As the individual difference of the volume of the fetus and the umbilical cord is thought to be very small, this result suggests that the amniotic fluid volume is regulated tightly in early pregnancy.

ISP-12-3

Uterine cervical elasticity of various cervical regions in normal singleton pregnancy between 14 and 35 weeks' gestation evaluated using shear wave ultrasound elastography Megumi Muto, Takashi Horinouchi, Toshiyuki Yoshizato, Shigeru Inoue, Takaaki Shinagawa, Yutaka Kouzuma, Daizo Hori, Kimio Ushijima *Kurume University Hospital, Maternal and Perinatal Medical Center*

Objective To quantitatively analyze the elasticity of various regions of the normal uterine cervix using shear wave ultrasound elastography. **Methods** Our subjects consisted of 129 cases of normal singleton pregnancy between 14-35 weeks' gestation, cared for at our hospital in July and August of 2016. The shear wave speed (SWS) of the cervix was measured using transvaginal ultrasound equipment (Aplio 500, Toshiba). Samplings were taken at 4 different stages of gestation (14-19, 20-25, 26-31 and 32-35 weeks' gestation), from the anterior (A), posterior (P), and cervical canal (C) on sagittal sections of the cervix in both the external os (EO) and internal os (IO) regions. Measurements were considered adequate when the shear wave propagation was regular. For each age-group, rates for detecting adequate measurements and SWSs were compared between sampling points using the χ^2 and Kruskal-Wallis tests, with the Wilcoxon

test as a post-hoc test. Significance was set at $p<0.05$. **Results** Rates for detecting adequate measurement of A/C in EO/IO were higher than those for P in all age-groups (98.4/96.1%, 90.7/76.5%, and 82.9/64.3% for A/C/P, respectively). As for EO, SWSs showed no difference in any region, for any age-group. In IO however, the mean SWSs of P/C were higher than those of A at 14–19 and 20–25 weeks (2.55/2.07 vs. 2.88/2.49 vs. 2.97/2.9 m/sec at 14–19/20–25 weeks for A/C/P, respectively), but there were no differences at 26–31 and 32–25 weeks. **Conclusion** The polarity of cervical elasticity in the internal os is lost after 26–31 weeks, suggesting an early physiological process of cervical maturation.

ISP-12-4

Gestational age-related changes in uterine cervical elasticity in normal pregnancy at 14–35 weeks' gestation evaluated using shear-wave ultrasound elastography Takashi Horinouchi, Megumi Muto, Toshiyuki Yoshizato, Yutaka Kouzuma, Takaaki Shinagawa, Shigeru Inoue, Daizo Hori, Kimio Ushijima *Kurume University Hospital*

Objective To analyze the gestational age-related changes in elasticity of the normal uterine cervix at 14–35 weeks' gestation, using shear-wave ultrasound elastography. **Methods** The subjects consisted of 163 cases of normal singleton pregnancy at 14–35 weeks' gestation, cared for in our hospital July-August, 2016. The shear-wave speed (SWS) of the cervix was measured using transvaginal ultrasound equipment. On the sagital section of the cervix, samplings were taken from the anterior/posterior cervix and the canal at levels of the external and internal os (EO/IO) at different stages representing four age-groups (14–19, 20–25, 26–31 and 32–35 weeks). The gestational age-related changes of the SWS at each point were analyzed using Spearman's linear regression analysis and the Mann-Whitney *U*-test. The significance was set at $p<0.05$. **Results** At each point, the relationship between SWS and gestational age showed a negative correlation with linear fashion. The SWSs of the cervical canal at the IO were higher than those at the EO until 20–25 weeks (3.73 vs 2.88, 3.02 vs 2.59, 2.72 vs 2.08 m/sec (mean), respectively), but showed no difference thereafter. The SWSs of the posterior cervix at the IO were higher than those at the EO until 26–31 weeks (4.48 vs 2.69, 3.49 vs 2.79, 3.10 vs 2.18, 2.83 vs 2.13 m/sec respectively), but showed no difference at 32–35 weeks. **Conclusion** In normal pregnancy, the uterine cervix softens in advancing gestation and differences in cervical elasticity between the internal and external os of the canal and posterior cervix disappear after 26 and 32 weeks, respectively.

ISP-12-5

Transition of fetal presentation during pregnancy Yu Takahashi, Takeshi Nagamatsu, Rieko Shitara, Seisuke Sayama, Toshio Nakayama, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

Objective Breech presentation is a common indication for caesarean section. Forecasting of final fetal presentation is important to give information on expected mode of delivery for pregnant women. This study aimed to gain knowledge on prediction of the final fetal presentation during pregnancy. **Methods** This study was conducted under approval of the ethics committee of our hospital. The records of fetal presentation at 24 wks and later were collected in 103 uncomplicated pregnancies (4 breech and 99 cepharic deliveries) managed in our hospital in 2015. Among those cases, spontaneous transition of fetal presentation was analyzed prospectively. Next, 100 cases in which elective cesarean section was scheduled for non-cephalic presentation from 2014 to 2015 was added to the previous 103 cases. Totally, 203 cases were separated into two groups by fetal presentations at delivery, cepharic (group CD) and non-cepharic (group NCD) deliveries. Fetal presentation at different gestational weeks was compared between the two groups retrospectively. **Results** Frequency of non-cepharic presentation decreased from 38% at 24 wks to 4% at delivery. Parity did not affect the frequency of cepharic presentation. In group CD, the frequency of non-cepharic presentation rapidly reduced at after 30 wks. In group NC, the non-cephalic rates were around 60% until 26 wks and stayed above 90% after 30 wks. Statistical difference of non-cepharic rate between the two groups was confirmed at 26 wks and later ($p<0.05$). **Conclusion** Our results suggest that the prediction of fetal presentation at delivery is associated with the findings at 26 wks and later.

ISP-12-6

Anxieties are strongly associated with postnatal depression in primiparous women Saiko Urayama, Akiko Ueda, Kei Okamoto, Masaaki Nakano, Takefumi Akagi *Miyoshi Central Hospital*

Objective Although postnatal depression is a common disorder, evidence on its characteristics and prevalence in Japan is limited. This study aimed to determine the prevalence and the associated factors of postnatal depression in Miyoshi City, Japan. **Methods** A Community-based cross-sectional study was conducted among 158 consecutively recruited pregnant women. Depression symptoms were evaluated using the Edinburgh Postnatal Depression Scale (EPDS), with postnatal depression defined as an EPDS score of ≥ 9. Statistical analysis was performed using one-way ANOVA and the chi-square test to examine differences in the mean values between women with postnatal depression and healthy. **Results** The prevalence of postnatal depression was 13.9%. All questionnaire item scores were significantly higher in women with postnatal depression than in healthy women. The scores were particularly high for Q3 "I have blamed myself unnecessarily when things went wrong" (2.0 ± 0.44 vs. 0.73 ± 0.81), Q6 "Things have been getting on top of me" (2.0 ± 0.69 vs. 0.99 ± 0.73), and Q4 "I have been anxious or worried for no good reason" (1.59 ± 0.73 vs. 0.36 ± 0.66; all $p<0.001$). Postnatal depression was significantly more prevalent among the primiparous women than among the multiparous women (20.3% vs. 9.0%, $p<0.05$). **Conclusion** The prevalence of postnatal depression was high, particularly among the primiparous women. Anxieties were strongly associated with postnatal depression. For the early identification and proper intervention, screening during routine postnatal care should be encouraged. Consideration should be given to establishing integrated support involving the obstetrics and pediatrics departments and the regional public health service.

ISP-12-7

Common marmoset as an animal model in pregnancy associated plasma proteins—PZP, A2ML1, PSG— Hirofumi Kashiwagi, Shunichiro Izumi, Mari Shinoda, Yoshihiro Nishijima, Takahiro Suzuki, Hitoshi Ishimoto, Mikio Mikami *Specialized Clinical Science, Tokai University School of Medicine*

Objective During pregnancy, the pregnancy associated proteins are induced for the maintenance of pregnancy. While the expression of pregnancy-zone-protein (PZP) and pregnancy-specific-beta1-glycoprotein (PSG) is highly enhanced more than hundred times in the sera of pregnant women, alpha-2-macroglobulin-like-1 (A2ML1) is not enhanced in the sera, although PZP and A2ML1 belong to the same A2M family. Moreover it is not well known how those proteins contribute to the maintenance of pregnancy. This study aimed to identify the structural and localized feature of those pregnancy associated proteins and

to figure out how the expression of those proteins changed in the evolution of primate pregnancy. **Methods** We focused on human and Common marmoset (CM). According to the research protocol approved by IRB, this research was performed. PZP, A2ML1 and PGS mRNA in the placenta were detected by reverse transcription polymerase chain reaction (RT-PCR). The protein levels in the plasma were analyzed by liquid chromatography-mass spectrometry (LC-MS). **Results** In human placental tissues, the mRNA of PZP, A2ML1 and PGS were detected. In the maternal plasma, PZP and PSG proteins but not A2ML1 protein were detected. In the CM, placental tissues expressed the mRNA of A2LM1 and low level of PZP. Only A2ML1 protein was detected in the plasma. **Conclusion** In human, PZP, A2ML1 and PSG were expressed during pregnancy, but CM almost exclusively expressed A2ML1 gene. PZP and A2ML1 proteins have been conserved in the primate evolution and suggesting they function alternatively. To analyze the common function of A2M family in pregnancy may support elucidating the preservation of the primate species.

ISP-12-8

Is pregnancy with ART associated with deteriorated delivery course in advanced age primiparous pregnancy? Kenji Kishida, Takahiro Yamashita, Aya Fuchioka, Noriko Yuzawa, Eiji Shuri, Nobuko Akamata, Rie Oi, Yukiko Kawana, Yoshiharu Takeda, Tomoko Adachi, Takashi Okai, Masao Nakabayashi *Aiiku Hospital*

Objective The pregnancy of advanced age women who got pregnant with assisted reproductive technology (ART) has been increasing worldwide. In this study, we analyzed whether pregnancy with ART was associated with deteriorated delivery course in advanced age primiparous women. **Methods** We analyzed retrospectively the chart of the 141 primiparous women who were over 40 years old and delivered between October 2015 and May 2016 in our hospital. Multiple pregnancy and pregnancy with donated eggs were excluded. Indices of delivery were compared between the pregnant women who got pregnant with and without ART. Fisher's exact test, Mann-Whitney U test, or t-test were used. **Results** Delivery time required was significantly longer in the pregnancy with ART than without ART (10.9 ± 6.2 v.s. 7.0 ± 4.6 hours, $p=0.02$). No significant differences were observed in the occurrence rate of PIH, GDM, threatened abortion, threatened labor, emergent cesarean delivery, and vacuum or forceps delivery. No significant differences were observed in the amount of blood loss, delivery weeks, UApH, and weight of the newborns. **Conclusion** In the advanced age primiparous women, delivery time was significantly longer in vaginal delivery cases after pregnancy with ART than without ART. However, no serious perinatal risks were increased in the pregnancy with ART.

ISP-12-9

Detection of optimal weight gain during pregnancy calculated by height and prepregnancy body mass index for reducing delivery of small-for-gestational-age infants : A large retrospective cohort study Arihiro Shiozaki, Masanori Yoshie, Mika Ito, Noriko Yoneda, Satoshi Yoneda, Shigeru Saito *University of Toyama*

Objective The aim of our study was to evaluate maternal risk factor for the delivery of small-for-gestational-age (SGA) infant and to examine optimal gestational weight gain (GWG) to reduce the delivery of SGA infant. **Methods** We used the Perinatal Registry Database of the Japan Society of Obstetrics and Gynecology from 2005 to 2011, with information about height, prepregnancy body mass index (BMI), and BMI at delivery (N=273,953). After determining the risk ratio of SGA infant delivery with the result of multivariate analysis of the maternal risk factors for the delivery of SGA infant, we calculated the GWG so as to keep the risk ratio equal to one. **Results** Preeclampsia, gestational hypertension, chronic hypertension, smoking, lower prepregnancy BMI, and lower BMI gain during pregnancy were risk factors for SGA. As feasible plan, to quit smoking and to have an adequate weight gain to each case are warranted. Then we have calculated the optimal weight gain for each prepregnancy BMI and height so that we could easily recommend the best weight gain during pregnancy. For a pregnant 150 cm-tall or 160 cm-tall woman with prepregnancy BMI of 18, 21, and 25 kg/m^2, the optimal GWG were 12.2, 9.0, and 4.7 kg, or 13.9, 10.2, and 5.4 kg, respectively. **Conclusion** To quit smoking and to keep the optimal GWG for one's height are recommended to reduce the delivery of SGA infants.

ISP-12-10

The role of Pbk in pancreas β cell proliferation during pregnancy Tadayoshi Uesato, Atsuo Itakura, Satoru Takeda *Juntendo University*

Objective Pancreatic β cells proliferate during pregnancy to compensate insulin resistance. According to microarray analysis, we found that an expression of PDZ binding kinase (Pbk) was increased in pregnant mouse islets compared with non-pregnant islets. As previous studies have shown that Pbk contributes malignant tumor growth through modification of p53 and p21 pathway, we investigated the role of Pbk in β cells proliferation. **Methods** After disturbance of Pbk expression in mouse insulinoma MIN6 cells by RNA interference, cell proliferation using BrdU incorporation were evaluated. Mouse islets from pregnant and non-pregnant mice treated with Pbk inhibitor, HI-TOPK-032. Expressions of molecules regulating cell cycle were analyzed by quantitative RT-PCR and western blotting. **Results** The augmentation of Pbk in pregnant mouse islets was confirmed by quantitative RT-PCR and immnoblotting. Pbk knockdown reduced BrdU incorporation in MIN6 cells, which was accompanied with increases of p53. Whereas the treatment with HI-TOPK-032 increased p53, the expression of Cdkn1a coding p21 demonstrated no remarkable changes in MIN6 cells. Therefore we measured expressions of the genes regulating cell cycle, and identified that Ccnb1 expression was attenuated by Pbk knockdown as well as HI-TOPK-032 treatment. Consistent with our results using MIN6 cells, Ccnb1 expression was upregulated in mouse islets during pregnancy. Also HI-TOPK-032 treatment inhibited Ccnb1 expression in islets isolated from pregnant mice. Finally, we found that estradiol upregulated Pbk expression in mouse islets. **Conclusion** Our results suggest that Pbk would contribute β cells proliferate during pregnancy through modification of Ccnb1 expression.

ISP-12-11

Impact of group prenatal care on pregnancy weight gain and postpartum weight loss Krystilyn Washington[1], Teresa Janevic[2,3], Lisa Gittens-Williams[1] *Rutgers University- New Jersey Medical School, USA[1], Rutgers University-School of Public Health, USA[2], Icahn School of Medicine at Mount Sinai Department of Population Health Science and Health Policy, USA[3]*

Obesity is associated with increased maternal and fetal morbidity and mortality. Weight gain in pregnancy above the Institute of Medicine (IOM) guidelines is associated with increased weight retention and decreased postpartum weight loss. A retrospective cohort study of obese and/or diabetic pregnant women who received prenatal care at University Obstetrics Associates, Newark, NJ was performed. Subjects enrolled in the Lifestyle pregnancy, a group model of care based on the Centering Pregnancy™ concept, comprised the study group ; subjects

who received traditional prenatal care were controls. Data on prenatal weight gain and postpartum weight loss were abstracted from medical records. There were 24 women in the study group and 48 in the control group. Mean pregnancy weight gain was 13.5 lbs (study group) (95% CI, 6.4–20.9 lbs) and 15.7 lbs (control group) (95% CI, 10.4–21.0 lbs) (p=0.65). Fifteen (73.3%) obese women (study group) and 42 (78.6%) obese women (control group) gained no more than 20 lbs, recommended by the IOM (p=0.68). Mean weight loss at the postpartum visit was −21.1 lbs (study group) (95% CI, −27.6–14.6 lbs) and −15.7 lbs (control group) (95% CI, −21.0 – −10.4 lbs) p=0.22. Among obese women, mean weight loss at postpartum visit was −23.4 lbs (study group) (95% CI −33.8 −13.0 lbs) and −15.5 lbs (control group) (95% CI −21.6 – 9.4 lbs) p=0.18. Preliminary findings suggest group prenatal care may be beneficial for management of pregnancy weight gain and postpartum weight loss in obese women, but a larger study is needed for conclusive results.

ISP-12-12

A Herniated Term Gravid Uterus from Previous Scar : A Case Report Katrina Albano, Nepthali Gorgonio, Ma. Cristina Fabella *Amang Rodriguez Memorial Medical Center, Philippines*

This is a case of a 43-year-old pregnant woman with unrepaired incisional hernia from a previous cesarean section. As her pregnancy progressed, there was gradual herniation of the enlarging gravid uterus through the previous abdominal scar. On her first consult at 35 weeks of gestation, an ultrasound done highly considered abdominal pregnancy. Upon thorough investigation of the patient's past medical and surgical history and her present findings, incisional hernia was confirmed. This patient underwent a repeat cesarean section and hysterectomy, followed by herniorrhaphy. For a rare condition such as this, each case should be individualized.

ISP-12-13

Undernourishment *In Utero* Primes Hypertrophy As Well As Enlargement Of Lipid Droplets In The Hepatocytes Of The Mice Offspring Under Obesogenic Diet Jeenat Ferdous Urmi, Keiko Muramatsu, Yukiko Kohmura, Chizuko Yaguchi, Toshiyuki Uchida, Kazunao Suzuki, Hiroaki Itoh, Naohiro Kanayama *Hamamatsu University School of Medicine*

Aim Recently we reported that the undernourishment *in utero* primes hepatic steatosis under obesogenic diet. Therefore to study the mechanism underlying we aimed to study the cell size and ratio of lipid deposition in the hepatocytes of undernourishment *in utero*. **Method** The study included sampling of blood and liver of CN57Bl mice (n=8) aged 17 weeks of age, pups (A group ; n=4) obtained from dams with free access to food (NN) and pups (B group ; n=4) from dams with 40% caloric restriction (UN). After weaning (upto 8 weeks) pups were fed high fat diet (HFD). Liver weight (gm), liver weight-bodyweight ratio (%), Triglyceride content (mg/gm tissue), total Triglyceride (mg) were measured. Slides were stained with Hematoxylin and Eosin (HE) and Oil Red O stain. Using WinRoof software we have calculated (in 3.88mm^2 field per slides) the mean size (μm^2) of the hepatocyte, percentage of the area of lipid deposition per cell size (%) and area of lipid deposition per cell numbers (μm^2/cell number). **Result** Liver weight, liver weight-bodyweight ratio, Triglyceride content and total Triglyceride amount ($P < 0.001$) was significantly elevated in group B. Hepatocyte size in the B group (mean size=1886 ± 206 (SD) μm^2, n=4) was significantly higher than A group (mean size=1450 ± 177 μm^2, n=4, $P < 0.05$). Oil Red O stained area measured revealed increase lipid deposition in B pups (42.2 ± 6.7%, n=4) than L pups (34.1 ± 8.7%, n=4, $p < 0.01$). **Conclusion** Undernourishment *in utero* significantly enlarged hepatocyte and aggravated intercellular lipid deposition in later life.

ISP-13-1

Timing is everything : What is the optimal timing to evaluate placenta accreta by magnetic resonance imaging? Aiko Okada, Shinya Matsuzaki, Yasuto Kinose, Tadashi Iwamiya, Kazuya Mimura, Keiichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

Objective Magnetic resonance imaging (MRI) is usually performed to evaluate placenta accretion. However, optimal timing to perform MRI remains unknown. The MRI findings of placenta accreta cases were retrospectively reviewed to identify differences of each finding at different gestational ages. **Methods** From January 2008 to August 2016, a retrospective review of prenatal MRI examinations of 70 patients was conducted to investigate placenta accreta in placenta previa cases. The cases were divided into two groups : MRI performed at <30 weeks gestation (group A) and >30 weeks gestation (group B). This study focused on the characteristic findings of placenta accreta on MRI, such as uterine bulging (UB), heterogeneous placenta (HP), intraplacental T2 dark band (DB), and myometrial thinning (MT). The sensitivity and specificity of each finding were compared between the groups. Two experienced obstetrician who had no knowledge of the pataients clinical data retrospectively evaluated the MR images. **Results** Groups A and B comprised 33 and 37 cases, respectively. The sensitivity of UB, HP, DB and MT was 25%, 43%, 63%, and 43% in group A and 39%, 62%, 54%, and 46% in group B, respectively. The specificity of UB, HP, DB and MT was 100%, 91%, 82%, and 91% in group A and 78%, 82%, 83%, and 64% in group B, respectively. A significant decrease in the specificities of MT and UB were observed in group B. **Conclusion** Specificity was greater for determination of placenta accrete among placenta previa cases by characteristic findings before 30 weeks of gestation.

ISP-13-2

Alteration of TrkB isoform expression in the Fetal growth restriction Akane Kondo[1], Yumiko Goto[2], Daichi Nakaoku[1], Mikio Yamasaki[1], Mikio Morine[1], Kenji Hinokio[1], Kazuhisa Maeda[1] *Shikoku Medical Center, National Hospital Organization[1], Tokai University School of Medicine[2]*

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 remodelling 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 14 cases of FGR and 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. The normal placenta showed reduced expression in Shc binding domain among the 24 exons, and in the non-pregnant endometrium, tyrosine kinase domain was absent. The other domains were expressed in normal placenta and endometrium tissues. **Conclusion** Multiple deficit of exons of TrkB were observed in FGR group. This result indicate that lack of signalling

of BDNF and TrkB would affects a dysfunction of EVT and STB.

ISP-13-3

Double-stranded RNA regulates BCL2 family molecules and induces apoptosis in human cultured syncytiotrophoblasts via toll-like receptor 3. A possible mechanism for pregnancy complications? Kenichiro Motomura[1], Haruhiko Sago[2] *National Research Institute for Child Health and Development[1], National Center for Child Health and Develpment[2]*

Objective Immune responses of the placenta mediated via toll-like receptors (TLRs) reportedly cause pregnancy complications. However, the molecular mechanisms involved are not fully understood. Here, we investigated apoptosis-related immune responses in syncytiotrophoblasts (STB) derived from term placenta-derived human cytotrophoblasts(CTB). **Methods** This study was approved by the ethics board of our institute. STB were obtained by culturing purified CTB derived from term uncomplicated human placentas in the presence of Y27632, EGF and FBS for 96 hours. Cultured STB were exposed to various TLR ligands. Then expression of mRNA for TLRs and BCL2 family proteins was analyzed by qPCR, and IL6 production was assayed by ELISA. TLR3 protein expression was detected by flow cytometry. Cell death was analyzed by caspase activity assay. **Results** Cultured STB predominantly expressed TLR3 mRNA and protein and produced greater amounts of IL6 after stimulation with poly I：C (TLR3 ligand) than with other TLR ligands. Only poly I：C stimulation induced caspase-dependent cell death in STB. Poly I：C stimulation of STB reduced BCL2 (apoptosis inhibitor) mRNA expression, while it increased NOXA, PUMA and BIK (apoptosis initiators) mRNA expression. **Conclusion** In placental immune responses to viruses, TLR3 modulates BCL2 family proteins and induces apoptosis, and may culminate in pregnancy complications.

ISP-13-4

The expression of syncytin 2 signaling genes in the differentiation process of cytotrophoblast into syncytiotrophoblast Kazuki Morita[1], Takeshi Nagamatsu[2], Seisuke Sayama[2], Takayuki Iriyama[2], Atsushi Komatsu[2], Yutaka Osuga[2], Tomoyuki Fujii[2] *Graduate School of Medicine, The University of Tokyo[1], Faculty of Medicine, The University of Tokyo[2]*

Objective In human placenta, differentiation from villous cytotrophoblasts (CTs) into syncytiotrophoblast (ST) is regulated by elaborated functions of numerous genes. MFSD2A plays an essential role in fatty acid transport in the brain. The function of MFSD2A in the placenta is unique and work as a receptor for syncytin 2, a transcript of retrovirus-derived gene (ERVFRD-1)to support syncytialization. This study aimed to clarify the detail of MSFD2A and ERVFRD-1 gene actions during syncytialization process. **Methods** This study was conducted under approval of the ethics committee in our facility. CTs isolated from term placentas with high purity were differentiated into ST in culture. Total RNA was extracted at three distinctive time points；day 1 (before fusion), day 2 (fusion progressing) and day 4 (fusion completed). The gene expression status in each time point was evaluated using RNA sequence and the expressions of MSFD2A and ERVFRD-1 were analyzed. **Results** Upregulation of CGB, LGALS13 and ERVW-1 was confirmed in the syncytialization, mimicking known in-vivo process. The expression level of MFSD2A was remarkably increased in the syncytialization, 7 times at day 2 and 30 times at day 4, compared with day1. In contrast, the expression of ERVFRD-1 was not significantly affected in the progress of syncytialization. **Conclusion** Syncytialization process was associated with the up-regulation of MFSD2A, but not with ERVFRD-1 expression. Our findings imply that syncytialization might be regulated by the expression level of MFSD2A rather than syncytin 2, a gene product of ERVFRD-1.

ISP-13-5

Management of placenta previa regarding operative timing of gestational age Aki Takase, Hiroko Katayama, Sakika Yanai, Natsuko Yokoi, Akihiro Hamuro, Takuya Misugi, Akemi Nakano, Daisuke Tachibana, Masayasu Koyama *Osaka City University*

Objective Placenta previa has high risk of massive bleeding, so it is recommended to schedule cesarian section by the end of 37 gestational weeks. The aims of this study are to compare the perinatal outcomes of the patients and neonates complicated with placenta previa. **Methods** The study period was between January 2012 and September 2016. The patients were divided into two groups；group A, the patients were admitted at 32 gestational weeks (GW) underwent cesarean section (CS) at 36 GW：group B, the patients were admitted at 33 GW underwent CS at 37 GW. The patients with multiple gestation or placentation at previous CS scar were excluded. The perinatal outcomes were compared between the groups using statistical analysis correctly. **Results** Fifty eight patients were contained in group A and 13 patients were in group B. There was no significant difference in rates of emergent operation, storage of autologous blood, blood loss during operation, Apgar score at 5 min, pH of umbilical artery, birth weight, and neonatal hypoglycemia. Respiratory supports were required significantly higher in group A ($p<0.01$；68%, and 13%, group A and group B, respectively). **Conclusion** Neonatal outcomes seemed to be improved in groups B, although maternal outcome is not affected. Scheduled CS at 37 GW may be recommended for usual cases complicated with placenta previa.

ISP-13-6

The obstetric complications and outcomes related to singleton pregnancies after embryo transfer Yusuke Kurokawa, Yutaka Kouzuma, Toshiyuki Yoshizato, Kunio Sou, Takashi Tachibana, Koru Goto, Daizo Hori, Kimio Ushijima *Kurume University Hospital Maternal and Perinatal Medical Center*

Objective The cases with pregnancy after embryo transfer (ET) are considered high risk pregnancies. The aim of this study is to determine the obstetric complications and outcomes related to the singleton pregnancy after ET. **Methods** The subjects were 1,733 cases of singleton pregnancy delivery at >22 weeks' gestation in our hospital between January 2013 and December 2015. There were 120 cases with ET (ET group) and 1,613 cases without ET (non-ET group). Both groups were compared with patients' characteristics, obstetric complications and outcomes. The comparisons of obstetric complication and outcome was done by using a univariate logistic regression analysis when $P<0.2$. A multivariate logistic regression analysis was made to determine the independent factors associated with ET. The significance was set at $P<0.05$. This study was approved by the Institutional Review Board of our hospital. **Results** The percentages of the cases with the maternal age of >35, primipara and smoking history were higher in ET than non-ET group. The independent factors regarding obstetric complication and outcome related to the singleton pregnancy after ET were the abnormal site of cord insertion including marginal insertion and velamentous insertion of the cord ($P=0.0017$, OR：2.79, 95% CI：1.50-4.93) and the blood loss at delivery of >800 ml ($P<0.0001$, OR：3.11, 95% CI：2.00-4.83). **Conclusion** The obstetrical complication and outcome related to the pregnancy after ET were the abnormal site of cord insertion and blood loss at delivery.

ISP-13-7

The association of placental post-transcriptional mRNA modification and fetal growth Kosuke Taniguchi[1], Jo Kitawaki[1], Haruhiko Sago[2], Kenichiro Hata[3] *Kyoto Prefectural University of Medicine[1], National Center for Child Health and Development[2], National Research Institute for Child Health and Development[3]*

Objective Recent studies revealed an abundant of post-transcriptional modifications. N6-methyladenosine (m6A) is one of them and suggested to regulate stability or fates of mRNAs. In perinatology, expression level of the fat mass and obesity-associated gene (*FTO*), which encodes an m6A demethylase, in human placenta have been reported to be positively correlated with birthweight. Thus we examined the association between fetal growth and m6A modification of placental mRNAs. **Methods** We isolated mRNAs from 16 placentas, including 5 appropriate for date (AFD), 6 small for date (SFD), and 5 heavy for date (HFD), and carried out methylated RNA immunoprecipitation followed by comprehensive genome-wide sequencing using next-generation sequencers. Among these groups, we compared amounts of m6A modification in three regions, which are 5' UTR, CDS, and vicinity of stop codon. **Results** m6A modification existed most abundantly in the vicinity of stop codon, while m6 A modification in 5' UTR was highly variable between individuals (correlation coefficient : mean, 5' UTR : 0.68, CDS : 0.81, stop codon : 0.83). Compared to AFD, SFD and HFD had many genes in which m6A modification was significantly increased in each region (numbers of increasing/decreasing genes in 5' UTR, CDS, stop codon, respectively : SFD ; 45/7, 66/28, 80/48. HFD ; 66/9, 101/24, 131/44), especially in 5' UTR. Among these m6A-modified genes, only 4% showed significant difference in mRNA amounts. Conversely, 96% showed higher modification with little change in expression level. **Conclusion** The placentas from SFD and HFD possessed more mRNAs with the modification. We will further analyze its elusive functions and fates involved in pathophysiology.

ISP-13-8

Regulatory mechanism of CD59 expression on human extravillous trophoblast Masashi Ueda[1], Akihito Horie[1], Yukiyasu Sato[2], Hirohiko Tani[1], Yumiko Miyazaki[1], Asuka Okunomiya[1], Ikuo Konishi[3], Noriomi Matsumura[1] *Kyoto University Graduate School of Medicine[1], Otsu Red Cross Hospital[2], Kyoto Medical Center[3]*

Objective In human placenta, although endovascular extravillous trophoblast (eEVT) makes direct contact with complement components contained in the maternal blood, eEVT is not eliminated by their activation. We focused on CD59, which is an 18-20 kDa glycosylphosphatidylinositol-anchored protein. CD59 inhibits the formation of membrane attack complex (MAC), a final product in the complement activation. Previously, we immunohistochemically showed that CD59 expression was higher on eEVT than on interstitial EVT (iEVT) that invades maternal decidua. In this study, we try to find out the factors that regulate CD59 expression on EVT. **Methods** The first-trimester chorionic tissues were obtained from artificial abortions and were subjected to the primary organ cultures to isolate EVT (isolated EVT cells). The isolated EVT cells were cultured in the hypoxic condition mimicking the environment around iEVT. In addition, the isolated EVT cells were treated with cytokines (TGF-β1, IL-1β, and PDGF). Changes in the CD59 expression levels were examined using q-PCR and/or flow cytometry. **Results** CD59 expression on isolated EVT was decreased in the hypoxic condition. No significant differences in CD59 expression were observed after the treatment with the examined cytokines. **Conclusion** High CD59 expression on eEVT may be partly due to the high oxygen environment inside the maternal spiral artery.

ISP-13-9

Sonic hedgehog pathway regulates placental growth factor expression in placenta Hiroshi Takai[1], Eiji Kondo[1], Mai Sato[1], Kaoru Kawasaki[1], Hikaru Kiyokawa[1], Mari Ujita[2], Yoshitsugu Chigusa[1], Haruta Mogami[1], Ikuo Konishi[2], Noriomi Matsumura[1] *Kyoto University Hospital[1], Kyoto Medical Center[2]*

Objective We previously reported that Sonic hedgehog (= Shh) pathway was involved in preeclamptic placentas. The aim of this study is to elucidate the association between Shh pathway and placental growth factor (=PlGF) 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 PlGF 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 PlGF 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. **Results** PTCH 1 and PlGF expressions were significantly down-regulated in preeclamptic placentas ($P<0.0001$, $P=0.0288$, respectively). PTCH1 expressions were correlated with PlGF expressions ($R=0.4821$, $P=0.0313$). PTCH1 expressions were highly correlated with fetal birth weight ($R=0.7807$, $P<0.0001$) and placental weight ($R=0.5839$, $P=0.0069$). PTCH1 and PlGF expressions in CTBs were significantly down-regulated by cyclopamine (n=5, $P=0.0003$, $P=0.0095$) and si-Gli2 (n=5, $P=0.0034$, $P=0.0026$). **Conclusion** Shh pathway may contribute to the regulation of PlGF expression in the placenta.

ISP-13-10

Decreased cell-free but not exosomal miR-518b in maternal plasma is caused by amniocentesis Kiyonori Miura, Ai Higashijima, Shoko Miura, Yuri Hasegawa, Hideaki Masuzaki *Nagasaki University*

Objective To get knowledge of relationship between cell-free and exosomal pregnancy-associated microRNAs in maternal plasma, we investigated their circulating levels before and after amniocentesis. **Methods** In 16 maternal plasma samples collected before and after amniocentesis, circulating levels of cell-free and exosomal pregnancy-associated microRNAs (miR-515-3p, -517a, -517c, -518b, and 323-3p) were measured by real-time quantitative RT-PCR. Changes in the plasma concentration and the association between circulating levels of cell-free and exosomal microRNAs were analyzed. Statistical significance was defined as $P<0.05$. **Results** The plasma concentration of cell-free miR-518b was significantly decreased after amniocentesis (Wilcoxon signed rank test, $P=0.001$), but no significant difference was observed for any other cell-free or exosomal microRNA ($P>0.05$). There was no association between the circulating levels of cell-free and exosomal microRNAs (miR-515-3p, -517a, -517c, -518b) in chromosome 19 microRNA cluster region. However, a significant association was detected between plasma cell-free and exosomal miR-323-3p levels in chromosome 14 microRNA cluster region (r and P values before amniocentesis ; 0.617 and 0.011, those after amniocentesis ; 0.899 and <0.001). **Conclusion** Amniocentesis caused a decreased cell-free but not exosomal miR-518b levels in maternal plasma. Correlations between plasma concentrations of cell-free and exosomal pregnancy-associated microRNAs were different for each microRNA.

ISP-13-11

A case of nonreassuring fetal status associated with umbilical cord thrombosis Yuko Takahashi, Tetsuaki Kaku, Chisato Kunitomi, Takehiro Tsukazaki, Yukari Kanbe, Koichi Hashimoto, Kimihiro Takechi *Showa General Hospital*

Umbilical cord thrombosis is related to fetal and perinatal morbidity and mortality. Recent studies have reported umbilical thrombosis is usually associated with umbilical cord abnormalities that lead to mechanical compression with consequent vascular ectasia. We reports a case of non-reassuring fetal status (NRFS) associated with umbilical cord thrombosis without umbilical abnormality. A 33-year-old woman was referred to our hospital at 28 weeks of gestational age for close examination of her electrocardiogram abnormality. In our examination, no abnormality was found. At 40 weeks, non-stress-test showed loss of variability and then fetal bradycardia was found. Doppler flow analysis did not show any abnormalities in the examination. Emergency Cesarean section was performed. The newborn was male, 3027g, Apgar score 8/8. It was observed that the umbilical cord was black-colored over the length. The histological analysis of placenta and umbilical cord showed thrombosis in umbilical cord and funititis. These results indicated that the thrombosis caused NRFS. It is difficult to differentiate thrombosis of umbilical cord from other diseases that caused NRFS. However, we should carry out precise assessment to decide the time for delivery and postnatal treatment when deterioration of fetal well-being occurred.

ISP-14-1

Characteristics of interventricular shunt flow in fetuses with isolated ventricular septal defect assessed by dual Doppler imaging Takashi Kaji[1], Kazuhisa Maeda[2], Atsuko Hichijo[1], Naoto Yonetani[1], Yohei Takahashi[1], Soichiro Nakayama[1], Minoru Irahara[1] *Tokushima University[1], Shikoku Medical Center for Children and Adults[2]*

Objective Prenatal diagnosis of ventricular septal defect (VSD) can be difficult, even using color Doppler imaging. One reason is that the interventricular shunt flow of fetuses is not as prominent as that of children because of the low pressure difference between ventricles. This study aimed to elucidate the characteristics of the interventricular shunt flow associated with the cardiac phase in fetuses with isolated VSD using dual Doppler imaging. **Methods** We prospectively studied 18 consecutive fetuses that were prenatally diagnosed with isolated VSD. We simultaneously recorded shunt flow across VSD and mitral/aortic flow using dual Doppler. The cardiac cycle was divided into five phases [isovolumetric relaxation time (IRT), early or late filling time, isovolumetric contraction time (ICT), and ejection time] by the mitral/aortic flow waveforms ; further, shunt flow direction and phase were decided. **Results** One fetus with muscular VSD was not evaluated due to difficulty in simultaneous recording of flow signals. The remaining 17 fetuses (11 perimembranous and 6 muscular) were assessed. During IRT, peak right-to-left shunt flow was demonstrated in 16 (94%) fetuses. In ICT and/or early ejection time, 15 (88%) fetuses showed peak left-to-right shunt flow. **Conclusion** This study revealed a commonality of the interventricular shunt flow in isolated VSD fetuses. Right-to-left flow during IRT and left-to-right flow in ICT and/or early ejection time were consistently observed. These shunt flow characteristics can help in prenatal diagnosis of isolated VSD and in understanding the physiology of fetal circulation.

ISP-14-2

Non-essential and branched-chain amino acids differently regulate insulin-like growth factor binding protein-1 production and phosphorylated status in cultured HepG2 cells Kei Tanaka[1], Keiji Sakai[2], Miho Matsushima[1], Yukiko Matsuzawa[1], Tomoko Izawa[1], Takashi Nagashima[1], Seishi Furukawa[1], Yoichi Kobayashi[1], Mitsutoshi Iwashita[1] *Kyorin University[1], South Miyagi Medical Center[2]*

Objective Phosphorylated isoform of insulin-like growth factor binding protein-1 (IGFBP-1) is secreted from fetal liver to inhibit activity of insulin-like growth factor-I (IGF-I) in growth restricted fetus under nutrient deprivation. Deprivation of branched-chain amino acids (BCAAs) is known to induce phosphorylated IGFBP-1 production in hepatic cells, while the role of non-essential amino acids (NEAAs) is unknown. We investigated possible changes in IGFBP-1 production and phosphorylated status induced by NEAAs, and examined its biological and physiological significances in IGF-I effects by using hepatocellular carcinoma cell-line, HepG2. **Methods** Secretion of IGFBP-1 from HepG2 cells under various concentrations of BCAAs and NEAAs were examined by ELISA. Phosphorylated status of IGFBP-1 was investigated by Native-PAGE. Phosphorylation of β-subunits of IGF-I receptors (IGF-IRβ) in HepG2 cells by exogenous IGF-I was evaluated by immunoblot. Glucose uptake into HepG2 cells by IGF-I was also assayed by using 2-deoxyglucose. **Results** Decreased BCAAs and increased NEAAs stimulated phosphorylated IGFBP-1 secretion. Decreased BCAA-to-NEAA ratios also enhanced phosphorylated IGFBP-1 secretion, while the changes in total amino acids (AA) did not affect it. Phosphorylation of IGF-IRβ by IGF-I was inhibited by decreased BCAAs, increased NEAAs, and decreased BCAA-to-NEAA ratios, not by total AA. 2-deoxyglucose uptake by IGF-I were inhibited by decreased BCAA-to-NEAA ratios, not by total AA in the media. **Conclusion** NEAAs and BCAAs differently regulated IGFBP-1 production and phosphorylated status in HepG2 cells. Moreover, the balance of BCAAs and NEAAs was also found to have regulatory effects on IGFBP-1 secretion and phosphorylated status.

ISP-14-3

Prenatal diagnosis of nine cases with supernumerary marker chromosomes Tomona Matsuoka, Osamu Samura, Naoya Kitamura, Haruka Hyuga, Takuma Sato, Akiko Konishi, Michihiro Yamamura, Momoko Inoue, Eri Yoshii, Yuki Ito, Hiroaki Aoki, Aikou Okamoto *The Jikei University School of Medicine*

Objective Small supernumerary chromosomes are marker chromosomes that cannot be unambiguously identified by chromosome banding techniques alone. However, the precise characterization of supernumerary marker chromosomes (SMCs) is important for prenatal diagnosis and proper genetic counseling. In this study, we investigated the clinical characteristics and fetal prognosis of SMCs detected by amniocentesis and chorionic villus sampling in a single institution. **Methods** The clinical records of pregnant women with fetal SMCs between April 2010 and September 2016 were reviewed. **Results** In a series of 1492 patients for whom cytogenetic analysis was requested, nine (0.6%) cases with SMCs were identified. The indications of seven cases were elderly pregnancies and of two cases were anomalies found in ultrasound imaging. Of the nine cases with SMCs, six were mosaic and three were nonmosaic. Of the seven cases with known parental origins, six were identified as de novo and one was maternally inherited. Two patients decided to terminate their pregnancies. There was one intrauterine fetal death at 14 weeks, and six patients had live births. Of these six babies, five had no severe complications ; however, one had multiple congenital anomalies. **Conclusion** Fetuses with SMCs have a wide spectrum of characteristics depending on their origin, thus making it important to identify them as soon as possible. It is also important to give proper genetic counseling to the

patients individually.

ISP-14-4

Therapeutic effects of CD133+ cells derived from human umbilical cord blood in a neonatal-immunodeficient mouse model of hypoxic-ischemic encephalopathy Yukie Kidani, Hiroshi Miyoshi, Takako Sadakane, Shiori Shinagawa, Norifumi Tanaka, Yoshiki Kudo *Hiroshima University*

Objective Hypoxic-ischemic encephalopathy (HIE) is a major cause of cerebral palsy in full-term infants. Recently, stem cell therapies have been used in several fields of medicine. We previously reported that $CD133^+$ cells, derived from human umbilical cord blood, induce nerve extension in an ex vivo hypoxic encephalopathy model. Here, we further investigated the therapeutic potential of $CD133^+$ cells using an in vivo neonatal mouse HIE model. **Methods** The Rice-Vanucci method was applied to neonatal SCID mice and $CD133^+$ cells were administrated by intraperitoneal injection to these mice 24h after hypoxic-ischemic injury. Motor function (Rotarod test) analysis, histological examination and immunohistochemical analysis were assessed on day 56. **Results** Motor function improved in $CD133^+$ cell-treated animals. Left (lesioned) and right (nonlesioned) hemisphere size was approximately the same in the sham-operated group at postnatal day 56. Large cystic lesions were found in the left hemisphere of mice with HIE by histological examination. These cysts contained several macrophage foci, and microglia were found in the surrounding area. Cystic lesions in the $CD133^+$ group were much smaller than those in the HI group. In addition, no or few macrophages around cystic lesions of the injured brain were found in the $CD133^+$ group. **Conclusion** These results indicated that peritoneal administration of $CD133^+$ cells derived from human umbilical cord blood may have therapeutic effects on neonatal HIE.

ISP-14-5

Telediagnosis system for congenital heart disease in a prefecture Aki Mabuchi, Tadahiro Yasuo, Miyoko Waratani, Haruo Kuroboshi, Koichi Iwasa, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Objective Spatiotemporal image correlation (STIC) is a three-dimensional technique for acquisition of volume data from fetal hearts. In 2009, we have constructed the world's first STIC-based telediagnosis system for a prefecture. This study aimed to evaluate the accuracy of prenatal diagnosis performed through the telediagnosis system at a single tertiary referral unit over a seven-year period. **Methods** This was a retrospective study of fetuses with suspected congenital heart disease (CHD) from 2009 to 2015. Three-dimensional ultrasonographic images, obtained at six referral hospitals in our prefecture, were forwarded to our hospital through an optical fiber network system and saved on hard disk. The STIC images were analyzed using the ViewPal software. The main outcome was accuracy of prenatal diagnosis instead of the presence or absence of CHD. **Results** During the seven year period, 108 cases were transferred and 16 were excluded because of unavailability of data or unclear images by STIC. The accuracy of prenatal diagnosis was 96.7%. The prevalence of CHD was 9.8% (9/92). The diagnosis of seven cases was same as the antenatal diagnosis, and two cases were diagnosed as ventricular septal defect after birth. Moreover, the prenatal detection rate of major CHDs that were either surgically treated or resulted in perinatal mortality was 100%, and the patients in these cases delivered at our hospital. **Conclusion** Our telediagnosis system contributes to the accurate prenatal diagnosis of CHDs and management of pregnancies for patients who are geographically remote from the tertiary referral hospital.

ISP-14-6

Eye movement activity in normal human fetuses between 24 and 39 weeks of gestation Hikohiro Okawa, Seiichi Morokuma, Kana Maehara, Yasuyuki Fujita, Kiyoko Kato *Kyushu University*

Objective Rapid eye movement (REM) sleep occurs throughout a relatively large proportion of early development, and normal REM sleep is required for healthy brain development. The eye movements (EMs) observed during REM sleep are the most distinctive characteristics of this state. EMs are used as an index of neurological function postnatally, but no specific indices of EM activity exist for fetuses. The present study aimed to identify and characterize EM activity, particularly EM bursts suggestive of REM periods, in fetuses with a gestational age between 24 and 39 weeks. **Methods** The study population consisted of 85 normal singleton pregnancies. Fetal EMs were monitored using real-time ultrasonography for 60 min and then recorded as video. The video recordings were manually converted into a time series of EM events, which were then analyzed by piecewise linear regression for various EM characteristics, including among others EM density, EM burst density, and continuous EM burst time. **Results** Two critical points for EM density, EM burst density, continuous EM burst time, and the number of EMs composing EM bursts were evident at gestation weeks 30-31 and 36-37. Overall EM activity in human fetuses increased until 30-31 weeks of gestation, then again from 36-37 to 38-39 weeks of gestation. **Conclusion** These findings may be useful for creating indices of fetal neurological function for prognostic purposes.

ISP-14-7

Adaptation of Cardiac Function in the Fetuses with Complete Atrioventricular Block Yuka Yamamoto[1], Ai Takamizu[2], Atsuo Itakura[2], Satoru Takeda[2] *Juntendo University Shizuoka Hospital[1], Juntendo University Faculty of Medicine[2]*

Objective Isolated fetal congenital complete atrioventricular block (CAVB) is a challenging lesion with high perinatal mortality. Less than fetal heart rate (FHR) 55bpm, endocardial fibroelastosis and fetal hydrops are the worse condition to induce high neonatal mortality, however, there was no effective parameter to evaluate fetal cardiac function with abnormal rhythm. Our purpose was to predict the perinatal outcome by evaluating the cardiac adaptation to compensate for decreased FHR in the CAVB fetuses. **Methods** Four CAVB fetuses were evaluated from the onset of CAVB to the birth. Three cases were positive with high anti-Ro antibodies. Stroke volume (SV) and FHR were collected to calculate the combined cardiac output (CCO) throughout gestation. Each parameter was compared to the normative data which had been published. **Results** The onset of CAVB and the FHR were variable. The CCO was preserved to term with the increased SV in all cases. According to the case with starting to show pleural fluid and arrhythmia, the SV was extremely increased more than 4× around 35 weeks of gestation compared to SV in the others, which increased up to 2×. **Conclusion** Increased SV in CAVB fetuses was the compensation to maintain the required CCO with decreased FHR. Unbalanced excessive SV, more than four times of the mean, might induce fetal arrhythmia or fetal hydrops even though the CCO still remained normal range.

ISP-15-1

Cord blood neurotrophins of neonates born to mothers with schizophrenia Yoshinori Moriyama, Tomomi Kotani, Hiroyuki Tsuda, Mayo Miura, Yukako Iitani, Masataka Nomoto, Yumiko Ito, Shima Hirako, Masako Sawada, Kenji Imai, Tomoko Nakano, Fumitaka Kikkawa *Nagoya University*

Objective There is an increasing attention to pregnancy complicated with mental disorders, and its impact on babies, which remains to be clarified. Brain-derived neurotrophic factor (BDNF) is reported to be decreased in peripheral blood of severe schizophrenia patients, while there have been only limited information on their baby. Here, we assessed whether cord blood neurotrophins including BDNF could be a neonatal biomarker for influence by maternal schizophrenia. **Methods** Twenty neonates of schizophrenic mothers and as many matched controls in terms of gestational age and mode of delivery were selected. For BDNF, pro-BDNF, nerve growth factor (NGF), pro-NGF, neurotrophin-3, neurotrophin-4/5 and glial cell-derived neurotrophic factor, their serum levels in cord blood collected at delivery were measured by ELISA. Comparison between the case and control groups as well as subgroup analysis was done. **Results** Neither BDNF nor NGF showed significantly different serum levels between the case and control groups. For the other neurotrophins, almost all the samples showed serum levels below measurable limit. Subgroup analysis revealed that male neonates had lower serum level of BDNF ($p=.019$). Maternal age, medication, deterioration of schizophrenia, hospitalization, or gestational age didn't have significant influence on BDNF or NGF. **Conclusion** No cord blood neurotrophins had significant difference between the case and control groups or reflected severity of maternal schizophrenia in this sample size-limited study. However, BDNF level was significantly lower in male neonates, which might have association with higher incidence and earlier onset of the disease. Further study is needed for a neonatal biomarker candidate of schizophrenia.

ISP-15-2

Fetal skeletal dysplasia : accuracy of prenatal diagnosis Miyoko Waratani, Aki Mabuchi, Tadahiro Yasuo, Koichi Iwasa, 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 12 cases of fetal skeletal dysplasia. **Method** 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, followed by postnatal radiography, and then made a definitive diagnosis through DNA testing. **Results** There were thanatophoric dysplasia, osteogenesis imperfecta, campomelic dysplasia, Desbuquois syndrome, achondroplasia (including 1 case with trisomy 21), 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-15-3

Successful prenatal diagnosis and cesarean delivery of a monozygotic twin with Pentalogy of Cantrell having a giant omphalocele firmly attached to the amniotic membrane Tomonobu Kanasugi, Akihiko Kikuchi, Hideyuki Chida, Yuri Sasaki, Gen Haba, Chizuko Isurugi, Rie Oyama, Toru Sugiyama *Iwate Medical University*

Pentalogy of Cantrell is a rare congenital malformation of the abdominal wall defect that consists of five characteristic findings : defect of the 1) supraumbilical thoraco-abdominal wall, 2) lower sternum, 3) anterior diaphragm, 4) diaphragmatic part of pericardium, and 5) presence of cardiac anomaly. A 24-year-old woman with spontaneous monochorionic and diamniotic twin pregnancy was referred at 20 weeks of gestation because one fetus (Twin A) had a giant omphalocele. Since ultrasound examination of the Twin A revealed ventricular septal defect, pericardial defect and a giant omphalocele including a heart, left lung, liver and intestines, we strongly suspected pentalogy of Cantrell in Twin A. Twin B had no anomalies. Transvaginal ultrasound showed placenta previa. Magnetic resonance imaging (MRI) and repeated ultrasonography demonstrated that a part of the surface of the giant omphalocele of Twin A was covered with the amniotic membrane. When we performed emergency cesarean section for massive bleeding from placenta previa at 34 weeks, at first we attempted to deliver Twin A in breech presentation but it was impossible because the omphalocele was firmly attached to the amniotic membrane covering it, as suggested by prenatal ultrasound and MRI. We therefore delivered Twin B first and then successfully delivered Twin A by cutting the amniotic membrane adhering to the surface of the omphalocele using cooper scissors. Although this condition may be extremely uncommon, we consider that careful prenatal ultrasound examinations are required for planning the delivery of a fetus with pentalogy of Cantrell and a healthy fetus in a twin pregnancy.

ISP-15-4

The role of sonographic evaluation of anal atresia in prenatal diagnosis of persistent cloaca : report of two cases Moe Yorozu, Saya Tsukahara, Katsuhiko Tada, Kao Fukui, Satomi Yamashita, Satoe Kirino, Mizuho Yoshida, Satoko Masahiro, Naoki Okimoto, Yoko Tateishi, Kazumasa Kumazawa *National Hospital Organizaion Okayama Medical Center*

Persistent cloaca is an uncommon (1 per 50000 live birth) congenital anomaly which constitute a group of severe anorectal malformations. Prenatal diagnosis is difficult due to its rarity and the complex multisystem anatomic variation. The purpose of this case report is to demonstrate the importance of sonographic evaluation of anal atresia for the prenatal diagnosis of persistent cloaca. We report two cases of prenatally suspected persistent cloaca between 2006 and 2015. Our first case was referred at 24weeks of gestation due to the bilateral hydronephrosis in a female fetus. The additional sonographic images were absence of anal mucosa (at 24weeks), dilated colon (at 26weeks), and enterolithiasis (at 31weeks). Based on these images, the fetus was suspected of persistent cloaca. A 3346g-female was born at 38weeks of gestation and was diagnosed as persistent cloaca by the pediatric surgeon. Our second case was referred at 30weeks of gestation due to the intraperitoneal cyst in a female fetus. The additional sonographic images were the pelvic septated cyst and bladder anteriorly (at 30weeks), left hydronephrosis, and absence of anal mucosa (at 31weeks). Based on these images, the fetus was suspected of persistent cloaca. A 2346g-female was born at 34weeks of gestation and was diagnosed as persistent cloaca by the pediatric surgeon. In a high risk population, the diagnosis of anal atresia in utero seems to be an important marker for prenatal diagnosis of persistent cloaca.

ISP-15-5

Diagnosis and effective treatment of a newborn with both fetal umbilical and neonatal arterial thromboembolism following fetal umbilical cord ulcer Takuo Nakayama, Hideki Takahashi, Hiromitsu Azuma, Akikazu Nakamura, Kaori Shinya, Erina Kato, Takehiro Nakao, Chuyu Hayashi, Go Ichikawa, Masahiko Matsuura, Fumihisa Chishima, Kei Kawana *Nihon University, Itabashi Hospital*

Objective Neonatal and fetal arterial thromboembolism are rare diseases with a high risk of neonatal mortality. The causes of fetal or neonatal death are hemorrhage from umbilical cord ulcers or intestinal atresia or transection following ishchemic changes. We here report a newborn who was diagnosed in utero as umbilical arterial embolism following umbilical cord ulcer. **Case** This case, 35 years-old and null para, got pregnancy by IVF-ET using intracytoplasmic sperm injection (ICSI). In our center, she diagnosed hydramnion following fetal intestinal atresia at 29-gestational weeks, and underwent amniocentesis which confirmed normal fetal karyotype (46XY) and high-level of gastrointestinal enzyme (trypsin=8640 ng/ml, phospholipase A=1410 ng/dl) in the amnion. At 31-gestational weeks, fetal ultrasound revealed that umbilical cord blood vessel was changed from 2-artery and 1-vein (2A1V) to 1-artery and 1-vein (1A1V), indicating the vascular compromise caused by the umbilical arterial thromboembolism following umbilical cord ulcer. Although the perforation and hemorrhage of the umbilical cord were negated by amniocentesis, we performed elective c-section at 31-gestational weeks to avoid risks of hemorrhage. Her baby was 1810g (Apgar score 8 (1min) and 9 (5min)). At one day-old, he diagnosed transection of duodenal cap and underwent duodeno-duodenostomy. Although he also diagnosed arterial embolism of the left femur with no pulse detected at birth, the blood flow was improved spontaneously. **Conclusion** Our case was successfully treated by timely diagnosis of umbilical arterial thromboembolism using fetal ultrasound and amniocentesis. Especially, change of umbilical cord blood vessels was the most important finding to reveal such rare phenomenon with high mortality.

ISP-15-6

Antenatal ultrasonography findings and magnetic resonance imaging in a case of Pena-Shokeir phenotype Xuan-Hong Tomai[1], Thanh-Xuan Jasmine[2], Thanh-Hai Phan[2] *University of Medicine and Pharmacy, Hochiminh City, Vietnam[1], Medic Medical Center, 254- Hoa Hao street, district 10, Hochiminh city, Vietnam[2]*

Background Pena-Shokeir phenotype (PSP) is a lethal anomaly characterized by neurogenic arthrogryposis, cranio-facial anomalies and pulmonary hypoplasia. This syndrome should be distinguished from trisomy 18 and arthrogryposis multiplex congenita to better inform fetal prognosis. **Case** We present the case of a pregnant woman diagnosed with a PSP affected fetus at 24 weeks of gestation. Prenatal ultrasonography and fetal magnetic resonance imaging (MRI) detected persistent hyperextension of the lumbar spine, micrognathia, absent septum pellucidum, and polyhydramnios, all characteristic features of PSP. Karyotyping was performed to exclude fetal chromosomal anomalies. **Conclusion** Antenatal ultrasonography is an essential tool in the diagnosis of PSP while fetal MRI is necessary to identify any associated anomalies of central nervous system.

ISP-15-7

The Simulated Transgender Patient Encounter : A Tool to Boost Provider Knowledge and Confidence Jennifer Villavicencio, Elizabeth Rubin, Beth Cronin *Brown University, USA*

Background Caring for transgender patients is an increasingly important component of comprehensive gynecologic and surgical care. Provider insensitivity, discrimination, and lack of awareness are often cited as reasons why transgender patients do not seek health care. There are multiple reasons why a GYN provider may feel unprepared to comprehensively care for transgender patients, including low volume and exposure. Simulation has been found to be a useful tool in ensuring that practitioners are prepared for a variety of situations, including patient encounters. We will describe an educational session that utilizes a Simulated Transgender Patient Encounter. By learning how to conduct this simulation both leaders and participants will be exposed to and therefore feel more comfortable and proficient in gathering pertinent patient history and using inclusive, appropriate language when caring for a transgender patient. Brief Description of Simulation : Begin with an overview of transgender healthcare, review of transgender-sensitive language, and discussion of the importance of gathering key sexual history details. Then practice utilizing this information in a simulated encounter in which a transgender man is being counseled and consented for a hysterectomy and bilateral salpingo-oophorectomy. Finally, a debriefing with the entire group, including the simulated patient should occur in order to review both the positive and to-be-improved aspects of the encounter. The debriefing should also allow time for further questions and suggestions for improving the simulation.

ISP-16-1

Long-term supplementation of young coconut juice does not prevent bone loss but alleviate body weight gain in ovariectomized rats Hiroshi Matsushita, Akihiko Wakatsuki *Aichi Medical University*

Objective Young coconut (*Cocos nucifera* Linn.) juice (YCJ) has traditionally been consumed to alleviate symptoms associated with menopause. Recently, we demonstrated that short-term (6-week) YCJ supplementation significantly reduced the rapid bone loss in ovariectomized rats. This study sought to determine how long-term (12-week) YCJ supplementation affects bone metabolism in ovariectomized rats. **Methods** Ten-week-old female Wistar rats were subjected to either a sham operation (Sham) or bilateral ovariectomy (Ovx). The Ovx+YCJ group received 5x-concentrated YCJ at a dose of 15 mL/kg body weight (BW) per day. Twelve weeks after surgery, the rats were anesthetized and sacrificed. **Results** 1) There were early increases in the BW of rats in the Ovx group, with significant difference between the Ovx and Ovx+YCJ groups. There were no significant differences in uterine weight between the groups. 2) Although there was no significant difference in femur bone mineral density between the Ovx and Ovx+YCJ groups, the bone area of the mid 1/3 of the femur, a site high in cortical bone, of the Ovx+YCJ group was significantly lower. 3) Serum osteocalcin, a bone formation marker, of the Ovx+YCJ group was significantly lower than the Ovx group. **Conclusion** The bone-sparing effects of estrogen are largely mediated by estrogen receptor (ER) α, however ERβ exerts only an inhibitory effect on periosteal apposition. Our findings indicated that the effects of YCJ might be exerted by phytoestrogens in YCJ through ERβ, resulting that long-term YCJ intake did not alter bone loss but alleviated cortical expansion and body weight gain after Ovx.

ISP-16-2

Effect of switching anti-resorptive agent during the treatment of postmenopausal osteoporosis—Minodronate is effective in patients who have lost response to raloxifene therapy Asuka Toda[1], Kenjiro Sawada[2], Akihiko Yoshimura[2], Hiromasa Kuroda[2], Erika Nakatsuka[2], Katsumi Kozasa[2], Koji Nakamura[3],

Kazushige Adachi[1], Tadashi Kimura[2] *Minoh City Hopspital, Osaka University Hospital[1], Osaka University Hospital[2], Osaka Saiseikai Nakatsu Hospital, Osaka University Hospital[3]*

Objective During several years of the treatment with anti-resorptive agent to the patients with postmenopausal osteoporosis, poor response is often seen in the clinical setting. The purpose of this study is to investigate the efficacy of switching raloxifene (RAL) to minodronate (MIN) in patients who have lost response to prior RAL. **Methods** This observational study was conducted based on a single-arm, non-randomized, open-label design and approved by the IRB of the institute. Postmenopausal women with osteoporosis who had turned unresponsive in their bone mineral density (BMD) after being administered with RAL for two or more years were enrolled. Patients were treated with 1 mg MIN daily or 50 mg MIN monthly. Changes in BMD and serum bone turnover markers were monitored at the baseline, 6, 12 and 24 months after switching the treatment. **Results** A total of 27 subjects were enrolled. Two discontinued treatment because of adverse events related to the study drug. Among 25 patients, lumbar BMD significantly increased by 3.67%, 5.08%, and 6.97% at 6, 12, and 24 months, respectively and femoral neck BMD increased by 1.63%, 2.18%, 3.85% at 6, 12, and 24 months, respectively. Serum bone-specific alkaline phosphatase (BAP) showed a significant reduction of 30.35% from the baseline ($p < 0.0001$) within the first 6 months. Serum N-terminal telopeptide of type I collagen (NTX) showed a tendency to decrease. **Conclusion** Switching RAL to MIN is effective in poor-responders in the treatment of osteoporosis and should be considered one of the treatment options.

ISP-16-3

Effects of Hyuganatsu orange extract containing drink on serum osteogenic parameter Masatoshi Yamaguchi, Hiroko Hata, Hiroshi Sameshima, Tsuyomu Ikenoue *University of Miyazaki*

Objective In former study, we presented large molecular weight Hyuganatsu orange extracts containing juice decreased under carboxylate osteocalcin (ucOC) level in postmenopausal women. In this study, we sought to test Hyuganatsu orange drink for practical use on serum osteogenic parameter. **Methods** Protocol of this study was approved by Ethical committee of institution. Forty-three postmenopausal women were nominated in this study. These women divided into 2 groups. Study group took 120ml of drink containing Hyuganatsu orange extracts for 3 months. Control group did not take drink. Under carboxylated osteocalcin, BAP, NTX, TRACP5b were measured at before, 1 month and 3 months after taking Hyuganatsu drink. Three women drop outed study due to personal reason other than adverse event. Finally, 40 women (21 study group and 19 control group) were analyzed. **Results** Under carboxylated osteocalcin concentration of before, 1month and 3month was 6.06 ± 2.90, 5.91 ± 3.42, 4.05 ± 2.37, in study group, respectively. Under carboxylated osteocalcin concentration of before, 1month and 3month was 6.38 ± 2.63, 5.49 ± 2.34, 4.11 ± 2.46, in control group, respectively. Drink intake significantly decreased ucOC level. However, there was no significant difference in ucOC concentration between study and control group. **Conclusion** Hyuganatsu orange extract containing drink may not change ucOC level in postmenopausal women.

ISP-16-4

Seasonal change of pelvic inflammatory disease (PID) in Kyoto Mari Minagawa, Masamune Masuda, Koki Kurihara, Mari Fukuyama, Aya Yamamoto, Seiko Kato, Miho Eto, Hiroyuki Fujita *Kyoto Red Cross Hospital Daini*

Objective It is well known many infectious diseases follow a seasonal trend. We aimed to determine seasonal variations of pelvic inflammatory disease (PID) in Kyoto. **Methods** We analyzed retrospectively data of the patients who came to our hospital between 2011 to 2015. 57 cases of PID were identified. **Results** PID was seen more frequent in spring and summer. Particularly, PID after rupture of endometriotic cysts were more frequent in spring. There was no significant seasonal change of responsible bacteria. **Conclusion** Although etiology of PID is multifactorial, our study may confirm the fact that like many other infectious diseases PID also has a seasonal trend.

ISP-16-5

Toxic shock-like syndrome presented as pelvic inflammatory disease : A case report Masafumi Katakura[1], Tomoko Taniguchi[1], Kazuo Masaki[2], Masaru Nagashima[1], Tsuyoki Kugimiya[1], Takehiko Tsuchiya[1], Toshimitsu Maemura[1], Yukiko Katagiri[1], Mineto Morita[1] *Toho University Omori Medical Center[1], Omori Red Cross Hospital[2]*

We report a case of toxic shock-like syndrome (TSLS), a syndrome with septic shock resulting from group A streptococci (GAS) infection, who presented with pelvic inflammatory disease (PID). A 46-year-old woman, gravida 0 para 0, with four years of oral contraceptive use was referred to our hospital because of fever, abdominal pain, and enlargement of the uterus with suspected infection. On pelvic examination she had a diffuse lower abdominal pain with rebound tenderness, and vaginal ultrasonography revealed adenomyosis of the uterus and a moderate amount of ascites. She was admitted to the hospital under the diagnosis of PID and ceftriaxone 2 g daily was administered intravenously. 12 hours after the admission, the systolic blood pressure of the patient fell down to 60 mmHg with elevated pulse rate of 110 per minute. We suspected a septic shock and started the administration of catecholamine, anticoagulant, and meropenem 3 g daily. On the third hospital day, GAS infection was suspected from blood culture and we changed the antibiotics to ampicillin 3 g every six hours plus clindamycin 600 mg every eight hours. On the fifth hospital day, a pelvic magnetic resonance imaging showed intrapelvic abscess. We performed an emergency laparotomy and found a large amount of infected ascites and bilateral tubal abscess. After the operation with hysterectomy, bilateral salpingo-oophorectomy, and intraperitoneal drainage, the infection was controlled and the patient was discharged on the 15th postoperative day. The final diagnosis was TSLS because two sets of blood culture were positive for GAS.

ISP-16-6

A case of pregnancy complicated with cervical ulcer caused by group C streptococcal infection Soonna Yun, Hiroaki Tsubouchi, Naho Umezawa, Azusa Wada, Hiroko Fukuoka, Chifumi Ooyagi, Aya Fukuda, Tateki Tsutsui *Japan Community Health Care Organization*

The causes of cervical ulcer include infection, collagen disease and malignant tumor. Cervical ulcer during pregnancy is rare. We present a case of cervical ulcer caused by group C streptococcal (GCS) infection at 37 weeks of gestation. A 36-year-old woman, G1P0, was referred to our hospital at 27 weeks of gestation for regular prenatal checkup. At 37 weeks of gestation, metrorrhagia appeared and a circular cervical ulcer of about 2-cm diameter was detected in her cervix. We performed biopsy of the ulcer and conducted a cultivation test. The pathologic diagnosis was suppurative inflammation, and GCS was detected. By the start of labor at 40 weeks of gestation, the ulcer had expanded to about 3-cm diameter. The mother developed a fever of 40 Celsius during labor ; thus, antibiotic treatment and labor augmentation were started. Seven hours later, an emergency cesarean section was performed because of induction failure. A male baby was delivered (Apgar score 6/6). The pathologic

evaluation of the placenta yielded a diagnosis of chorioaminionitis, and GCS was detected on the surface of the fetal side of the placenta, which was considered an ascending infection from the cervical ulcer. Meconium aspiration syndrome was diagnosed in the baby, and he was admitted to the neonatal intensive care unit. The mother developed endometritis on the 4th day after surgery and surgical site infection on the 7th day. Antibiotic treatment was administered from the 4th through the 18th days. The ulcer became progressively smaller after delivery, and completely vanished on the 30th day.

ISP-16-7

Objective assessment of tension of a mesh during laparoscopic sacral colpopexy Yoshiyuki Okada, Tetsuya Ishikawa, Takashi Mimura, Makoto Nakabayashi, Yusuke Hirose, Shingo Miyamoto, Mamiko Onuki, Koji Matsumoto, Akihiko Sekizawa
Showa University School of Medicine

Objective Laparoscopic sacral colpopexy (LSC) has been established as minimally invasive pelvic reconstructive surgery for POP, because of safety and efficacy. However, the appropriate tension of a mesh fixed onto the sacral promontory remains unknown. The present study was designed to examine whether weak or excessive traction of the mesh may be associated with POP recurrence or short-term complications. **Methods** We prospectively analyzed 12 consecutive women who underwent LSC for POP between November 2015 and May 2016 (age 68 ± 10 years, operation time 221 ± 33 min and blood loss 77 ± 100g). An expert gynecologist (qualified endoscopic surgeon) with experience of >80 cases of LSC performed the procedure. Using a spring scale linked to the cervix, we measured the tension of the mesh immediately before fixing it onto the sacral promontory during LSC. The spring scale results were masked to the operator. **Results** Based on the spring scale measurement, the mesh tension ranged from 230 to 800g (mean 400g). No case had POP recurrence, postoperative pain or other short-term complications. In all women, POP-Q scores were improved after LSC. **Conclusion** The present study demonstrated that the tension of a mesh may be monitored by the spring scale measurement during LSC. However, the sample size of this study was small. To fully evaluate possible associations of the mesh tension with recurrence and postoperative complications, larger scaled study will be warranted.

ISP-16-8

Mid-term outcome after reconstructive surgery with anterior vaginal mesh and uterosacral ligament colpopexy for pelvic organ prolapse Akihiro Hamuro, Ryo Uemura, Sakika Yanai, Koyumi Enomoto, Hiroko Katayama, Takuya Misugi, Daisuke Tachibana, Tomoyo Yasui, Toshiyuki Sumi, Masayasu Koyama
Osaka City University

Objective The suitable surgical procedure for pelvic organ prolapse (POP) has been confusing since FDA's alert for vaginal mesh implant. The main aim of the study was to evaluate the outcome after combination of uterosacral colpopexy and anterior tension-free vaginal mesh. **Methods** This study was conducted as a single-center prospective cohort. Reconstructive surgery was performed in fifty-two POP patients with stage III to IV cystocele and uterine prolapse (Ba : +4.7+/-1.6, C : +3.9 +/-3.16). Uterosacral colpopexy (McCall culdeplasty) and trocar-guided anterior vaginal mesh implantation followed after conventional vaginal hysterectomy. Postoperative outcomes and patients' satisfaction were analyzed by consecutive POP-Q assessments and the modified SF-12v2 questionnaire including quality of life (QOL) assessment and sexual behaviors, respectively. Recurrence was defined when the most distal point was beyond the hymen. **Results** Mean operation time and blood loss were 125.2+/-16.7 min, 71.4+/-56.4 ml respectively. Intraoperative tissue injury (bladder perforation) occurred in one case. Recurrence of vaginal descent observed in two cases (Ba : +4 and +1, cure rate : 96.2%). Reoperation was carried out in only one case. In two patients, asymptomatic mild cystocele was observed (Ba : 0) but additional treatments were not required. Any other mesh-related complications, such as protrusion, chronic pain, or chronic inflammation did not occur through follow-up period (1-5.5 years). Postoperative modified SF-12 scores at 12 months were significantly improved in all 8 domains. **Conclusion** The combined operation of vaginal hysterectomy and uterosacral ligament colpopexy augmented by anterior vaginal mesh implantation was safe and durable surgical treatment with satisfactory maintenance of QOL.

ISP-16-9

Validation of a augmented reality ultrasound app—UPPS (Ultrasound aPP Study) Florian Ebner, Kriztian Lato, Nikolaus Degregorio, Christiane Lato, Amelie Degregorio, Akadius Polasik, Wolfgang Janni, Fabienne Schochter *Ulm University, Germany*

Purpose Traditionally ultrasound is taught by learning by doing. Besides access to a ultrasound machine and a supervisor this also requires a patient patient. In order to improve the learning curve we used our previously published raytracing/-casting-based rendering method (Lato et al. 2016) and a digital human model with a urogenital system inside to create a smart phone app. This app simulates the ultrasound head and display in one device simulating an ultrasound examination. The perspective of the UPPStudy is to evaluate the acceptance of this training possibility and prove its clinical effectiveness. **Material & Methods** In our tertiary teaching hospital up to 14 4th year students visit the ultrasound department every week. At the end of their day they had to scan the kidney of the departments consultant in two planes. The time and measurements were collected. In order to evaluate the effectiveness of the app every week the students were randomized in one of the following groups (text book only, text book + app, app only). A statistical analysis between the groups is planned. Currently randomization has met 50% of the planned number (n=100). **Results** Preliminary results after 40 students show a trend towards faster and more accurate imaging in the group of text book + app group. With the app only group not yet contributing. **Conclusion** Augmented/virtual reality simulation seem to improve the motorical skills faster and more efficiently and also enable students to train on various pathological findings.

ISP-16-10

Contraceptive practice and behavior among women attending the family planning clinic at north okkalapa general and teaching hospital Wint Thida Htay[1], Mie Mie Shwe[1], Khaing Lay Mon[2], Khin Htar Yi[1], Kyi Kyi Nyunt[1] *University of Medicine (2), Yangon, Myanmar[1], University of Public Health, Myanmar[2]*

This study was undertaken to identify the contraceptive practice and behavior among women at North Okkalapa General and Teaching hospital (NOGTH), Myanmar. This was a hospital-based cross-sectional descriptive study (Quantitative and Qualitative) in Family Planning Clinic at NOGTH during one year period. There were 196 clients interviewed with structured questionnaires and eight clients were in-depth interviewed (IDI) to identify the social, family, behavioral factors influencing their decision on contraceptive usage. All women knew about Injection depo medroxy progesterone acetate (DMPA) and oral combined contraceptive pills (COC) and ninety-three percent had knowledge about long-term contraception. Most women had

high knowledge level (110 out of 196 women) and good attitude level (100 out of 196 women). Most clients had awareness to consult the skillful persons (92.9%) but male involvement is still influencing (81.1%) on decision. Forty-five percent had switched their methods mostly from COC to injection DMPA. Fifteen percent had contraceptive failure mostly due to inappropriate usage and wrong choice of contraceptive methods. There was statistically significant association between education status and knowledge score on contraception ($p<0.001$) but for attitude level it was not significant (p 0.498). Of eight IDI, majority had awareness of birth spacing and four clients had experienced the contraceptive failure. Most unmarried women had induced abortion for social stigmas and health service barriers. The result of study point out to expand the family planning programs and dissemination of contraceptive knowledge to out of reach areas in order to fulfill the Sustainable Development Goal of reducing maternal mortality.

ISP-16-11

SR-16234, a selective estrogen receptor modulator, represses development of endometriosis-like lesions in murine model

Khine Yin Mon, Fuminori Taniguchi, Kei Nagira, Takashi Uegaki, Tasuku Harada *Tottori University Faculty of Medicine*

Objective Endometriosis is a common estrogen-dependent disorder. Medical treatments consist of GnRH agonists, oral contraceptives, and progestins, however, neither is fully effective nor entail side effects. Selective estrogen receptor modulators (SERM) have tissue-selective actions. SR-16234 (Nobelpharma Co.,) is a newly developed SERM, which has an estrogen receptor (ER) alpha pure antagonist and ER beta partial agonist activity. We investigate the efficacy of SR-16234 for the treatment of endometriosis in the murine model. **Method** A mouse endometriosis model was established by transplanting autologous endometrial tissue (7 weeks, BALB/c mice). All mice were ovariectomized and injected the estradiol (E2) subcutaneously. Mice with surgically induced endometriosis (n=10) were injected with lipopolysaccharide (LPS) intraperitoneally. After 4 weeks of subcutaneous treatment with SR-6234 (1mg/kg/day), the endometriosis-like lesions were evaluated. Gene expression in the lesions was analysed by real time RT-PCR. **Results** SR-16234 significantly decreased the weight of the endometriosis-like lesions. By E2 and LPS treatment, Interleukin (IL)-6, vascular endothelial growth factor (VEGF), monocyte chemotactic protein (MCP)-1 and cyclooxygenase (COX)-2 mRNA expression in the lesions was upregulated. Among them, SR-16234 repressed E2 and LPS-induced IL-6 mRNA expression. **Conclusion** SR-16234 had a regressive effect on the development of murine endometriosis-like lesions. It can be predicted to have a clinical efficacy and presented as a novel agent for the treatment of endometriosis.

ISP-17-1

Acetic acid-induced tumor cell death in cervical cancer cells : Does acetic acid have potential antitumor effect? Madoka Matsuya, Toshiaki Shibata, Hirotake Murakami, Naoaki Tamura, Chizuko Yaguchi, Hiroaki Ito, Kazuhiro Sugihara, Naohiro Kanayama *Hamamatsu University School of Medicine*

Objective Three percent acetic acid is used as a diagnostic reagent for visualizing the uterine cervical epithelium during colposcopy. In a previous study, we suggested that acetic acid had an antitumor effect in combination with photodynamic therapy. Acetic acid affects human metabolism, but elucidating the mechanism underlying this effect is challenging. A previous study reported that acetic acid-induced cell death in stomach cancer cells. Thus, we aimed to evaluate the effect of 3% acetic acid in cervical cancer cells. **Methods** In vitro, we evaluated cytotoxicity in acid condition via MTT assay, using human uterine cervical cancer cells (HeLa). In vivo, we used an immunodeficient mouse model with subcutaneous tumors of HeLa cell and evaluated the progress of tumor volume and histopathological assessment of the tumors glued to tampons dipped in acetic acid. **Results** Cytotoxicity rates depended on adhesion time and acid concentration. At the same pH, acetic acid had higher cytotoxicity than hydrochloric acid. The tumor increase in 30 days later was suppressed in less than 20% of control. Hematoxylin and eosin staining of the tumors showed consecutive necrotic tissues. We assessed DNA fragmentation via TUNEL assay to elucidate the cause of tumor cell death, but no apoptosis was observed. **Conclusion** In vitro, regarding acidity, another mechanism apart from pH existed and had a cytotoxic effect. In vivo, tumor proliferation was inhibited by this mechanism, with no apoptosis. We suggest that 3% acetic acid may be used for treatment in combination with photodynamic therapy or radiation.

ISP-17-2

HER-2 expression in Gastric type adenocarcinoma of the uterine cervix. Ayano Holmes, Ken Yamaguchi, Ryusuke Murakami, Kaoru Abiko, Junzo Hamanishi, Eiji Kondo, Tsukasa Baba, Noriomi Matsumura *Kyoto University Hospital*

Objective Mucinous carcinoma, gastric type of the uterine cervix is a new disease category, which is newly proposed in 2014 WHO classification of tumors of the female reproductive organs. There is no effective treatment for Gastric type adenocarcinoma, so gastric type adenocarcinoma are thought to be worse prognosis to the usual type. On the other hand, 20% of Gastric cancer express HER2 and we can use anti-HER2 (human epidermal growth factor type2) monoclonal antibody for these cases. We studied about HER2 expression in gastric type adenocarcinoma of the uterine cervix. **Methods** We studied 12 cases that were diagnosed gastric type of the uterine cervix from 2007 to 2015. Immunohistology, and using Dual color in situ hybridization (DISH) we judged HER2 expression. We used the determination method of HER2 expression in gastric cancer. **Results** In 391 cases of cervical cancer, adenocarcinoma was 74 cases (18.9%) and gastric adenocarcinoma was 12 cases (16.2%) in these 74 cases adenocarcinoma. 8 cases were suspected gastric adenocarcinoma from biopsy tissue before operation. In immunohistology, all 12 cases of gastric carcinoma stained positive for MUC6 and 8 cases stained positive for HIK1083. In the 12 cases gastric adenocarcinoma, 6 cases express HER2 2+in immunohistology. HER2 amplification is recognized in 1 case in these cases. **Conclusion** This result indicate that the gastric type of uterine cervix express HER2 as in the same percentage of gastric cancer. We have to establish the new determination method of gastric adenocarcinoma of uterine cervix and we hope to apply the use of anti-HER2 monoclonal antibody.

ISP-17-3

Clonal composition and copy number variation of epithelial ovarian cancer Hisamitsu Takaya[1], Hidekatsu Nakai[1], Masayo Ukita[2], Kosuke Murakami[1], Mamoru Shigeta[1], Risa Fujishima[1], Chiho Miyagawa[1], Shiro Takamatsu[1], Takako Tobiume[1], Ayako Suzuki[1], Isao Tsuji[1], Masaki Mandai[1] *Kindai University[1], Kyoto University[2]*

Objective The aim of this study is to reveal the relationship between copy number variation and clonal composition and clinical findings of epithelial ovarian cancer. **Methods** Whole genome SNP-based copy number array were used for the detection of clonal composition in 24 ovarian formalin-fixed, paraffin-embedded tissues. The data of genome wide segmentation consisted of log2 ratio and B-allele frequency provided the number of clonal composition for each tumor. In parallel, somatic mutations profiles of 50 cancer related-genes for the samples were detected by next generation sequencing. **Results** The average number of clonal composition was 1.6 ± 1.0 (range ; 0-3). A somatic mutation in at least one gene was identified in 91.6% of ovarian cancer tissues. The cancers with one or more oncogenic mutations such as KRAS and BRAF showed significantly less numbers of clonal composition (1.0 ± 0.8 versus 2.2 ± 0.8, $p=0.005$), suggesting that cancers with driver oncogenes have less heterogeneity than those with passenger mutations. The recurrence was occurred in 10 cases and 4 in 10 cases including 3 platinum-resistant serous adenocarcinoma and 1 clear cell carcinoma were performed whole genome copy number analysis. The changes of copy number alterations between primary and recurrent tumor were detected in platinum-resistant serous adenocarcinoma, but not detected in clear cell carcinoma. **Conclusion** Epithelial ovarian cancer with no driver mutation may develop poly-clonally, and changes of copy number alteration may be cause of tolerance against chemotherapy.

ISP-17-4

The establishment of patient-derived-xenograft (PDX) model of malignant transformation of mature cystic teratoma which will contribute to novel clinical management Satoshi Tamauchi, Shiro Suzuki, Jun Sakata, Fumi Utsumi, Kaoru Niimi, Ryuichiro Sekiya, Hiroaki Kajiyama, Kiyosumi Shibata, Fumitaka Kikkawa *Nagoya University, School of Medicine*

Objective Recently, the patient-derived-xenograft (PDX) models have been used in the oncologic field to develop new therapeutic agents, which preserve tumor microenvironment and tumor characteristics, and well reflect patient's histological features. In other major malignancies including ovarian high-grade serous carcinoma, practical uses of PDX models have been reported, however, PDX models of malignant-transformation of mature cystic teratomas (MTMCT) have not been established. MTMCT is a rare malignancy of gynecology, and its standard treatment except surgery have not been confirmed. Hence, we established a novel PDX model of MTMCT, and report its achievement. **Methods** A 31-year-old woman received right salpingo-oophorectomy because of huge right ovarian tumor. The pathologic result was SCC arisen in MCT. Because of no evidence of residual disease, adjuvant chemotherapy was performed, however, relapse was occurred in 2 months. Thereafter, secondary debulking surgery was performed. At the time, the tumor tissue was isolated from the resected left ovary, and transplanted into severe immunodeficient mice. Tissues collected from these mice were immunohistochemically analyzed. **Results** The tumor engraftment in the mice was confirmed in 4 weeks of implantation, and became about 4 cm diameter in 6 weeks. After 10 weeks, first replantation was performed, and at this time, in vivo passages have been achieved twice. **Conclusion** The novel PDX model of MTMCT will contribute to the de-

velopment of treatment strategies.

ISP-17-5

Comparison in outcome of laparoscopic surgical treatment for Mayer-Rokitansky-Küster-Hauser syndrome Keiko Tanaka[1], Masahito Tachibana[1], Takashi Kuno[1], Ayako Fujimine[1], Masumi Ishibashi[1], Zen Watanabe[1], Naomi Shiga[1], Hitoshi Niikura[1], Hiroshi Nabeshima[2], Nobuo Yaegashi[1] *Tohoku University Hospital[1], Nippon Medical Care[2]*

Objective In females with Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), laparoscopic surgical vaginoplasty, such as Davydov and Vecchietti procedures are available to lengthen the vagina and facilitate sexual intercourse. The purpose of this study is to compare two procedures about surgical complications and outcomes. **Methods** This is a retrospective follow-up study. Patient's age, operative time, hemorrhage volume, complications, and vaginal depth of 15 patients with MRKH who underwent surgical vasinoplasty after 2002 were investigated. This study was approved by the Ethical Committee of our hospital. **Results** Thirteen females met the criteria ; 11 underwent Davydov procedure, whereas Vecchietti procedure was used in 2 others since 2011. The average age, operative time and hemorrhage volume for Davydov and Vecchietti were as follows ; 21.4 (18-32) years old and 22 (20-24) years, 191 minutes (range) and 128 minutes (range), 91.5 g (range) and 0 g (range), respectively. Complications of Davydov procedure were intraoperative bladder injury (1 case) and wound dehiscence (1 case). No severe complication in Vecchietti procedure was observed. Average vaginal depth after operation were 6.4 cm (5-8 cm) and 5.5 cm (3-8 cm), respectively. One female with Vecchietti procedure required re-intervention with Davydov due to insufficiency of vaginal depth. **Conclusion** Comparison in two procedures, Vecchietti procedure had less surgical complication, but equal or worse in vaginal depth. Thus, the both procedures would not be universal for patient with MRKH. Further study is needed in order to determine suitable methods for individual case.

ISP-18-1

Obstetric application of ultrasound elastography as a novel tool for assessing placental health Nanae Tsuchida, Tomoya Hasegawa, Toru Sasaki, Hirotaka Nishi, Hiroe Ito, Naoaki Kuji, Keiichi Isaka *Tokyo Medical University*

Objective Ultrasound elastography (UE), a non-invasive imaging tool for the assessment of elasticity in biological tissues, is widely used to examine breast, prostate, and thyroid tissues to distinguish malignant tumors from the surrounding normal tissues. Recently, it was found that UE is also useful for the evaluation of noncancerous tissues, such as liver cirrhosis. Pathological changes to placentas, including acute sclerosis of the blood vessels and fibrosis of the villus, are associated with obstetrical diseases, such as pregnancy-induced hypertension and fetal growth retardation. In this study, we evaluated the potential of UE as a novel tool for assessing placental health. **Methods** Seventy-nine pregnant women were enrolled between February 2014 and September 2016 in this prospective cohort study, which was approved by the Institutional Review Board. A total of 316 transabdominal, real-time UE were performed at the prenatal checkup. After delivery, pathological examinations were performed on 30 placentas. **Results** Elastographic images of placentas were classified into 3 groups based on the elasticity. The average Z-score of the estimated fetal body weight was significantly lower in group 3 (most solid, -1.63SD), compared with that in group 2 (-0.46SD) or group 1 (+0.19SD). Six of 9 patients (66.0%) with group 3 showed abnormal pathological findings. On the contrary, only 1 of 15 patients (6.7%) with group 1 showed abnormal findings. **Conclusion** These results suggested that UE may provide useful information on placental health, aiding the identification of pregnant women at high risk who require further evaluation, thus reducing the perinatal risk.

ISP-18-2

Measurement of PlGF, sFlt-1, sFlt-1/PlGF ratio, and sEndoglin at the 2nd trimester is useful for predicting pregnant women with fetal growth restriction (FGR) who will subsequently develop preeclampsia (PE) Sakiko Nanjyou, Madoka Yamamoto, Mika Mizoguchi, Tamaki Yahata, Aya Kobayashi, Michihisa Shiro, Nami Oota, Yasushi Mabuchi, Shigetaka Yagi, Sawako Minami, Kazuhiko Inou *Wakayama Medical University*

Objective It is reported that FGR and PE are associated with abnormal profiles of angiogenic markers in maternal circulation. Mothers with FGR fetuses are at increased risks for developing PE. The aim of our study is to determine whether maternal serum levels of angiogenic factors can predict mothers diagnosed with FGR will subsequently develop PE or not. **Methods** This study included women with singleton pregnancies diagnosed with FGR before 24 weeks of gestation (n=50). The protocol was approved by ethics committees and participants provided written informed consents. The serum levels of PlGF, sFlt-1, sEndoglin and sFlt-1/PlGF ratio were measured at 20-24 weeks of gestation. The cut-off value of each angiogenic factor was determined by ROC curve analysis for identifying mothers with FGR at risk of developing PE. **Results** The prevalence of patients with FGR preceding PE was 40% (n=20/50). The mean of onset period of subsequent PE was 30.1 ± 4.8 weeks of gestation. The optimal cut-off levels were PlGF level＜274.8 pg/mL (AUC=0.93, p＜0.001), sFlt-1 level ＞1829.3 pg/mL (AUC=0.884, p＜0.001), sEndoglin level ＞7.4 ng/mL (AUC=0.967, p＜0.001), and sFlt-1/PlGF ratio ＞7.4 (AUC=0.941, p＜0.001). sEndoglin and sFlt-1/PlGF ratio were the most powerful predictors for developing PE with sensitivity of 88.9% and 86.7%, and specificity of 92.6 and 92.0% respectively. **Conclusion** Angiogenic factors measured in maternal sera between 20 and 24 weeks of gestation can identify mothers diagnosed with FGR who subsequently develop PE. Measurement of these markers may contribute to the risk assessment of mothers with FGR, and their clinical outcomes.

ISP-18-3

The utility of fetal E/e' ratio by Dual gate Doppler method in the cases complicated with Twin-to-Twin Transfusion Syndrome and selective IUGR Mayumi Takano, Masahiko Nakata, Nahomi Umemura, Sumito Nagasaki, Rei Ueyama, Ayako Oji, Toshimitsu Maemura, Yukiko Katagiri, Mineto Morita *Toho University*

Objective To investigate the feasibility and efficacy of E/e' ratio in the identical cardiac cycle by using Dual gate Doppler method (DD method), and to assess temporal changes of ventricular diastolic function of monochorionic twins treated by fetoscopic laser photocoagulation (FLP). **Methods** This is a prospective study involving 15 pregnancies complicated with twin-to-twin transfusion syndrome or selective IUGR, which were performed FLP between December 2015 and July 2016. In the four-chamber view, each velocity of E wave by pulsed wave Doppler and e' wave by tissue Doppler imaging was measured simultaneously, using DD method. Fetal E/e' was estimated within 24 hours before and after FLP and 4-7 days after the procedure. Reference values acquired from normal 53 singleton fetuses in our previous study were used to compare with the present data. This study was approved by the institutional ethics committee. **Results** Preoperative right E/e' value in recipient or larger twin was likely elevated than reference values of normal fetus, and significantly decreased 4-7 days after FLP (p=0.009).

Left E/e' in recipient or larger twin was also increased than those in normal fetus, but there was no significant change after FLP. As for donor or smaller twin, no significant change was seen in bilateral E/e'. **Conclusion** The measurement of fetal E/e' using DD method was convenient and stable. Interestingly, right E/e' of recipient twins indicated higher than normal fetuses preoperatively and significant decrease within 7 days after FLP. These findings might imply FLP improves pathological condition of diastolic dysfunction of right ventricles in recipient twins.

ISP-18-4

A case of endometriosis under treatment with dienogest complicated suddenly with acute myelocytic leukemia Mari Hirano, Kazuya Nanjyo, Fumihisa Miyauchi *Ehime Rosai Hospital*

One of the side effects of dienogest is metrorrhagia. Here, we report a case of the endometriosis treated with gienogest happened heavy metrorrhagia and diagnosed acute myelogenous leukemia. The patient was 46-year-old woman. Past history was hydatidiform mole. Family history was unremarkable. She has endometriosis, so she had been taking gienogest for one year. From the beginning, she recognized a little metrorrhagia. From one month ago, she recognized that quantity of the bleeding was gradually increasing and she felt general malaise, she consulted our course. We confirmed no abnormality in the uterus by ultrasonography but we recognized tachycardia, anemia, thrombopenia. So we immediately admitted her to our hospital and we performed a blood transfusion. By a blood transfusion, we recognized improvement of her general condition, the hemoglobin level and the number of the platelets temporarily, but we recognized significant anemia and thrombopenia again in spite of a blood transfusion, we introduced her to the specialist of the blood internal medicine. As a result of careful inspections she was diagnosed with acute myelocytic leukemia. Because there was the need of the treatment in emergency, we introduced her to the university hospital. This case suggests an importance of the confirmation whether severe anemia and other diseases do not hide when amounts of bleeding increase and bleeding continues for a long time during a period of taking gienogest.

ISP-18-5

Introduction of cine MRI for the evaluation of pelvic organ prolapse Mana Hirano, Osamu Hiraike, Nana Akino, Shinya Fukuda, Tomoko Makabe, Naoko Yamamoto, Akari Nakazawa, Michihiro Tanikawa, Kaori Koga, Tomoyuki Fujii, Yutaka Osuga *Graduate School of Medicine, The University of Tokyo*

Objective It is occasionally difficult to accurately evaluate the degree of POP because the degree of POP could differ at pelvic examination table. Herein we report the introduction of cine MRI as an objective modality for evaluating the degree of POP. **Methods** We introduced laparoscopic sacrocolpopexy (LSC) for the treatment of POP since 2013 October, and currently 37 patients were treated by LSC. For these patients, we introduced cine MRI since 2014 October, and 11 (1 ; stage II, 7 ; stage III, 3 ; stage IV) patients with visible prolapse were enrolled. This study had institutional review board approval. Functional dynamic balanced fast-field echo images were used in detecting abnormalities in pelvic supporting structures. **Results** POP was associated with levator muscle weakness in 3 (27%) of 11 patients, with level I and II fascial defects in 11 (100%) of 11 patients, and with both defects in 7 (64%) of 11 patients. Using H-line and M-line defined as the shortest distance between the posterior aspect of the puborectalis muscle sling and the pubococcygeal line, 10 were classified into grade 1 of Pelvic Floor Relaxation, and one was grade 0. Surprisingly, 6 were classified into grade 1 of POP, 3 were grade 2, and one was grade 0 by MRI and the results was not in concordant with POP-Q stage. Two exhibited same stage at Valsalva maneuver. **Conclusion** It is sometimes difficult to exactly predict deficits provoking POP by pelvic examination, and we can analyze the deficits using cine MRI without imposing a heavy burden to the patient.

ISP-19-1

Significance of p53-binding protein 1 nuclear foci in cervical intraepitherial neoplasm : endogenous DNA double strand breaks and genomic instability during carcinogenesis Sayaka Kawashita, Kiyonori Miura, Michio Kitajima, Masanori Kaneuchi, Hideaki Masuzaki *Nagasaki University School of Medicine*

Objective A defective DNA damage response can result in genomic instability (GIN) and lead to transformation to cancer. As p53-binding protein 1 (53BP1) localizes at the sites of DNA double strand breaks (DSBs) and rapidly forms nuclear foci (NF), the presence of 53BP1 NF can be considered to be an indicator of endogenous DSBs reflecting GIN. In this study, to clarify the significance of GIN during carcinogenesis, we analyzed the presence of DSBs by immunofluorescence for 53BP1 expression in a series of cervical intraepithelial neoplasm. **Methods** The expression analysis of 53BP1 NF and p16 (INK4a), and human papillomavirus (HPV) test were performed in a total of 80 archival cervical tissue samples, including 11 normal cervical epithelium, 16 cervical intraepithelial neoplasia (CIN) 1, 15 CIN 2, 24 CIN3 and 14 squamous cell carcinoma (SCC). **Results** The pattern of 53BP1 immunoreactivity was classified into three types : stable type (faint and diffuse nuclear staining), low DDR type (one or two discrete NF), high DDR type (three or more discrete NF). The rate of high DDR type were 11.6% in normal cervical epithelium group, 15.0% in CIN1 group, 22.6% in CIN2 group, 45.3% in CIN3 group, and 66.0% in SCC group, respectively ($p<0.0001$). The distribution of 53BP1 NF expression was similar to that of p16 (INK4a) overexpression, and it was also compatible to the punctate HPV signals. **Conclusion** Expression analysis of 53BP1 in cervical tissues may be a useful test to estimate the progress degree from normal cervical epithelium to high-risk HPV infected cancer.

ISP-19-2

Clinicopathological significance of p53 mutation in endometrial cancer Ranka Kanda[1], Shunsuke Nakagawa[1], Takayuki Ichinose[1], Shiho Fukui[1], Yuko Sasajima[2], Shigeki Takeshita[1], Eiji Ryo[1], Takuya Ayabe[1] *Teikyo University[1], Teikyo University[2]*

Objective Tumor suppressor p53 is thought to be a guardian of genome. Its expression is elevated due to DNA damage and suppresses cell cycle progression to maintain genomic integrity. We explore clinicopathological significance of its expression in endometrial cancer. **Methods** We analyzed p53 expression in 160 endometrial cancer cases by immunohistochemical staining. Its expression was compared with age at onset, clinical stage, histological grade, nodal and vessel involvement, distant metastasis, myometrial invasion, and progression and overall survival. Expression level of p53 was classified into the following three groups : null pattern, overexpression, and wild-type. Null pattern and overexpression of p53 are categorized into the p53 mutant group. Informed consent was obtained from all patients and the ethical committee of the university approved this study (No.13-003). **Results** Null pattern, overexpression, and wild-type pattern of p53 were observed in 1.3%, 15.6%, and 83.1%, respectively in 160 endometrial cancers. Overexpression of p53 was predominantly observed in cases with high-grade histology (endometrioid carcinoma grade 3, serous carcinoma, and clear

cell carcinoma). The cases with p53 mutation showed higher distant metastasis and poorer progression and overall survival. Interestingly, all the p53 null-pattern cases had the low-grade histology and experienced no recurrence. **Conclusion** These data suggested that p53 mutation has a critical role in definition of aggressiveness of endometrial cancer. Our data also shed light on the difference between p53 null pattern and its overexpression in the involvement in control of endometrial cancer progression.

ISP-19-3

Characteristics of recurrence during bevacizumab treatment in ovarian carcinomas Tomoko Kashiyama[1], Katsutoshi Oda[2], Michihiro Tanikawa[1], Kazunori Nagasaka[1], Ayumi Taguchi[1], Kenbun Sone[1], Mayuyo Mori[1], Katsuyuki Adachi[1], Takahide Arimoto[1], Kei Kawana[2], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2]*

Objective Bevacizumab (BEV) is a cytostatic molecular-targeted agent which inhibits angiogenesis. BEV has been broadly administered since 2013 in both primary and recurrent ovarian cancers. We aimed to clarify the relationship between residual tumors and recurrence, as well as discordance between CA125 and detection of diseases during the BEV therapy. **Methods** We analyzed 47 ovarian cancer patients, which include 18 with BEV therapy (15mg/kg every 3 weeks/14 primary stage III/IV patients as a front-line treatment and 4 recurrent patients as 2nd or 3rd line treatment). Eleven patients with recurrence during BEV therapy were compared with 29 recurrent patients without BEV treatment. **Results** Eleven of 18 patients (61%) relapsed during BEV therapy. Eight of the 11 relapsed patients (73%) had post-operative residual or measurable diseases, while 1 of 7 patients (14%) without recurrence during BEV therapy had residual tumors (the remaining 6 patients were positive for intraperitoneal cytology alone) (p=0.049 by Fisher's exact test). There are no significant clinicopathological differences (such as age, stage, and histology) between relapsed and non-relapsed cases. The median time between CA125 elevation (<35 U/ml) and radiographic detection of recurrence (CT or PET-CT) was 2.5 month (95%CI 0-11 month) in relapsed patients and significantly longer compared with the BEV-free group (1 month, 95%CI 0-4 month) (p=0.01 by student t-test). **Conclusion** Post-surgical residual disease and presence of measurable disease are associated with early relapse in BEV-treated ovarian cancers. Recurrent tumors may be more difficult to be identified by diagnostic imaging in patients during treatment of BEV.

ISP-19-4

Recurrence of uterine myoma after Laparoscopic Myomectomy and Abdominal Myomectomy Mamoru Shigeta, Yasushi Kotani, Kiko Yamamoto, Shiro Takamatsu, Yoshie Yo, Kousuke Murakami, Hisamitsu Takaya, Masao Shimaoka, Takako Tobiume, Hidekatsu Nakai, Isao Tsuji, Masaki Mandai *Kindai University*

Objective In recent, LM (Laparoscopic Myomectomy) has been more often performed than before. The problem of postoperative recurrence in both LM and AM (Abdominal Myomectomy) sometimes occurs, however, the comparison of recurrence rates between LM and AM at a single institution has not been seen. This retrospective study examined the recurrence rates. **Methods** Between 1995 and 2014, 474 patients who underwent LM and 279 patients who underwent AM at our hospital were followed from the postoperative 6th month to the 8th year semiannually for recurrence by ultrasound or MRI. Mean age, the number of births, BMI, preoperative gonadotropin releasing hormone agonist (GnRHa) therapy, the number of removed myomas, the largest myoma diameter, operative time, blood loss and hospitalization days, were compared between LM and AM. Moreover, the cumulative recurrence rates were also compared between LM and AM in first, third, 5th, and 8th year. **Results** There were significant differences between LM and AM in mean age, the number of births, administration of GnRHa, the mean number of removed myomas, the mean largest myoma diameter, mean operative time, mean blood loss, postoperative hospitalization days. There was no significant difference in BMI. In the cumulative recurrence rates, Log-rank test showed a significant difference between LM and AM. **Conclusion** Postoperative recurrence rate of AM was lower than that of LM. AM enables us to touch the uterus and myomas directly and to remove smaller myomas. This may cause lower recurrence rate of AM. Close attention to the higher recurrence rate of myomas should be paid in LM.

ISP-19-5

Decreased expression of indoleamine 2, 3-dioxygenase in villous stromal endothelial cells of placentas with preeclampsia Naoyuki Iwahashi, Madoka Yamamoto, Sawako Minami, Kazuhiko Inou *Wakayama Medical University*

Objective Indoleamine 2, 3-dioxygenase (IDO), an immunosuppressive enzyme that converts tryptophan to kynurenine, is expressed in the placenta and might play a role in the maintenance of pregnancy. The objective of the study was to investigate the difference in IDO expression among normal, PE, and FGR placentas. **Methods** Immunohistochemical studies of IDO and Flt-1 expression were performed in human placenta that were complicated with FGR alone (n=19), PE alone (n=20), or both PE+FGR (n=39) compared to controls (n=23). This study was approved by the institutional ethic boards. The informed consent was obtained from all patients. **Results** IDO was expressed on endothelial cells in the villous stroma, while Flt-1 was located on trophoblasts, and there was an inverse correlation between the expression levels of IDO and Flt-1. The IDO expression level of the PE alone group was significantly lower than those of the FGR alone and control groups. The IDO expression of the PE+FGR group was significantly lower than that of the FGR alone group. Lower IDO expression was significantly correlated with more severe maternal hypertension or proteinuria in PE patients. The late onset PE patients exhibited significantly lower IDO expression than the early onset PE patients. Serum cystatin C, an inflammation marker, in umbilical vein was higher in late onset PE compared to those in early onset PE. **Conclusion** This study demonstrated that the downregulation of IDO expression on the endothelial cells of the villous stroma was associated with PE, suggesting that IDO might play a key role in the pathophysiology of PE.

ISP-20-1

Clinico-pathological Features and Prognosis of Cervical Cancer in Adolescents and Young Adults Noriko Yamaguchi[1], Masaru Sakamoto[1], Kiyohiko Miyake[1], Kenji Umayahara[1], Tadao Tanaka[2], Aikou Okamoto[2] *Sasaki Foundation Kyoundo Hospital[1], The Jikei University School of Medicine[2]*

Objective Little is known about the features and informations of adolescents and young adults (AYAs ; age-35years) with cervical cancer. The aim of this study is to investigate clinico-pathological features and prognosis of AYAs with cervical cancer in comparison with non AYA with cervical cancer and to evaluate whether age can be the prognostic factor of the cervical cancer. **Methods** Both AYA and non AYA cervical cancer patients were identified at our hospital (2004-2015). Several clinico-pathological factors and progression free survival (PFS) and overall survival (OS) after treatment were determined for both

patients with AYAs and non AYAs. **Results** Among 424 cervical cancer patients, 88 patients (20%) were AYAs, while 336 patients (80%) were non AYAs. FIGO staging were showing a tendency to be diagnosed at early stage Early stage cervical cancer were diagnosed more frequently in AYAs than in non AYAs (p =0.0008). In addition, compared to non AYAs, AYAs were more likely to metastasize to lymph nodes (p=0.056). There were no significant differences in both OS and PFS between AYAs and non AYAs. **Conclusion** Cervical cancer patients in AYAs were diagnosed at early stage. Although the rate of lymph node metastasis was significantly high, AYAs cancer did not show poor prognosis suggesting that AYAs were more sensitive to cancer treatments. This evidence might support the needs and safety to perform fertility preservation therapy such as trachelectomy in AYAs cervical cancer patients.

ISP-20-2

Effect of postoperative enoxaparin sodium injection on the prevention of deep vein venous thrombosis in cervical cancer : Analysis of a single-center cohort study of 3333 patients
Yoichi Aoki, Hidetaka Nomura, Kuniko Utugi, Kazuyoshi Kato, Hiroyuki Kanao, Kohei Omatsu, Sanshiro Okamoto, Maki Matoda, Takeshi Hisa, Syuhei Okamoto, Takeru Sugihara, Nobuhiro Takeshima *Cancer Institute Hospital*
Objective The reported rate of deep vein thrombosis (DVT) in gynecologic cancer patients is about 10%. DVT can cause life-threatening complications such as pulmonary embolism (PE). We evaluated the effect of enoxaparin natrium for the prevention of postoperative DVT in patients with cervical cancer. **Methods** Between 2006 and 2015, we investigated the rate of perioperative DVT and injection of enoxaparin sodium. Venous ultrasound imaging was performed to screen for preoperative DVT. Enoxaparin sodium was administered until one week postoperatively. **Results** Surgeries performed included radical hysterectomy in 649, modified radical hysterectomy in 445, abdominal hysterectomy in 448, vaginal hysterectomy in 77, and conization in 1666 patients. Administration of postoperative enoxaparin sodium for DVT prophylaxis started in April 2009. Prophylaxis for DVT was performed in 479 patients with radical hysterectomy, 361 with modified radical hysterectomy, 42 with laparoscopic radical hysterectomy, and 6 with laparoscopic cervical resection. We identified 27 cases of DVT perioperatively, which included 8 postoperative cases. PE occurred in two patients, but no patients died. Two patients recieved enoxaparin sodium for DVT that developed on postoperative days 30 and 42, respectively. DVT occurred in one patient who required re-operation and on postoperative days 4, 6, 7, 18, and 27 in another five patients, respectively, who did not receive enoxaparin sodium. **Conclusion** We recognized an effect of enoxaparin sodium for the prevention of DVT in the early postoperative period, although DVT occurred in two patients one month after surgery. We will evaluate the best period during which to administer enoxaparin sodium.

ISP-20-3

Analysis of recurrence after conization in patients with uterine cervical lesions
Hidenori Sasa, Hiroki Ishibashi, Hideki Iwahashi, Kento Kato, Masaya Nakatsuka, Takahiro Sakamoto, Takahiro Natsuyama, Tadashi Aoyama, Morikazu Miyamoto, Tomoyuki Yoshikawa, Masashi Takano, Kenichi Furuya *National Defense Medical College*
Objective To detect recurrence after conization, cervical cytology was usually performed regularly. We retrospectively analyzed the recurrence after conization in patients with uterine cervical lesions in our hospital. **Methods** During the past 7 years, 255 patients (mean age : 41.8 years old) with uterine cervical lesions underwent conization at our hospital. Of these, 13 patients underwent cold-knife conization, 5 patients underwent harmonic scalpel conization, and 237 patients underwent electrosurgical excision procedure. The cervical cytology was performed every three months after conizaton and colposcopy and biopsy was used for the additional examination. The patients who relapsed after conization were analyzed retrospectively. **Results** The 11 patients (4.3%) relapsed among 225 patients who underwent conization for seven years between 2009 and 2015 in our hospital. The mean duration of recurrence was 20.8 months (6-75) and 6 patients relapsed within one year after conization. The histology of the first conization revealed CIN3 in 10 cases, microinvasive carcinoma in one, and positive surgical margin in 8 cases. Two cases were diagnosed by only abnormal cytology, the remaining 9 cases were diagnosed by cytology and histology. Five patients underwent re-conizaton, 5 patients underwent hysterectomy and one patient was followed without treatment. Final diagnosis revealed CIN3 in 7 cases, no lesion in 2 and invasive carcinoma in 2 cases. **Conclusion** The recurrence after conization might be associated with positive surgical margin of the specimen and the duration after conization. The human papillomavirus test seemed to be useful for predicting recurrence after conization.

ISP-20-4

Does prophylactic irradiation to para-aortic lymph node lead to the positive effects for uterine cervical cancer? : a retrospective propensity score adjusted study
Kosuke Yoshida, Masato Yoshihara, Jun Sakata, Fumi Utsumi, Kaoru Niimi, Ryuichiro Sekiya, Shiro Suzuki, Hiroaki Kajiyama, Kiyosumi Shibata, Fumitaka Kikkawa *Nagoya University*
Objective Efficacy of prophylactic irradiation to para-aortic lymph node is controversial. The purpose of this study was to compare patients who were received prophylactic irradiation with those who weren't, and evaluate the clinical outcomes. **Methods** We retrospectively reviewed all the clinical records of uterine cervical cancer patients who were treated in our institution from 2005 to 2015. Eighty-three patients who had pelvic lymph node metastasis, and were treated radical surgery and concurrent chemo-radiotherapy were analyzed. Baseline imbalance between patients with and without prophylactic irradiation to para-aortic lymph node was adjusted using an inverse probability of treatment weighting using propensity scores (PS) composed of the following independent variables : age, clinical stage, tumor size, surgical procedure, remote after loading system, and pathological subtypes. We evaluated survival and clinical outcomes of the patients with the PS adjustment. **Results** In total, 83 of 886 patients admitted to our department during the study period fulfilled the required criteria ; of these, 34 and 49 patients were included in the treatment and control group, respectively. There were no differences in overall survival [median, 93.8 (95%CI, 48.9-92.4) vs. 70.6 (95%CI, 55.1-132.5) months] and in 10-year survival rate [0.316 (SD= ± 0.089) vs. 0.265 (SD = ± 0.075)] in treated and untreated groups, respectively. After PS adjustment, prophylactic irradiation showed no significant effect for prevention of the recurrence of cervical cancer in para-aortic lymph node (OR, 0.94 ; 95%CI, 0.31-2.85). **Conclusion** Based on our study, prophylactic irradiation to para-aortic lymph node might have no significant clinical benefits.

ISP-20-5

Risk stratification in patients with stage IB-IIA cervical cancer without any of parametrial invasion or pelvic lymph node metastases after radical hysterectomy
Shunichi Ikeda, Yutaka Yoneoka, Takafumi Tsukada, Mayumi Kobayashi, Yae Takehara, Kenta Takahashi, Keisei Tate, Hanako Shimizu,

Takashi Uehara, Mitsuya Ishikawa, Tomoyasu Kato *National Cancer Center Hospital*

Objective This study was designed to identify risk factors in stage IB–IIA cervical cancer without any parametrial invasion or pelvic lymph node metastases after radical hysterectomy. **Methods** In retrospective study, we reviewed 432 patients of stage IB–IIA cervical cancer without any parametrial invasion or pelvic lymph node metastases after radical hysterectomy between January 1989 and December 2010. The first 305 subjects, studied between 1989 and 2003, served as the training set and another 127 subjects, studied between 2004 and 2011, comprised the test set. To evaluate the risk factors for recurrence, cox's proportional–hazards model was used. **Results** On multivariate analysis, tumor size (>4 cm), corpus invasion, and vessel infiltration were significant predictors of poor survival. Patients were divided into low– and high–risk groups on the basis of these factors. The low–risk group comprised patients with 0 or 1 factor. The high–risk group consisted of patients with 2 or 3 factors. The 5YS of low–risk group and high–risk group were 95.7% and 52.6% and the 5YRFS of low–risk group and high–risk group were 95.0% and 57.9%, respectively ($p<0.001$). Similar results were obtained with the test set, that is, relapse free rate at 5–years of low–risk group and high–risk group were 97.7% and 33.7%, respectively. **Conclusion** Two and three factors out of tumor size (>4 cm), corpus invasion and vessel infiltration are useful for predicting recurrence in patients with stage IB–IIA cervical cancer without any of parametrial invasion or pelvic lymph node metastases after radical hysterectomy.

ISP-20-6

Retrospective analysis of the perioperative outcome of the laparoscopic radical hysterectomy Eiji Kobayashi, Mamoru Kakuda, Aiko Kakigano, Michiko Kodama, Kae Hashimoto, Seiji Mabuchi, Yutaka Ueda, Kenjiro Sawada, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

Objective The objectives of this study were to analyze the safety and feasibility of conducting laparoscopic radical hysterectomy (LRH) for early–stage cervical cancer. **Methods** From January 2013 to August 2016, we performed 35 cases of LRH. The case inclusion criteria for this study was having a cervical cancer of stage IA2, IB1 or IIA1. The operative strategies used were similar to those for an abdominal radical hysterectomy. We performed all procedures laparoscopically, with the exception of the vaginal cuff incision and closure. **Results** The patient's median age, BMI, operation time, and blood loss were : 41 years, 20.7kg/m^2, 434 min, and 150 ml, respectively. Twentynine patients were FIGO stage IB1, four were stage IA and two were IIA1. As for postoperative voiding function, the median time to achieve a residual urine of <50 ml was 8 days. There was four complications which requiring surgical, endoscopic or radiological intervention, one intraoperative ureteral burn injury, one postoperative urinary fistula, one bladder injury, and one intrapelvic abscess which required IVR. There was no reoperation due to perioperative complication. During the follow up period, to date, out of 35 patients, two have had recurrence to paraaortic lymph nodes. **Conclusion** Sufficient knowledge, experience and meticulous laparoscopic technique now enable us to perform laparoscopic surgery for cervical cancer routinely, safely and effectively. With compliance to indications, safe accumulation of surgical experience, and full disclosure of the results of this procedure, minimally invasive surgery for cervical cancer can now be adopted in Japanese healthcare system.

ISP-20-7

Solitary adrenal metastasis derived from small cell carcinoma of the uterine cervix Yosuke Kawai, Seiko Matsuo, Satoru Katsuki, Atsushi Yabuki, Kei Fujita, Kazuhisa Kitami, Yoshiki Ikeda, Mizuki Takano, Kota Umemura, Mayumi Okada, Hisao Ando, Michiyasu Kawai *Toyohashi Municipal Hospital*

Introduction Small cell carcinoma (SCC) is a well–known tumor that occurs predominantly in the lung. SCC of the uterine cervix comprises less than 2% of all cervical cancers and is know to be highly undifferentiated. The majority of the metastatic lesions of the adrenal gland normally originate from lung cancer, colon cancer, gastric cancer, breast cancer and melanoma. We report a rare case of a solitary adrenal metastasis derived from SCC of the uterine cervix that was successfully treated with surgical resection. **Case report** A 37–year–old woman (gravida 1, para 1) came to our hospital due to irregular vaginal bleeding. Cervical cytology demonstrated small cells with coarse chromatin and prominent nucleoli. Punch biopsy of the uterine cervix was suggestive of SCC. The patient underwent radical hysterectomy for stage IB1 cervical cancer. Histologically, tumor cells were monotone, with scanty, ill–defined cytoplasm and hyperchromatic nuclei. The tumor consists of solid growth of small cells showing positive immunohistochemical staining for chromogranin, synaptophysin and neural cell adhesion molecule (NCAM). She received concurrent chemoradiotherapy postoperatively. Nineteen months after surgery, follow–up CT and FDG–PET/CT showed a solitary mass enhanced heterogeneously in the left adrenal gland. There was a solitary left adrenal metastasis without any other metastasis. The adrenal metastasis was removed in abdominal surgery. **Conclusion** The authors suggest that solitary adrenal metastasis should be routinely considered for surgical management. To the best of our knowledge, this is the first case of solitary adrenal metastasis derived from SCC of the uterine cervix.

ISP-20-8

A case of spontaneous pregnancy after abdominal radical trachelectomy and adjuvant chemotherapy for stage 1B1 cervical cancer Hiroko Fukuoka[1], Naho Umezawa[1], Soonna Yun[1], Azusa Wada[1], Chifumi Ooyagi[1], Hiroaki Tsubouchi[1], Aya Fukuda[1], Kiyoshi Yoshino[2], Tateki Tsutsui[1] *Japan Community Healthcare Organization Osaka Hospital[1], Osaka University[2]*

Radical trachelectomy (RT) has become a useful and oncologically safe treatment modality for patients with early invasive cervical cancer who wish to preserve their fertility. Here, we present a case of spontaneous pregnancy after abdominal RT and adjuvant chemotherapy for stage 1B1 cervical cancer. In this case, the tumor was 35 mm. A 31–year–old nulligravid married woman presenting with vaginal discharge visited a local clinic. A cervical papillary growth was detected and she was referred to our hospital. The tumor was hemorrhagic and fragile, and tumor biopsy revealed squamous cell carcinoma. A pelvic MRI showed a uterine cervical tumor with exophytic growth, measuring about 3 cm in diameter and mainly located on the anterior cervical lip. Distant or lymph node metastases were not suspected ; hence, we diagnosed stage 1B1 cervical cancer, and abdominal RT was performed. The tumor had a maximum diameter of 35 mm, and the final pathological diagnosis was non–keratinizing squamous cell carcinoma without pelvic lymph node metastasis or interstitial infiltration. Our operative indication for RT is that the tumor is below 30 mm in cases of exophytic tumor ; however, the patient did not wish to undergo hysterectomy. Adjuvant chemotherapy was administered three times after surgery. She was followed closely without additional treatment and no relapse was detected. One year and six months after surgery, the patient became pregnant spontaneously. In further studies, we would like to investigate past case reports to add bibliographic value.

ISP-20-9

Clinical application of photoacoustic imaging for uterine cervical lesion : a preliminary report Kiguna Sei, Hidenori Sasa, Ayako Suzuki, Tomoyuki Yoshikawa, Tadashi Aoyama, Morikazu Miyamoto, Masashi Takano, Kenichi Furuya *National Defense Medical College*

Objective Colposcopy is the important technique for detailed histological assessment in the screening for uterine cervical cancer. However, it has limitations in its accuracy, especially in adenocarcinomas or lesions in deep cervical ducts in elderly women. The photoacoustic (PA) imaging provides microvessel images by using the wavelength of light strongly absorbed by hemoglobin. The aim of this study is to evaluate the capacity of PA imaging system in detection of cervical lesion. **Methods** The PA imaging system used in this study provides ultrasound echo images with superposition of PA images by linear and transvaginal probes. Transvaginal scanning of cervix was performed for all participants, and linear scanning was done in the samples of conization. We retrospectively analyzed the PA images and compared with reports of histology and magnetic resonance images. **Results** Cancer and severe squamous intraepithelial lesion (SIL) associated with high-density microvessels generated significantly higher PA signal intensity than low-grade SIL. In many cases, high-intensity PA signals were found in biopsy regions equal or severer than cervical intraepithelial neoplasia (CIN) grade 2. Biopsy regions with no malignancy or CIN grade 1 generated weak or no signals. PA images also provided the information of deep lesion in some cases. In the conization cases, high PA signal was found in the region of CIN grade3 or carcinoma in situ. **Conclusion** The results indicated that the PA image detected severe lesions, which may improve efficacy of the cervical cancer screening strategies.

ISP-20-10

Leukocytosis and thrombocytosis at the first diagnosis predicts clinical outcome in uterine cervical cancer patients Yoshiya Miyahara[1], Senn Wakahashi[1], Yasuhiko Ebina[1], Shoji Nagao[2], Tamotsu Sudou[2], Satoshi Yamaguchi[2], Hideto Yamada[1] *Kobe University[1], Hyogo Cancer Center[2]*

Objective To analyze the prognostic values of leukocytosis and thrombocytosis at the first diagnosis in patients with uterine cervical cancer in comparison with various risk factors and, to clarify whether leukocytosis and thrombocytosis can predict the prognosis of patients. **Methods** We assessed retrospectively the characteristics and outcomes of 2,266 patients with FIGO stage I–IV cervical cancer between January 1990 and January 2012 in our Hospital and the other hospital. We investigated the effects of age, clinical stage, histology, and leukocytosis or thrombocytosis at the first diagnosis on Overall survival (OS), and which factor predominantly affects the OS, leukocytosis or thrombocytosis at the first diagnosis by dividing the patients into 4 groups. OS was determined using the Kaplan-Meier method and compared using log-rank test. A Cox proportional hazards regression model was used to calculate the prognostic significance. **Results** Leukocytosis and thrombocytosis at the first diagnosis was observed in 318 patients (14%) and in 134 patients (5.9%), respectively. Multivariate analysis revealed that leukocytosis (HR : 1.5, $p<0.01$) and thrombocytosis (HR : 2.0, $p<0.01$) were independent predictors of decreased OS. The group 1 [T (p) and L (p)] showed significantly shorter OS than the group 2 [T (p) and L (a)] ($p<0.05$) and the group 3 [T (a) and L (p)] ($p<0.001$). And the group 2 [T (p) and L (a)] showed significantly shorter OS than the group 3 [T (a) and L (p)] ($p<0.001$). (T : Thrombocytosis, L : Leukocytosis, p : presence, a : absence) **Conclusion** Our results suggested much attention should be payed to patients with thrombocytosis because patients with thrombocytosis had poorer OS than those with leukocytosis.

ISP-20-11

To increase the populations participation in uterine cervical cancer screening process—Uterine cervical cancer screening at the physical checkup of the company— Yusuke Matsuura, Makoto Yoshioka, Toru Hachisuka *University of Occupational and Environmental Health*

Objective The population with cervical cancer screening experience is quite low compared to other developed countries. We studied the status of uterine cervical cancer screening in annual company checkups and clarified problems. **Methods** Of questionnaires sent to occupational health physicians, the 127 valid responses showed that cervical cancer screening is conducted in 100 companies (79% ; including health insurance society). We obtained detailed information from 50 of these 100. **Results** Mandatory cervical Pap tests are conducted at just 6 companies (12%) and annual Pap tests at 35 of 48 (73%). Only 18 of 49 companies (37%) start Pap tests for employees 20 years old, and Pap test is started at 30 years at 9 of 49. Of the 31,294 of 86,695 women (36%) screened for cervical cancer, abnormal Pap smear results were found in 3.0%. The cervical cancer screening rate have been increasing compared to our previous studies (17% in 2004, 23% in 2008). Colposcopy and punch biopsy were conducted in 70% (61 of 87 women) of those with abnormal results. Twelve of 26 companies had no information about detailed examination results. **Conclusion** Uterine cervical cancer screening by companies is very useful because of growth in the female working population. Physicians at companies should therefore survey female health care by including uterine cervical cancer screening. We have to give the information that cervical cancer incidence and mortality have been increasing among young women in Japan.

ISP-20-12

Multi-institutional survey of QOL after treatment for uterine cervical cancer—Comparison between radical radiotherapy and surgery— Yuko Kaneyasu[1], Hisaya Fujiwara[2] *National Hospital Organization Fukuyama Medical Center[1], Chugoku Rosai Hospital[2]*

Objective Quality of life (QOL) after early-stage uterine cervical cancer treatment is an important criterionwhen patients choose treatment. However, the effects on QOL of different treatments remainunknown. Multi-institutional report on QOL in a joint study of the JASTRO problem study andJROSG gynecologic cancer committee is presented. **Methods** A questionnaire survey was conducted on patients 20 to 70 years old with stages Ib1-IIb by radicalradiotherapy (RT) or radical operation (OP), who were outpatients without recurrence more thansix months after the treatment. **Results** A total of 100 patients was registered with 50 in each group. The RT group included stage I/II : 17/33 cases, the OP : 33/17 cases. The OP group included 28 patients with postoperative RT. The average age was 53 in the RT and 44 in the OP group. Combination chemotherapy was performed in 42 patients in the RT and 24 in the OP group. After adjustment for age and stage on logistic analysis, significant differences were evident in BMS/rectal bleeding in the RT, and leg edema in the OP group on the physicians questuonnaire. On the patient questionnaire, although no significant difference was found in the incidence of leg edema with postoperative RT, the degree of irreversible leg edema was significantly higher in the post OP-RT than in the surgery only group. As for the sexual activity, no significant differences were found between the groups. **Conclusion** The present findings about complications and sexual activity of both treatments will be useful for patients

when making treatment choices in the future.

ISP-20-13

Teaching on the run training program for post-graduate-first-year residents effectively improves accuracy and quality of Papanicolaou smears Shih-Chieh Liu, Hsin-Ju Chiang, Yu-Che Ou, Hao Lin, Kuo-Chung Lan *Kaohsiung Chang Gung Memorial Hospital, Taiwan*

Introduction Papanicolaou smear (Pap smear) with cervical cytology could reduce incidence and mortality rate of cervical cancer. However, poor quality of Pap smears would negatively affect the power of screening. We are interested if a new teaching skill, Teaching On The Run (TOTR) tips, effective in training residents to perform Pap smear and reduing the rate of unidentifiable smears. **Materials** Through May to December 2015, post-graduate-first-year (PGY1) residents were divided into two groups. Residents in without-TOTR group, would receive traditional teaching, whereas with-TOTR group would receive TOTR program described as following. Before the beginning, learning materials were provided. Residence would be oriented about the program and learn the procedure by seeing and doing. Teachers would demonstrate the procedures and residences would practice under supervision from senior gynecologist. In the end, we would evaluate their skills by using Direct Observation of Procedural Skills (DOPS). They were also required to review the smear reports. There were two feedback timings, when residents could share experience and difficulty with teachers. **Results** There were 22 and 18 residents receiving TOTR and traditional teachings. As a whole, TOTR reduced the rate of unidentifiable smears from 34.1% to 24.1% ($p<0.0001$). In PGY1, the rate of unidentifiable smears was lower in the with-TOTR group (2.16% vs. 5.81%, $p=0.018$). After TOTR traing, residents had less scarce cells (12.8% to 8.2%) and overlapping cells or contained blood (5.8% to 3.6%) (both $p<0.005$). **Conclusion** Our study proved that TOTR program indeed improved accuracy of Pap smears performed by PGY1 residents.

ISP-21-1

Retrospective study on ovarian cancer treatment for the patients older than 80 years Takafumi Ujihira, Yasuhisa Terao, Kazunari Fujino, Tsuyoshi Oota, Atsuo Itakura, Satoru Takeda *Juntendo University*

Objective Along with the aging society, the opportunities to treat for elderly ovarian cancer patients are increasing in Japan. To provide the appropriate treatment of cancer in the elderly patients has become a very important issue on the base of the postoperative QOL. We conducted our study to investigate the current status, patient's prognosis and QOL of ovarian cancer treatment for elderly patients over the age of 80 patients which takes into account the patient's prognosis and QOL. **Methods** In the facilities that belong to the Kanto Society of Obstetrics and Gynecology, with respect to more than 80 years of ovarian cancer treatment between January 2007 and December 2011, a questionnaire survey was conducted.. **Results** From the survey results obtained from the 17 facilities. Sixty-five cases were reported from the survey. Majority of the patients was in good performance status (0-1 ; 65%) and had some preoperative complications (85%) at the time of diagnosis. The patients treated surgical treatment were 41 cases. None of patients treated lymphadenectomy, none of surgery related death within 4 weeks, but chemotherapy related death within 4 weeks was 2 patients in this study, both of patients were in PS3. Difference of 5-year survival rate for the patients with FIGO stage I -II disease depended on their performance status, but did not have a difference with FIGO stage III-IV. **Conclusion** In the ovarian cancer cases over the age of 80 from our survey, if performance status is good, systemic chemotherapy or surgical treatment without lymphadenectomy can be considered as an option for the treatment.

ISP-21-2

Efficacy of Secondary Debulking Surgery for Multiply Relapsing Ovarian Cancer : single institute retrospective review of eight cases Taito Miyamoto, Tsukasa Baba, Yoshimi Kitawaki, Ryusuke Murakami, Kaoru Abiko, Ken Yamaguchi, Junzo Hamanishi, Noriomi Matsumura *Kyoto University Hospital*

Objective The prognosis of recurrent ovarian cancer remains unsatisfactory as most cases are resistant to current chemotherapy. Secondary debulking surgery (SDS) is expected to prolong post-recurrence survival by diminishing chemo-resistant tumors, but is designated applicable only in cases all macroscopic disease could be excised. Thus, SDS for multiple site relapse (MS-SDS) is often discouraged and its efficacy and feasibility are not well elucidated. **Methods** The clinical outcomes of eight ovarian cancer patients who underwent MS-SDS in years between 2004 and 2016 were retrospectively reviewed. **Results** The mean age of patients was 58.6 years (n=2, 1, 3, and 2 at FIGO stage I, II, III, and IV, respectively). Complete or optimal resection had been achieved in the prior treatment for all cases. The mean disease-free interval was 28.0 months. Peritoneal involvements were observed in all patients, and half of them were accompanied with more than 3 distinct lesions. In six cases, MS-SDS was collaboratively operated with other departments. Complete or optimal resection was achieved again in five or one patients, respectively. The mean blood loss was 1145ml and operation time was 395 minutes. Perioperative death was not observed, but two patients were complicated with ileus or wound dehiscence. Three patients are still alive without disease, while three died of disease. The mean survival after MS-SDS was 20.3 months. **Conclusion** The safety and efficacy of MS-SDS for recurrent ovarian cancer were satisfactory. Developing a forecasting system for complete excision and pursuing a prospective investigation are warranted to make MS-SDS standardized.

ISP-21-3

Evaluation of weekly paclitaxel and carboplatin therapy in primary ovarian and peritoneal cancer Aiko Nagumo[1], Michihiro Tanikawa[1], Tomoko Kashiyama[1], Kenbun Sone[1], Mayuyo Mori[1], Kazunori Nagasaka[1], Katsuyuki Adachi[1], Takahide Arimoto[1], Katsutoshi Oda[1], Kei Kawana[3], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2], School of Medicine, Nihon University[3]*

Objective Weekly paclitaxel and carboplatin therapy (wTC) is practically considered to increase the feasibility for patients with poor performance status (PS) and complications. The aim of this study is to clarify the adverse events and clinical outcome in ovarian and peritoneal cancer patients treated with wTC. **Methods** Total 34 primary ovarian and peritoneal cancer patients were treated with wTC (paclitaxel 80mg/m^2, carboplatin AUC2, 3 weekly courses with 1 week break) from 2002 to 2016 in our hospital and retrospectively reviewed. Response rate and toxicity was analyzed using RECIST and CTCAE (ver 4.0). **Results** Median age was 66 (range, 35-81). PS was generally poor (median 3, range 1-4) and stage was mainly advanced (stageI ; 1, stageII ; 1, stageIII ; 14, stageIV ; 18). Sixteen cases had severe complications, including bowel obstruction, thrombosis, infection and renal failure before wTC therapy. wTC was initiated from the 1st course in 23 cases, and the remaining 11 cases received weekly TC, following tri-weekly TC regimen due to adverse effects. Grade 3/4 hematologic toxicity was ob-

served in 29 cases (85%) and Grade 3/4 non hematological toxicity was observed in 7 cases (21%). Overall response rate was 56%. The general condition (such as PS and complications) was improved in 15 (65%) out of 25 patients, and the 15 patients could receive triweekly TC (or dose-dense TC) and/or interval debulking surgery, following wTC (median 3.2 courses ; range, 1-8). **Conclusion** Considering the feasibility and response rate, wTC may be an alternative option for ovarian and peritoneal cancer patients with poor general condition.

ISP-21-4

Clinical outcome after fertility-sparing surgery for patients with epithelial ovarian cancer Kazunari Fujino, Yasuhisa Terao, Miki Kimura, Takafumi Ujihira, Kensuke Hamamura, Tsuyoshi Oota, Atsuo Itakura, Satoru Takeda *Juntendo University*

Objective Along with late marriage and late birth, facility has increased to perform a fertility-sparing surgery (FSS) for ovarian cancer patients younger than 40 years old. We aim to consider clinical outcome of epithelial ovarian cancer patients who has performed FSS, and to verify the adaptation of FSS. **Methods** We conducted retrospective analysis about the mean onset age, procedure, histopathological type, stage, recurrence, pregnancy and childbirth outcomes for epithelial ovarian cancer 25 cases that performed FSS between 1994 and 2015 at our hospital. **Results** The median age is 33 years old, approach of the initial surgery had occupied 28% of the total laparoscope. Surgical procedure is mainly salpingo-oophorectomy 36% or salpingo-oophorectomy + partial omentectomy 32%, tumor enucleation has been enacted in 16%. Lymphadenectomy or biopsy has been performed in 16%. Histopathological type were 41% mucinous adenocarcinoma, 22% clear cell adenocarcinoma, 19% serous adenocarcinoma, 7% endometrioid adenocarcinoma, and mixed type 4%. Clinical stage classification were stage IA 40%, stage IC 44%, the rest were classified beyond stage IIA in 16%. Recurrence was observed in 20%. After the initial treatment, reproductive outcome until now was 5 pregnancy in 5 cases, and 4 live birth got from 3 delivery. **Conclusion** 10 cases of stage IA regardless of the presence or absence of postoperative adjuvant chemotherapy, all of which can be confirmed disease-free survival, is considered to be a good adaptation of the FSS. All recurrences are observed in stage IC or more, some cases were also poor prognosis at the time of relapse. There is a necessary to careful observation.

ISP-21-5

Nogitecan for recurrent ovarian/peritoneal carcinomas : a preliminary result of 21 cases Masashi Takano[1], Tadashi Aoyama[2], Morikazu Miyamoto[2], Tomoyuki Yoshikawa[1], Kento Kato[2], Hiroki Ishibashi[2], Hideki Iwahashi[2], Hiroaki Soyama[2], Masafumi Kato[2], Tomoko Goto[2], Hidenori Sasa[2], Kenichi Furuya[2] *Department of Clinical Oncology, National Defense Medical College Hospital[1], National Defense Medical College Hospital[2]*

Objective Nogitecan is one of the key drugs for recurrent ovarian cancers (ROC). However, tailored-therapy for ROC has not been established. The aim of the study was to evaluate the effects and toxicities of nogitecan monotherapy for the patients with ROC. **Methods** Clinicopathologic factors of the patients with ROC treated with nogitecan at our hospital were retrospectively analyzed. Response was evaluated with RECIST 1.1, and adverse effects were assessed by CTCAE v4.0. **Results** A total of 21 cases were treated, and median age of the patients was 57 years (range : 34-76). Median number of previous regimen was 4 (range : 1-8), and median treatment-free period was one months (range : 1-11 months). Fourteen cases (67%) had refractory ROC tumors. Initial dose of daily nogitacen was 1.0 or 1.2 mg/m^2 on days 1-5, q4weeks. Median cycle number of nogitecan was 3, ranging from one to six. Grade 4 hematologic toxicities were observed in a case (5%) with thrombocytopenia and three cases (14%) with neutropenia. Grade 3 non-hematologic toxicities were detected in a case (5%) with diarrhea and another (5%) with arthritis. Nogitacan treatment was discontinued due to toxicities in two cases. Response was evaluable in 18 cases : 5 cases with Stable disease, and 13 cases with progressive disease. **Conclusion** The present case series did not show the effectiveness of nogitecan monotherapy in patients with ROC. The results might be affected by the characteristics of the cases, such as heavily pretreated cases, or refractory ROC. A tailored therapy using Nogitecan should be further evaluated in a large cases with ROC.

ISP-21-6

Improvement of Surgical Cytoreduction in Advanced Ovarian Cancer Through Combined Neoadjuvant Chemotherapy and Interval Debulking Surgery Mitsuhiro Nakamura[1], Ryusuke Murakami[1], Tsukasa Baba[1], Yoshimi Kitawaki[1], Taito Miyamoto[1], Kaoru Abiko[1], Ken Yamaguchi[1], Junzo Hamanishi[1], Noriomi Matsumura[1], Masaki Mandai[2], Ikuo Konishi[3] *Kyoto University[1], Kinki University[2], Kyoto medical center[3]*

Objective In advanced ovarian cancer, complete surgical resection of the tumor significantly affects patients prognoses. The aim of our study is to examine the effects of neoadjuvant chemotherapy (NAC) **Methods** 156 patients diagnosed and treated for ovarian, fallopian tube and peritoneal cancer at FIGO stage 3C and 4 from 1998 to 2016 at our hospital were retrospectively assessed. For ascertaining a better NAC regimen in order to achieve complete cytoreduction at surgery, we compared one group treated with triweekly TC (TC : paclitaxel and carboplatin) and another with dose dense TC (ddTC). **Results** 84 patients were treated with primary debulking surgery (PDS) and 74 were treated with NAC followed by interval debulking surgery (IDS). The rate of complete surgery was significantly higher in the IDS group (n=74, complete/optimal/suboptimal= 46/18/10) compared to the PDS group (n=84, 30/23/29) (p= 0.0013). Overall survival was also significantly longer in the IDS group compared with the PDS group (p=0.017, HR=0.55, 95%CI 0.335-0.900). The rate of complete surgical cytoreduction was significantly improved in the ddTC group (n=25, 21/2/2) compared to the TC group (n=45, 22/16/7) (p=0.01). **Conclusion** In advanced ovarian cancer, NAC followed by IDS may improve the rate of complete surgery and overall survival. Dose dense TC may be the superior regimen for achieving complete cytoreductive surgery.

ISP-21-7

Bevacizumab is safe in appropriately selected and managed patients with recurrent ovarian cancer : a multicenter prospective observational study Tatsuya Matsunaga[1], Megumi Furugoori[2], Yukio Suzuki[1], Yoshinobu Sugo[1], Izumi Nakashima[3], Yumi Ishidera[4], Ken Sugiura[5], Tae Mogami[1], Naho Ruiz Yokota[1], Mikiko Sato[1], Etsuko Miyagi[1] *Yokohama City University Hospital[1], Yamato Municipal Hospital[2], Yokohama South Mutual Aid Hospital[3], Yokohama Municipal Citizen's Hospital[4], Yokosuka Mutual Aid Hospital[5]*

Objective We investigated the safety and efficacy of bevacizumab in combination with chemotherapy in women with recurrent ovarian cancer in Japan. **Methods** This multicenter prospective observational study enrolled patients with recurrent ovarian cancer following remission or during maintenance therapy, irrespective of time to relapse and previous regimens. Patients with >three prior regimens or a history or bowel obstruction were ineligible. The primary endpoint was incidence

of adverse events, and secondary endpoints were response rate and progression-free survival. The protocol was approved by the hospitals' ethics committees. **Results** We enrolled 19 patients from four hospitals between October 2014 and August 2016. Time to recurrence was <6 months in two cases (10%), 6–12 months in seven (37%), and >12 months in 10 cases (53%). The median follow-up duration was 10.6 months, median number of chemotherapy cycles was 4.4, and median number of bevacizumab cycles was 11.8. Chemotherapy included a taxane + carboplatin in 12 cases, gemcitabine + carboplatin in six, irinotecan + cisplatin in two, and gemcitabine in two. Among 14 evaluable cases, eight achieved complete responses (57%), three achieved partial responses (21%), and three had progressive disease (22%). Bevacizumab-related adverse events occurred in eleven patients (57%), including grade 2 (G2) hypertension in eight, and G3 hypertension, G2 bowel obstruction, and G4 thrombosis in one patient each, though the role of bevacizumab in the case of thrombosis was unclear. **Conclusion** These results suggest that bevacizumab is safe in appropriately selected and managed patients with recurrent ovarian cancer.

ISP-21-8

Safety and Efficacy of Gemcitabine plus Carboplatin with or without Bevacizumab in Patients with Platinum-Resistant/Refractory Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer Hiroki Nasu, Shin Nishio, Kana Fujisaki, Teruyuki Yoshimitsu, Masahiro Momozaki, Ken Matsukuma, Sumire Mishima, Atsumu Terada, Naotake Tsuda, Koichiro Kawano, Kan Komai, Kimio Ushijima *Kurume University Hospital*

Objective Synergistic effects of gemcitabine in combination with carboplatin thorough inhibition of repair of DNA cross-links was reported in platinum-resistant ovarian cancer. We evaluated the safety and efficacy of gemcitabine plus carboplatin (GC) with or without bevacizumab (B) in patients with platinum-resistant/refractory ovarian, cancer(PROC). **Methods** Patients of PROC with evaluable lesion received C AUC4 (day 1), G 1,000mg/m^2 (day1, day8) ±B 15mg/kg (day1) repeated every 3 weeks. Treatment was continued until disease progression or unacceptable toxicity. After discontinuation of GC, triweekly B as maintenance therapy was allowed. **Results** Among 12 patients, most frequent histologic subtype was serous. And the median platinum-free interval was 4.5 months (range 0–5). Totally, 81 cycles of GC were administered, and median cycles administered were 6 (range 2–11). 6 of 12 patients received GC with B. Overall response rate was 50% (n=10 ; CR 1, PR 4, SD 4, PD 1, NE 2), and median progression free interval was 8 months (range 2–16). The major toxicity was neutropenia (grade 3/4 ; 83.3%), but no neutropenic fever occurred. Grade3 carboplatin hypersensitive reaction was seen in only one patient. No other grade 3/4 non-hematologic toxicity was observed. **Conclusion** GC±B is a safe and effective treatment for the patients with PROC.

ISP-22-1

Efficacy of combination chemotherapy with topotecan plus bevacizumab for patients with platinum-resistant first recurrent ovarian cancer Tetsuya Kokabu, Taisuke Mori, Hiroshi Matsushima, Hisashi Kataoka, Kaori Yoriki, Kyoko Akashi, Haruo Koroboshi, Hiroshi Tatsumi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Objective To investigate the efficacy of combination chemotherapy with topotecan and bevacizumab for patients with platinum-resistant first recurrent ovarian cancer. **Methods** Between April 2014 and September 2016, patients with the platinum-resistant recurrent ovarian cancer who received the combination chemotherapy with topotecan, 1.25 mg/m^2, day 1–5, q3 weeks, and bevacizumab, 15 mg/kg, day 1, q3 weeks, were examined. The response to the regimen were evaluated in accordance with RECIST guidelines. Adverse events were evaluated by grade in accordance with CTCAE version 4.0. Progression-free survival and overall survival were evaluated by Kaplan-Meier analysis. **Results** A total of 10 patients were examined. Median follow-up period was 6.8 months (range 2–17). The median age was 64 year-old (range 46–76), and the number of pre-treatment regimens was 1–3. Histological subtype consists of 6 serous, 2 clear, 1 serous borderline, and 1 mixed (serous and clear). Objective response rate (CR+PR) was 40% and clinical benefit rate (CR/PR/SD) was 60%. Especially, two of three cases with peritoneal or pleural effusion were dramatically improved. Median progression-free survival was 4.9 months and overall survival was 15.5 months. The incidence of grade 3/4 adverse events included neutropenia (50%), cerebral infarction and pulmonary embolism (10%), gastrointestinal perforation (10%) and febrile neutropenia (10%). Six patients have been alive with recurrent ovarian cancer. **Conclusion** Combination chemotherapy with topotecan and bevacizumab could be one of therapeutic strategies for patients with platinum-resistant recurrent ovarian cancer, although careful case selection should be considered since some of adverse events are severe.

ISP-22-2

Trousseau's syndrome in association with ovarian clear cell carcinoma Kentaro Kai[1], Chiharu Mizoguchi[2], Kaei Nasu[2], Yuichi Furukawa[1], Hisashi Narahara[2] *Nakatsu Municipal Hospital[1], Oita University Faculty of Medicine[2]*

Introduction Trousseau's syndrome is a paraneoplastic neurologic syndrome that is the most common cause of death in cancer patients other than the cancer itself. Although ovarian clear cell carcinoma (CCC) is well known to be associated with a high incidence of thrombosis in deep veins and pulmonary arteries, Trousseau's syndrome associated with ovarian CCC is rare. **Case** A 55-year-old right-handed Japanese woman was referred to our hospital complaining of anarithmia. A left frontal lobe cerebral infarction had been identified by MRI at another facility. Enhanced-contract computed tomography revealed a left renal infarction, peritoneal dissemination and massive ascites. A cytological examination of the uterine cervix, endometrium and ascites demonstrated adenocarcinoma. Pelvic enhanced MRI demonstrated a left tubal tumor. The patient then developed a left parietal robe infarction, deep venous thromboses, pulmonary artery thrombosis, and a left atrium thrombus. The results of screening lab tests for thrombophilia were all negative. We diagnosed Trousseau's syndrome in association with the tubal cancer (cT3cN0M0). An inferior vena cava filter was installed, and the patient underwent neoadjuvant chemotherapy and concomitant low-molecular-weight heparin therapy. After three cycles of dose-dense paclitaxel plus carboplatin, the patient underwent interval debulking surgery. The pathological examination showed primary ovarian CCC (ypT3 cN0M0). She completed four cycles of adjuvant chemotherapy and has been free from relapse for 6 months. **Discussion** When Trousseau's syndrome is suspected in a patient with both cancer and cerebral infarction, an early diagnosis, tumor control of the primary disease, and anticoagulation therapy can improve the patient's quality of life.

ISP-22-3

Ovarian high grade serous carcinoma initially presenting as axillary lymphadenopathy Kazuya Oonuma, Takanori Fukuda, Yutaka Kohata, Kenji Hishikawa, Takeshi Kusaka, Naomi Ochiai, Yoshie Uzawa, Remi Watanabe, Yuri Aihara, Ayumi

Kumagai, Hiromi Inoue *Shonan Kamakura General Hospital*
Background High grade serous carcinoma of the ovary frequently presents in advanced stage with symptoms related to intraabdominal tumor burden. It is very rare to have palpable axillary lymphadenopathy as the initial presentation without intraabdominal tumor spread. **Case** A 65 year-old woman presented to breast surgery clinic with a palpable right axillary mass. Biopsy of the mass showed metastatic adenocarcinoma. While comprehensive imaging studies did not reveal breast lesions, a computed tomography demonstrated a right adnexal mass of 10 cm. She was referred to our clinic with the presumptive diagnosis of ovarian carcinoma and axillary metastasis. MRI demonstrated a right adnexal mass consistent with ovarian carcinoma. These two masses were the only lesions detected by imaging studies. Of tumor markers, CA125 and CA15-3 were only slightly elevated. Exploratory surgery revealed an 11 cm solid mass of the right ovary with irregular surface and adherent fallopian tube, but no intraperitoneal tumor spread was noted. The right axillary mass was also excised. Histopathologic examination of both masses showed high grade serous carcinoma with the identical immunohistochemical profile. She received a 6-cycle of carboplatin and paclitaxel chemotherapy, and is currently without evidence of disease. **Conclusion** An isolated distant metastatic lymphadenopathy without intraabdominal disease is an exceptionally uncommon presentation of ovarian carcinoma. Pathologic examination with immunohistochemical markers of the metastatic tumor is the key of determining the primary site. Tumor markers may not be useful. Previous reports indicate that ovarian carcinoma with this atypical presentation may have relatively good prognosis in spite of stage IV disease.

ISP-22-4

Alpha-fetoprotein (AFP) produced by ovarian adenocarcinoma : a report of two cases Rei Gou, Makiko Oomori, Hiroko Fukasawa, Yumika Watanabe, Satoko Sasatsu, Nozomi Hirata, Tsuyoshi Kasai, Akihiko Hashi, Shuji Hirata *University of Yamanashi*
Alpha-fetoprotein (AFP) producing ovarian in postmenopausal women is an uncommon neoplasm. We report here two cases of AFP-producing ovarian adenocarcinoma. **Case 1** A 63-year-old woman was admitted because of suspected ovarian tumor. MRI demonstrated a 13×8cm multilocular cystic mass in the right ovary with solid portions. CT scan showed intrapelvic, paraaortic, and left supraclavicular lymph node involvement, liver and lung metastasis. She had a past history of uterine prolapse, which had been treated by total hysterectomy and left salpingo-oophorectomy. Right salpingo-oophorectomy and omentectomy was conducted. The patient was diagnosed with stage IV and treated postoperatively with six cycles of chemotherapy using intravenous paclitaxel and carboplatin. Serum AFP decreased from 24158 to 12ng/ml after the treatment. **Case 2** A 80-year-old woman presented with abnormal vaginal bleeding. MRI and CT showed a 10×10cm multilocular cystic mass containing solid portions. There were no findings that suggested lymph node metastasis or distal metastasis. Preoperative serum AFP level was 2671ng/ml. The patient underwent abdominal total hysterectomy, bilateral salpingo-oophorectomy and subtotal omentectomy. Lymphadenectomy was not conducted because of old age. As ascitic fluid was cytologically positive, she was diagnosed with stage I C3. Serum AFP decreased after operation. Histologically, in both cases, some glands had clear cytoplasm with prominent subnuclear or supra nuclear vacuoles resembling fetal gut. Immunohistochemically, these tumor showed positive for AFP. There were no typical findings of yolk sac tumor or hepatic carcinoma. Subset of AFP-producing ovarian adenocarcinoma in postmenopausal women may be a proposal for a new histological and biological category.

ISP-22-5

Ovarian mucinous carcinoma with mural carcinosarcomatous components in a premenarchal girl Kayo Suzuki, Hiroki Imada, Akihiro Igarashi, Yoko Saitou, Mao Hisamatsu, Kanami Saitou, Nobuhiko Yamashita, Shin Oonota, Yoshinobu Hamada, Shuichi Sakamoto, Yoshihiko Ueda, Satoshi Takakura *Dokkyo Medical University Koshigaya Hospital*
Malignant ovarian tumors in children are very rare, comprising approximately 1% of all childhood malignant tumors. Although germ cell tumors are relatively frequent, development of epithelial ovarian cancer before menarche is extremely rare. We report a case of a 13-year-old premenarchal girl who developed ovarian mucinous carcinoma with mural carcinosarcomatous components. She visited our hospital for abdominal distention and weight gain. Magnetic resonance imaging (MRI) demonstrated a polycystic ovarian tumor measuring 24 cm. We removed the left adnexa and the tumor ruptured spontaneously. The tumor showed mucinous multilocular cysts with several mural nodules. Histologically it was composed of both benign and malignant mucinous tumor with mural carcinosarcomatous components. We diagnosed FIGO stage IC2. After three weeks from operation, however, MRI detected ascites and peritoneal metastasis in the pouch of Douglas. Although biopsy of peritoneum in the first operation were negative, we considered FIGO stage IIB clinically. The patient was treated with combination therapy of paclitaxel (175 mg/m2) and carboplatin (AUC 5) (TC therapy) every three weeks. Interval debulking surgery (IDS) was performed after four cycles of therapy. We removed the right adnexa, uterus, partial omentum and pelvic peritoneum. Tumor metastasis of right ovary, broad ligament and pelvic peritoneum were confirmed histologically. Additional four cycles of TC therapy were administered after operation. Our case is the first report of ovarian mucinous carcinoma with mural carcinosarcomatous components in premenarchal girls in the world. We suggested importance of IDS even if children.

ISP-22-6

Hypercalcemia induced by ovarian clear cell carcinoma ; a case report Ryosuke Tajiri, Seiji Kagami, Rie Urabe, Taeko Ueda, Tomoko Kurita, Toshinori Kawagoe, Toru Hachisuka *University of Occupational and Environmental Health*
Objective Parathyroid hormone-related peptide (PTHrP) appears as the major causative agent responsible for the humoral hypercalcemia of malignancy. However, the mechanisms of hypercalcemia in small cell carcinoma are still unclear. In the following case report, we tried to determine the etiology of hypercalcemia and also to demonstrate the management of hypercalcemia diagnosed preoperatively. **Case** A 62-year-old woman presented with hypercalcemia caused by elevated serum PTHrP. She was diagnosed as ovarian tumor by computerized tomography and magnetic resonance imaging. She received treatment with elcatonin and zoledronic acid that promptly normalized the serum calcium level prior to her primary surgery. Ovarian cancer was diagnosed as small cell carcinoma by pathological study and she is now receiving postoperative chemotherapy combination of paclitaxel and carboplatin. Post operation, her serum PTHrP declined and hypercalcemia treated. Immunological dyeing demonstrated PTHrP expression in the primary ovarian lesion and she was diagnosed as having a malignant ovarian tumor with hypercalcemia caused by elevated serum parathyroid hormone-related protein. **Conclusion** Humoral hypercalcemia of malignancy in this case has been conclusively shown to be due to the production of PTHrP at the primary ovarian tumor, based on both immunohistochemical and molecu-

lar analyses.

ISP-22-7

Neoadjuvant chemotherapy in primary gynecologic cancers : timing of interval debulking following dose-dense versus traditional paclitaxel dosing regimens Megan Kennedy Burns, Kevin Schuler, Ganga Deviah *TriHealth, USA*

Objective To determine whether patients undergoing dose-dense paclitaxel/carboplatin neoadjuvant chemotherapy for advanced stage ovarian, fallopian tube, or primary peritoneal carcinomas have a higher rate of optimal cytoreduction after 3 cycles of treatment than patients undergoing a traditional 3-week paclitaxel/carboplatin neoadjuvant chemotherapy regimen. Secondary outcomes included pre-operative normalization of CA-125, absolute and percent reduction in CA-125, rate of optimal cytoreduction, and the ability of pretreatment platelet count to predict optimal cytoreduction. **Methods** Forty patients with Stage III and IV ovarian, primary peritoneal, and fallopian tube cancers undergoing neoadjuvant chemotherapy were identified in this retrospective cohort study. Retrospective data was collected and analyzed regarding number of chemotherapy cycles prior to interval debulking, CA-125 decrease, debulking success, and survival for patients undergoing standard every 3-week chemotherapy, compared to patients undergoing dose-dense chemotherapy. **Results** There were no differences in the rate of optimal cytoreduction or pre-operative normalization of CA-125 between standard and dose-dense chemotherapies. The absolute and percentage decrease in CA-125 was greater for the dose-dense group, but this difference was not statistically significant. Survival was slightly prolonged in the dose-dense group, but this was not statistically significant. **Conclusions** This study demonstrates no statistical difference in the number of neoadjuvant chemotherapy cycles needed prior to interval debulking, nor in the preoperative decrease in CA-125 between a standard 3-week paclitaxel regimen and a dose-dense weekly paclitaxel regimen in advanced stage ovarian, fallopian tube, or primary peritoneal carcinomas.

ISP-22-8

Morbidity, mortality and survival in patients with bowel resection in advanced epithelial ovarian cancer and complete cytoreduction Mignon-Denise Keyver-Paik[1], Lucia Otten[1], Eva Egger[1], Alina Abramian[1], Christina Kaiser[1], Thomas Hecking[1], Tiyasha Ayub[1], Anna Doeser[1], Tobias Hoeller[2], Walther Kuhn[1] *Universtiy Womens Hospital Bonn, Germany[1], Institute for Medical Biometry Bonn, Germany[2]*

Introduction We previously showed patients with advanced epithelial ovarian cancer (AEOC) not to benefit from aggressive bowel resection while perioperative morbidity and mortality was increased. We now analyzed the influence of initial tumor burden and aggressive surgical procedures on perioperative morbidity, mortality and survival in completely cytoreduced patients. **Methods** Data of patients FIGO IIIA-IVA, completely cytoreduced between 2002 and 2014 in our institution (n=127) were collected and patients characteristics, perioperative data, rates of bowel resection, perioperative morbidity and mortality and survival data were analyzed. **Results** Patients were FIGO IIIC in 63%, FIGO IVA in 19% (IIIA 5.5%, IIIB 12.6%), median age was 61.6 years (25.0 to 82.8 years). Bowel resections were carried out in 51.2% (3.1% small bowel, 40.9% colon, 4.7% small bowel and colon). Higher grade postoperative complication rates were 29%, including anastomotic leak and postoperative haemorrhage. There was no significant difference between patients receiving bowel resection or none (p=0.159), one patient died perioperatively. OS was 51.0 months, PFS 26.5 months in patients with bowel resection and 47.6 months (OS) and 20.9 months (PFS) without bowel resections (p=0.418/p=0.983). **Discussion** In contrast to previous data shown by our institution on patients with incomplete cytoreduction, patients with AEOC, complete cytoreduction and bowel resections have no increased morbidity and mortality and a comparable survival time to patients where bowel resection was not necessary during tumor debulking. Complete cytoreduction therefore remains the single most important factor for survival, and bowel resection should be done whenever complete cytoreduction can be achieved.

ISP-23-1

A case of disseminated peritoneal leiomyomatosis, occurring after laparoscopic myomectomy with morcellation device. Yusuke Inomata, Katuko Egashira, Tomoko Matsushita, Kana Hiasa, Kiyoko Kato *Kyushu University*

We encountered a case of disseminated peritoneal leiomyomatosis occurring after laparoscopic myomectomy using a morcellation device. A 41-year-old, gravida 1, para 1 woman underwent laparoscopic myomectomy using a morcellation device 8 years ago. The histopathological report was a benign leiomyoma. She felt abdominal fullness 1 year ago and visited us. CT showed 5 nodular intraperitoneal masses those were well enhanced. The diameter of the biggest mass was 20cm. There were no findings indicating malignancy such as bleeding or necrosis inside the tumors in MRI and we planned to perform laparotomy after six times of GnRHa treatment. GnRHa was very effective, and we performed abdominal total hysterectomy, bilateral salpingo-oophorectomy in addition to removal of tumors. In the abdominal cavity, there were 5 masses ranging from 5cm to 9cm, involving the omentum, right abdominal wall, paralectal peritoneum, respectively. The surface of all masses was smooth, and all masses were rich in blood flow. The hystopathological report was leiomyomas and parasitic leiomyomas. Recently, it is known morcelation devices cause disseminated peritoneal leiomyomatosis. We warn disseminated leiomyomas could become this enormous and threaten health of patients. It is imprtant for surgeons not to overlook small fragments of myoma during and after morcellation and make efforts to remove every piece of tissue.

ISP-23-2

Fertility and Perinatal Outcomes following Laparoscopic Myomectomy for Infertile Women : Changes over the Last Decade with Growing Surgical Indication Keisuke Murakami, Mari Kitade, Yuko Ikemoto, Rie Ozaki, Ayako Masuda, Yuki Ujihira, Makoto Jinushi, Keiji Kuroda, Jun Kumakiri, Satoru Takeda *Juntendo University*

Objective In 2005, we reported favorable pregnancy rate and perinatal prognosis after laparoscopic myomectomy (LM). Recently, however, cases of multiple uterine myomas are increasing. We aimed to re-evaluate postoperative fertility and perinatal outcomes. **Methods** 178 infertile women who underwent LM at our hospital from 2010 to 2014 and had at least 1-year follow-up were studied retrospectively. Postoperative pregnancy rate, factors influencing postoperative fertility, perinatal outcomes were reviewed. Postoperative conception was permitted after 6 months of LM. **Results** Of 178 cases, 99 cases (56%) conceived after LM. Compared with previous our report, pregnancy rate was comparable, however, age at LM and count of enucleated myomas were increased (age : from 35.5±3.5 to 37.2±3.8, count of enucleated myomas : from 3.5±3.2 to 7.0±7.4). Spontaneous pregnancy rate after LM correlated with diameter of enucleated largest myoma (OR 1.27, 95% CI 1.04-1.54, p=0.02), count of enucleated myomas (OR 1.06, 95% CI 1.00-1.13, p=0.04) and age at LM (OR 0.79, 95% CI 0.66-0.94, p<0.0001). In ART, pregnancy rate correlated with the presence of preoperative embryo cryo-

preservation (OR 5.02, 95% CI 1.99–12.7, p=0.0006) and age at LM (OR 0.79, 95% CI 0.66–0.94, p=0.006). Spontaneous pregnancy rate was decreasing over 37 years, whereas, pregnancy rate in ART was favorable under 42 years. Of 74 pregnancies who delivered at our hospital, uterine rupture was none, however, 3 cases who were enucleated large number of myomas suffered placenta percreta. **Conclusion** LM is effective for infertile women with uterine myoma, however, indication should be determined carefully with consideration of negative effect by age and perinatal prognosis.

ISP-23-3

Analysis of pregnancy following laparoscopic or abdominal myomectomy Sachiko Morioka, Hiroko Kaniwa, Shoichiro Yamanaka, Sumire Sugimoto, Kana Iwai, Emiko Niiro, Natsuki Koike, Hiroshi Shigetomi, Yasuhito Tanase, Ryuji Kawaguchi, Hiroshi Kobayashi *Nara Medical University*

Objective Impacted by late marriage, myomectomies for uterine symptomatic myomas have been increasingly performed. The rate of laparoscopic myomectomy has also been increasing because of the widespread use of laparoscopic surgery. This study aimed to determine the peripartum risk following myomectomy at our institute. **Methods** This retrospective study was based on a cohort of 207 consecutive cases that underwent myomectomy at our institution between April 2008 and March 2016. **Results** Twenty-two and six pregnancies occurred in the laparoscopic and abdominal myomectomy groups, respectively. The median interval from myomectomy to conception was 18.8 months. The median gestational age was 38 weeks, and the median birth weight was 2886 g. The median Apgar score at 5 min was 10. There were no cases with uterine rupture or threatened premature labor. Only one patient was diagnosed with placenta accreta following laparoscopic myomectomy. The enucleated myoma in this patient was located in the anterior wall of the uterus, whereas the placenta accreta was located in the posterior wall. **Conclusion** At our institution, a prior myomectomy was not associated with higher risks of uterine rupture and placenta accreta. Maternal and neonatal outcomes were favorable. However, further research on the risk of pregnancy following uterine surgery is needed.

ISP-23-4

Risk factors for recurrence after laparoscopic cystectomy in women with ovarian endometriomas Riho Fukutani, Takashi Mimura, Chiaki Iitsuka, Shingo Miyamoto, Mamiko Onuki, Tetsuya Ishikawa, Koji Matsumoto, Akihiko Sekizawa *Showa University*

Objective Recurrence of ovarian endometriomas (OEs) occurs in approximately 40% of women receiving laparoscopic excision. The goal of the present study was to determine risk factors for OE recurrence following laparoscopic surgery. **Methods** We retrospectively analyzed clinical data from 173 women who underwent laparoscopic cystectomy for OEs between January 2008 and December 2015. They were followed up for one year without postoperative hormonal therapy. We compared preoperative MRI imaging data and intraoperative findings between women with and without OE recurrence. Mann-Whitney U test, 2 test and logistic regression models were used for analyses. **Results** Of the 173 study subjects, 23 women had OE recurrence within one year, while 150 women had no recurrence. In univariate analyses, OE recurrence was significantly associated with higher serum CA125 level (median 48.6 vs. 35.0, p=0.02), bilateral OEs (48% vs. 23%, p=0.03), higher r-ASRM score (66 vs. 40, p=0.04) and frozen pelvis (43% vs. 21%, p=0.02), respectively. However, womens age or cyst size did not correlate with OE recurrence. In a multivariate analysis, the risks of OE recurrence were significantly higher among women with bilateral OEs (odds ratio [OR] 17.5, 95% confidential interval [95%CI] 3.3–91.2) and frozen pelvis (OR 9.1, 95%CI 1.6–50.1). **Conclusion** Our data suggested that women with bilateral involvement and/or frozen pelvis may be at increased risks of OE recurrence after laparoscopic excision.

ISP-23-5

Long-term prognosis of ovarian reserve after laparoscopic cystectomy for ovarian endometrioma Rie Ozaki, Jun Kumakiri, Mari Kitade, Keiji Kuroda, Makoto Jinushi, Yuki Ujihira, Shinichiro Ikuma, Keisuke Murakami, Yuko Ikemoto, Ayako Masuda, Satoru Takeda *Juntendo University Faculty of Medicine*

Objective We previously demonstrated evaluation of the preoperative anti-Mullerian hormone (AMH) value was useful for prediction of being postoperative poor ovarian responder (POR) according to Bologna criteria at 6 months after laparoscopic cystectomy (LC). The aim of the study is to evaluate factors influencing on long-term prognosis of ovarian reserve after LC for ovarian endometriomas. **Methods** From 2009 to 2015, 92 patients who underwent LC for ovarian endometriomas at our hospital, and who were followed up to 12 months after surgery were retrospectively analyzed. Patients with less than 1.1 ng/mL referred to the criteria were defined as adverse diminished ovarian reserve (aDOR). **Results** Pre-and postoperative AMH values at 3, 6, 12 months after surgery were 3.4, 1.9, 2.0, and 1.9 ng/mL, respectively. 34 patients (40%) were being aDOR at 12 months after surgery. Age (37.2 vs 33 years, $p<0.001$) and number of patients who underwent bilateral cystectomy (61.8% vs 37.9%, p=0.03) were significantly higher in aDOR patients than non-aDOR patients. Contrary, the preoperative AMH value was significantly lower in aDOR (1.5 vs 4.6 ng/mL, $p<0.001$). The age and preoperative AMH value for prediction of postoperative aDOR were 38.5 years [AUC : 0.735, $p<0.001$], 2.1ng/mL (AUC : 0.885 $p<0.001$), respectively. **Conclusion** Our data demonstrated not only the preoperative AMH value but also patients age at surgery were useful for the prediction of long-term prognosis of ovarian reserve after LC. Therefore, it is considered optimal time for surgery by the evaluation of patients age should be considered to prevent the postoperative decline of ovarian reserve.

ISP-23-6

What is the best medication to prevent post-operative recurrence of endometrioma in the long term? Yoshiaki Oota, Masaaki Andou, Fuyuki Ichikawa, Tsuyoshi Matsumoto, Ryuji Kojima, Keisuke Oyama, Kiyoshi Kanno, Akira Shirane, Shiori Yanai, Saori Najiama, Keiko Ebisawa, Tomonori Hada *Kurashiki Medical Center*

Objective In Japan, it unsuitable as medication for endometriosis, which requires long-term administration. It took about 20 years to develop medication suitable for long-term administration, when Dienogest entered the market in 2008. The 21/7 regimen COC became covered by insurance in 2008, and the 24/4 regimen COC did so in 2010, gradually facilitating medication without dose-period restriction for Japanese people. **Methods** With the consent of the ethics committee of the hospital and adequate informed consent from the patients, the post-operative recurrence rate of ovarian endometrioma during the 5 years after the operation was analyzed in 550 patients in whom the course was followed up without medication or who received post-operative medication for more than 3 years after the operation from 2008 to 2014. The definition of recurrence is endometrioma observed by transvaginal ultrasound and pelvic MRI larger than 2 cm. The control group was the post-operative no-medication group consisting of 293 patients, and there were

89, 51, and 117 patients in the 21/7 regimen COC group, 24/4 regimen group, and Dienogest group, respectively. **Results** The cumulative recurrence rate at the 5th operative year in the post-operative no-medication group was more than 50%. However, it was significantly reduced to 30% in the 21/7 regimen COC group. Furthermore, it was significantly reduced to 5-8% in the 24/4 regimen COC and Dienogest groups compared with the 21/7 regimen COC group. There were no significant differences between 24/4 regimen COC and Dienogest groups. **Conclusion** Dienogest, which is suitable for long-term administration, and a 24/4 regimen of drospirenone, which has a long half-life (30 hours), are considered effective for reducing post-operative recurrence.

ISP-23-7

Usefulness of complete resection of bladder endometriotic lesions by laparoscopic surgery to obtain fertility Takehiro Nakao, Fumihisa Chishima, Akiko Kasuga, Takahiro Nakajima, Hiromits Azuma, Erina Kato, Go Ichikawa, Chuyu Hayashi, Kenji Sugita, Shinichi Takada, Kei Kawana *Nihon University School of Medicine*

Objective Bladder endometriotic lesion is sometime an indication of surgical resection, including laparoscopic surgery. However, usefulness of surgical resection of bladder endometriosis to obtain fertility remains controversial. We here report two cases who got pregnant after laparoscopic resection of bladder endometriotic lesions during infertility treatment. **Cases** Case 1 was a 35-years-old null para women who desired for pregnancy and was diagnosed as ovarian endometrial cyst at 30 years-old. At 34 years-old, she tried IFV-ET but failed. Voiding pain and hematuria appeared at 32 and 35 years-old at menstruation and bladder endometriotic lesion was detected by trans-urethral endoscopic biopsy. She underwent laparoscopic partial resection of bladder with 30mm of bladder endometriotic mass and cystectomy of 40mm of ovarian endometrial cyst (total ASRM score 28). After surgery she got pregnancy by IVF-ET. Case 2 was a 31-years-old null para women who desired for pregnancy and felt cyclic voiding pain and hematuria/abnormal genital bleeding. CT and MRI suggested strongly 18mm of bladder endometriotic mass. She underwent laparoscopic resection of the lesion with combined partial resection of bladder (total ASRM score 4). After surgery, she got pregnancy naturally. **Coclusion** Our two cases received complete resection of bladder endometriotic lesions by urologists and then got pregnancy. In these case, the bladder endometriotic lesions formed mass. For cases with endometriosis forming mass, complete resection of bladder endometriosis with combined resection of bladder may be useful for a goal to obtain fertility, rather than pharmacotherapy.

ISP-23-8

Resection of deep infiltrating endometriosis and continuous hormonal therapy is effective to reduce dysmenorrhea Takeshi Kato, Yuri Kadota, Kana Kasai, Kaoru Keyama, Sumika Matsui, Kanako Yoshida, Minoru Irahara *Tokushima University*

Objective In the treatment of endometriosis, to improve dysmenorrhea is an important task. The patient of endometriosis with dysmenorrhea often has deep infiltrating endometriosis (DIE). We select hormonal therapy or surgery in these cases. In the surgery for the patient with dysmenorrhea, we resect all endometriosis lesions including DIE. Surgery to completely excise DIE, usually needs extensive dissection with advanced laparoscopic skills. Then, because of the high risk of organ injury than usual, it is necessary to consider carefully to indicate surgery. In this study, we examined retrospectively dysmenorrhea improvement effect of DIE resection surgery, and the role of post operative hormonal therapy. **Methods** The subjects of this study were targeted 22 patients who received DIE resection surgery and follow-up more than 1 year after surgery. We conducted a retrospective study to compare the change of dysmenorrhea before and after surgery by Visual analog scale (VAS) score. It was also similarly examined the effect of the presence or absence of hormonal therapy after surgery. **Results** Surgery complications such as organ damage and massive bleeding were not observed. VAS score showed decrease after surgery in 18 cases (81.8%). It incruded 13 cases that have received the hormonal therapy to prevent relapse endometriosis. **Conclusion** DIE resection surgery showed a highly effective against dysmenorrhea. Moreover, postoperative hormonal therapy, it can affect pain improvement was suggested. Moreover, it was suggested that postoperative hormonal therapy can be improved dysmenorrhea.

ISP-23-9

Treatment outcomes of uterine artery embolization with embosphere for symptomatic uterine fibroids : a single-center experience Masaki Koubayashi, Kenjiro Sawada, Kyoso Ishida, Asuka Toda, Tomoyuki Sasano, Tadashi Kimura *Osaka University Hospital*

Objective Uterine artery embolization (UAE) with embosphere for the treatment of symptomatic uterine fibroids has been covered by insurance since January 2014 in Japan. Herein, we present the efficacies and clinical outcomes of UAE with embosphere. **Methods** From January 2014 to August 2016, a total of 26 premenopausal women with symptomatic uterine fibroids underwent UAE with embosphere. Patients were routinely followed up at 1, 3, 6, and 12 months after the procedure. At each visit, uterine fibroids-related symptoms and any UAE-related complications were evaluated by interview. 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** In all cases, UAE was successfully and uneventfully performed. Median age was 45 (range : 38-51) years, and the median follow-up period was 9.9 (1-32) months. Among patients, 24 (93%) patients apparently relieved their fibroids-related symptoms after UAE. The volumes of maximum uterine fibroids on MRI decreased by 37.1% (2-99.3) at 3 month and 50% (-31.9-100) at 12 month compared to the baseline, respectively. During the follow-up period, one patient (3.8%) presented myoma delivery and it was successfully resected at outpatient clinic. One (3.8%) required hysterectomy because of re-growth of fibroids after UAE. **Conclusion** UAE with embosphere is one of good minimally invasive methods to treat symptomatic uterine fibroids.

ISP-23-10

The comparison of continuation rate of low dose estrogen-progestin (LEP) and dienogest in women with endometriosis Michio Kitajima, Ken Taniguchi, Yuriko Kitajima, Ayumi Harada, Naoko Murakami, Masanori Kaneuchi, Kiyonori Miura, Hideki Masuzaki *Nagasaki University Hospital*

Objective Endometriosis is an estrogen dependent chronic inflammatory condition. Medical treatment with low dose estrogen-progestin (LEP) or dienogest (DG) may be chosen for symptom alleviation and recurrence reduction which may deserve long-term management according to women's life stage. Therefore, we compared confounding variables that affect continuation rate of these two popular medications of recent management. **Methods** From 2008 to 2015, 185 women that received prescription of LEP (n=101) and DG (n=84) were retrospectively analyzed. Age at commencement of medication, the period of administration, age and reason of discontinuation, and confounding

clinical background were compared. **Results** The age at commencement and discontinuation were significantly younger in women prescribed LEP than those of DG (33±8 vs. 36±8 years, P=0.02 ; 36±8 vs. 39±7 years, P=0.03, respectively). Mean duration of administration and the number of women who withdrawal medication within one-year were not significantly different between two groups (24±30 vs. 21±23 month ; LEP59% vs. DG56%, respectively). Non-gynecological symptom as a cause of discontinuation was significantly higher in women had prescribed LEP (LEP27% vs. DG11%, P=0.01). **Conclusion** Continuation rate of LEP and DG were comparable though over half of women who started medication stopped within one-year from varieties of reason. Non-gynecological side effects were major factor that affect continuation of LEP in women with endometriosis.

ISP-23-11

The success rate of GnRH agonist for small recurrent endometrioma Oh Sung-Tack *Chonnam National University Medical School, Korea*

The endometrioma is usually treated surgically. However, almost patients do not want re-operation and the decrease of ovarian function is also afraid when endometioma is recuured. Therfore 3-6 months GnRH agonist therapy was performed before final decision of re-operation. The 63 patients with recurred endometrioma received 3-6 GnRH agonist therapy. If endometrioma is disappeared, operation was canceled. We divided two groups ; group A (42 patients) is cyst size 3cm or less, group B (21 patients) is cyst size above 3 cm. We got the result of the effect of 3-6 months GnRH agonist therapy before determination of re-operation in group A and B. Group A : In the 32 of 42 patients, cysts were disappeared after GnRH agonist therapy for 3 months ($p<0.01$). In the 7 of 42 patients, cysts were not disappeared and decreased in size after GnRH agonist therapy for 3 months. The GnRH agonist therapy for 6 months for these patients, and then cyst was disappeared in the 5 of 7 patients (<0.05). Group B : In none of 21 patients, cysts were disappeared after GnRH agonist therapy for 3 months. In only 1 of 42 patients, cysts were not disappeared and decreased in size after GnRH agonist therapy for 3 months. However this one patients had also cyst after the GnRH agonist therapy for 6 months. Therefore, the 3-6 months GnRH agonist therapy can be performed before re-operation in the patients with recurrent endometrioma with cyst size 3 cm or less.

ISP-24-1

Stepwise increase of MIB-1 index in frequently relapsed malignant peritoneal mesothelioma Ryosuke Saito, Satoshi Yanagida, Yuta Kasahara, Daito Noguchi, Keiji Morimoto, Hiroshi Kuroda, Seiji Isonishi *The Jikei University School of Medicine*

Objective Malignant peritoneal mesothelioma (MPM) is a highly aggressive and treatment-resistant cancer ; at present, based on the degree of MIB-1 expression the prognosis of this disease is predictable. This study investigated the stepwise increase of MIB-1 index in a long surviving MPM patient with a history of frequent relapse. **Methods** A 29-year-old Japanese woman showed upper abdominal induration with adnexal tumor. On primary surgery all tumors were resected completely without any residual tumor. Histologically, the tumor was diagnosed as MPM, for which she received adjuvant chemotherapy containing platinum agent. Two years later, the tumor relapsed in her pelvic cavity, but was resected completely with hysterectomy and salpingo-oophorectomy. Histologically, the tumor was diagnosed as MPM relapse. She underwent intraperitoneal chemotherapy with cisplatin that achieved progression-free survival of 5 years. However, relapse was detected again in pelvic cavity. The Tumors were completely removed and were diagnosed as MPM. She received gemcitabine and carboplatin chemotherapy. Now she is alive without any tumor burden for 9 years after initial treatment. To investigate the longevity of this patient in association with the histologic findings, the MIB-1 index and the mitotic index were examined in the primary and relapse tumors. **Results** MIB-1 indices were 4.2±1.1 (mean±SE), 11.8±2.3, and 37.3±2.5 in primary, 1st- and 2nd-relapsed tumor respectively, demonstrating stepwise increase of MIB-1 expression over the surviving time of more than 9 years without any changing of mitotic index. **Conclusion** Stepwise increase of MIB-1 index after frequent relapse and chemotherapy may be indicative of potential drug sensitivity, coming down to a long surviving of this patient.

ISP-24-2

Retrospective analysis of 16 cases of uterine sarcoma Kengo Nakashima, Kotaro Sueoka, Takuya Kajimura, Fumie Shibuya, Toshiaki Taketani, Norihiro Sugino *Yamaguchi University Graduate School of Medicine*

Objective To study the treatment outcome of uterine sarcoma in our hospital **Methods** Sixteen patients with uterine sarcoma (except for carcinosarcoma) were retrospectively analyzed from 2008 to 2016 in our hospital. **Results** The histological types of 16 cases were shown leiomyosarcoma in 4 cases, high grade endometrial stromal sarcoma (ESS) in 1 case, undifferentiated endometrial sarcoma in 3 cases, rhabdomyosarcoma in 1 case, malignant mesenchymal tumor in 1 case and low grade ESS (LGESS) in 5 cases. The patients were classified into 2 groups, LGESS and the other uterine sarcoma (US) group. In eleven cases in the US group, 8 patients from stage I to III had complete tumor resection and one patient had incomplete resection. Four of 8 complete resection cases had relapsed. Four recurrent patients had received the multimodal therapies with poly-surgery, chemotherapy and radiotherapy, and their overall survival time after recurrence were 24, 31, 34 and 37 months, respectively. Two of 5 LGESS patients were initially received surgery alone and resulted in no recurrence. One patient with multiple bone metastases at the first diagnosis was dead of disease at 9 months against hysterectomy, radiotherapy and MPA. One patient was treated with MPA, but her tumor was progressed 5 years after MPA treatment. Another patient was diagnosed by a biopsy para-aortic mass, and the tumor disappeared by MPA therapy. **Conclusion** Aggressive multimodal therapies were useful for the patients with recurrence of uterine sarcoma except for LGESS.

ISP-24-3

Investigation of patients with uterine leiomyosarcoma or high-grade endometrial stromal sarcoma treated at our institution Seiji Kagami[1], Yasuyuki Kinjyo[1], Ryosuke Tajiri[1], Rie Urabe[1], Taeko Ueda[1], Tomoko Kurita[1], Toshinori Kawagoe[1], Yusuke Matsuura[2], Toru Hachisuka[1] *University of Occupational and Environmental Health[1], Nursing of Human Broad Development, University of Occupational and Environmental Health[2]*

Objective Uterine leiomyosarcoma and high-grade endometrial stromal sarcoma are rare tumors with a poor prognosis. New regimens and drugs, gemcitabine-docetaxel (GD), pazopanib, eribulin, and trabectedin, are used in the treatment recently. We examine patients treated for these diseases at our hospital from 1995 to 2016 retrospectively. **Methods** 17 patients (uterine leiomyosarcoma : 15, high-grade endometrial stromal sarcoma : 2) performed the operation were made into the subject. We performed the retrospective study about clinicopathologic findings, treatment, prognosis and others. **Results** Most symptom was

atypical genital bleeding (41%, 7 of 17 patients). 2 of 10 patients (20%) examined were positive in endometrial cytology or biopsy. 11 of 16 patients (60%) elevated serum LDH level. Hysterectomy was performed on all the patients. FIGO stage1 was 14, and stage3–4 was 3 patients. The adjuvant chemotherapy was performed by 12 patients (regimen included ADM : 7, GD : 5). 2nd chemotherapy was performed by 6 of 8 patients recurred (regimen included ADM : 3, GD : 2, BEP : 1). 2 patients were treated by pazopanib, 1 patient was treated by eribulin followed by 2nd line therapy. 5 patients with measurable lesions treated by GD combination therapy. disease control rate was 60% (partial response : 1, stable disease : 2). 2 patients with measurable lesions treated by pazopanib, disease control rate was 50% (partial response : 1, stable disease : 1). 5-year survival rate 43.5%, and 10-year survival rate was 29%. **Conclusion** GD combination therapy was highly effication with advanced or recurrent uterine leiomyosarcoma and high-grade endometrial stromal sarcoma, though our object was a few number of cases. The multi-institutional collaboration in Japan should be started in new therapies.

ISP-24-4

Clinical Outcome of Malignant Melanoma Arising from the Female Genital Tract : a single institute retrospective review of ten cases Yoshimi Kitawaki, Noriomi Matsumura, Tsukasa Baba, Junzo Hamanishi, Kaoru Abiko, Ken Yamaguchi, Ryusuke Murakami *Kyoto University*

Objective Malignant melanoma (MM) arising in the female genital tract (MM-FGT) belongs to mucosal MM which exhibits different tumor genetics from usual cutaneous MM. Due to its rareness, the clinical outcome of MM-FGT has not been well revealed, while the efficacy of immune checkpoint inhibitors including anti-PD-1 antibody has been recently confirmed in the treatment of cutaneous MM. **Methods** Clinical courses of MM-FGT treated from 2005 to 2016 were retrospectively reviewed. **Results** The mean age was 65.2 years. The primary sites of tumor were vulva, vagina, vulva and vagina, urethra, and cervix (n =3/2/1/2/2, respectively). All were at stage 2-3. 1-year survival rate was 87.5% and 3-year rate was 38.3%. Four patients primarily underwent radical excision including pelvic exenteration, while three received local excision and one underwent radiotherapy. Among these eight patients, six further received interferon-β therapy, but in four of them and two without adjuvant therapy, it recurred in 8.8 months. All six had distant recurrence and died of the disease 11.3 months after recurrence. Two patients received anti-PD-1 antibody therapy (nivolumab) for recurrent tumors, and one lived for 26 months after recurrence. Two other patients received nivolumab without surgery or radiation as the initial treatment, and neither tumor progression nor serious adverse events have been observed so far. **Conclusion** MM-FGT is diagnosed at advanced stage with deep stromal invasion and the prognostic outcome is poor even in cases primary tumors are widely excised. Interferon-β therapy is not satisfactory, but the efficacy of nivolumab seems expected to a certain extent although further study is warranted.

ISP-24-5

Large cell neuroendocrine carcinoma of vulva : a case report Yu Kanzaki, Mayo Hino, Eriko Yasuda, Asako Iemura, Nobuyoshi Yokoyama, Reiko Yokoyama, Shogo Yamamura, Harumi Sakata, Aya Toyofuku, Takaaki Yoshida, Kosaku Nakamura *Japanese Red Cross Wakayama Medical Center*

Introduction Neuroendocrine carcinoma (NEC) of the vulva is a rare and aggressive disease, and there hasn't been any report on large cell neuroendocrine carcinoma (LCNEC) of the vulva found. Here we report the first case of a woman with LCNEC. **Case** A 49-year old female presented at our hospital with a tumor in the right major labium. A walnut-sized tumor was palpable, and biopsy proved it to be poorly differentiated adenocarcinoma. Invasion to the fat tissue below was suspected by CT and MRI. Radical vulvectomy, flap reconstruction, and pelvic and inguinal lymphadenectomy was performed. On the histopathological examination, large and sometimes polygonal tumor cells were noted with diffuse growth. Tumor cells were with prominent nucleolus and high mitotic activity. Necrosis within the tumor was also seen. Immunostaining showed positive with CD56, synaptophysin, NSE, EMA and vimentin, and it showed negative with CK20 and chromogranin. She was diagnosed with LCNEC of the vulva, StageIB, pT1bN0M0, and there were no signs of recurrence 6 months after the operation. **Discussion** NEC accounts for only 2% of all gynecologic malignancies. On vulva, most of the case reports are that of Merkel cell carcinoma, and there is no consensus on management of LCNEC. Prognosis of NEC in the genital tract is generally poor.

ISP-24-6

Giant polyp of the uterine cervix : a case report Yasunori Sato[1], Kuniaki Oota[1], Maki Ooishi[1], Arata Kobayashi[1], Keizo Yoshida[1], Yoichi Kobayashi[2], Satoru Shiraishi[1], Mitsutoshi Iwashita[2] *Nasu Red Cross Hospital[1], Kyorin University[2]*

Background Cervical polyps are most commonly seen in the female with uterine bleeding. On the other hand, giant cervical polyps with a size greater than 4 cm are rare and until now only several cases have been described in literature. The size and the clinical presentation can mimic a cervical neoplasia. The management is surgical and can be conservative regarding to the benign pathological feature of this entity. **Case report** We report the case of a giant cervical polyp of 12.0 cm which was protruding from the external cervical os and that developed spontaneously in a multiparous 48-year-old woman who clinically presented vaginal bleeding. Colposcopic examination showed a mass originating from posterior lip of external cervical os. On MRI, there was the appearance of multicystic lesion with an inner solid component. We performed that the lesion was resected by the ultrasonic harmonic scalpel. The histological examination showed benign polyp. At 10 months follow-up, there was no recurrence seen after surgery. **Conclusion** Although carcinomatous change occurs in 1.7% of cervical polyps, malignant degeneration did not occur in the previous reported cases.We concluded that it is possible to resect tumor as noncancerous simply although giant polyp of the uterine cervix is rare. The diagnosis, management and outcome of this rare entity had been reviewed according to the literature.

ISP-24-7

A case of benign multicystic peritoneal mesothelioma Hana Oda, Kiyoshi Hasegawa, Shoko Ochiai, Chiyori Sakamoto, Emi Motegi, Nobuaki Kousaka, Takanori Sakamoto, Ichio Fukasawa *Dokkyo Medical University*

Benign multicystic peritoneal mesothelioma (BMPM) is a rare benign tumor derived from the peritoneal mesothelium. We herein report a case of BMPM along with a review of the literature. A 56-year-old Japanese woman who presented with lower abdominal pain was referred to our hospital due to persisting symptoms. At the previous hospital, computed tomography scans showed multicystic lesions surrounding the ovaries and appendix. She underwent exploratory laparotomy biopsying the multicystic lesions. Pathological findings revealed BMPM. After referral to our hospital, she underwent re-exploratory laparotomy including bilateral salpingo-oophorectomy, appendectomy and tumor debulking to obtain definitive pathological diagnosis, especially to make differential diagnosis from pseudomyxoma

peritonei, and to reduce her persistent symptoms. Pathological findings revealed BMPM same as that of the report from the previous hospital. Her symptoms rapidly reduced and so far there have been no relapse. BMPM is a rare tumor, and although it is considered benign, it has a high recurrence rate, also having the potential for malignant transformation. Surgical resection is said to be the only effective treatment. Preoperative diagnosis of this disease is relatively challenging. Clinicians should be aware of the possibility of BMPM when multicystic lesions are present in the abdomen and pelvis.

ISP-24-8

A case of life-threatening pulmonary embolism after the removal of huge pelvic tumor successfully treated with multidisciplinary therapy Noriko Karakida[1], Marie Mori[2], Akio Tokudome[2], Yoshiko Kijima[2], Shunitirou Ota[1], Shintaro Yanazume[1] *Kagoshima Medical Center[1], Kagoshima University[2]*
We encountered a case with life-threatening pulmonary embolism after the operation of huge pelvic tumor. She was successfully treated with multidisciplinary therapy. The patient was 64 year-old woman. She was refereed to our hospital complaining of abdominal distension. She was diagnosed as having huge pelvic tumor. In pre-operative examination, deep vein thrombosis was not observed. Huge retroperitoneal borderline tumor was surgically removed. During post-operative period, she was treated with elastic stocking, foot pump, low molecular weight heparin, and enoxaparin sodium for 5 days. On post-operative day 11, however, pulmonary embolism suddenly occurred. Thirty minutes after the chest pain, cardiac arrest occurred and she was urgently transferred to ICU. In ICU, on PCPS and artificial respirator, t-PA, heparinization, and anti-coagulant therapy were performed. Three days after the onset, trans-catheteric removal of embolism was attempted. However, anti-coagulant therapy induced copious intraabdominal and subcutaneous bleeding. Her weight gain was 40 kg. A large amount of RCC (152 U), FFP (154 U), and PLT (110 U) were transfused. Six days after the onset, hemodynamics got worse. Eleven days after, intraabdominal hematoma was surgically removed, and then hemodynamics became stabilized. Everything gradually improved. She was discharged without any after-effects.The mortality rate of acute pulmonary embolism is 30%. However, even in this disease, multidisciplinary therapy can reduce mortality rate to 2-8%. Thus, patient with high risk for thromboembolism should be treated at general hospital having multidisciplinary treatment modalities, and having doctors including cardiologist, pulmonologist, and emergency specialist.

ISP-24-9

Onset of Adult T-cell Leukemia-lymphoma during the treatment of peritoneal cancer recurrence: case report Hiroshi Kaneda, Asako Kumagai, Eri Kitamura, Sachi Sukegawa, Kanako Murata, Yoshiko Murase, Satomi Tanaka, Shotaro Yata, Yuka Yamamoto, Toshitaka Tanaka, Naoki Mitsuhashi *Juntendo University Shizuoka Hospital*
Introduction Adult T-cell leukemia lymphoma (ATL) accompanied by HTLV-1 (human T-lymphotropic virus type-1) is peripheral T-cell tumor with a high grade atypical nuclear. We reported a case of ATL that developed during the treatment of recurrent peritoneal cancer. **Case report** 65-year-old woman pointed out a large amount ascites was diagnosed peritoneal cancer because of thickness of peritoneum and high degree of CA125. DC (docetaxel and carboplatin) therapy was undergone as for initial therapy. The relapse of ascites and re-rise of CA 125 level was seen despite of the therapy of Pegylated liposomal doxorubicin and Bevacizumab, and Gemcitabin. Afterwards DC and Bevacizumab therapy decreased the level of CA125. Leukocyte 9100/uL and CRP 22.2 mg/dl became the diagnosis of bacterial infection. Improvement of the level of CRP was observed by antibiotics but did not improve the leukocyte 187700/uL. In the peripheral blood there were a number of immature lymphocytes, including like flower-cell. HTLV-1 antibody values and IL-2R indicates a high level. CT examination showed splenomegaly and lymph node enlargement. Bone marrow puncture could not be enforced because of severe status, but ATL has been diagnosed. The standard chemotherapy for ATL could not be performed but only steroids therapy as for anti-inflammatory. Temporary improvement of state was seen after aspiration of the chylous ascites, but only symptomatic treatment could be done. **Conclusion** Double cancer is rare and difficult to treat at the same time. ATL developed in the recurrence of peritoneal cancer is small frequency and the treatment in such a case is difficult.

ISP-24-10

Lobular endocervical glandular hyperplasia presenting as a large and protruded unilocular cyst outside uterine cervix : Proposal for a new terminology of cystic loblar endocervical glandular hyperplasia Maki Kusunoki, Fumiko Ito, Fumitaka Saitou, Ritsuo Honda, Takashi Ohba, Hidetaka Katabuchi *Kumamoto University*
Lobular endocervical glandular hyperplasia (LEGH) is a pseudoneoplastic glandular lesion of the uterine cervix. We reported the first case of LEGH presenting as a large protruded unilocular cyst. A 37-year-old nulligravida woman was referred to our hospital due to the presence of continued watery vaginal discharge. Magnetic resonance imaging demonstrated a 6.5×7.5×9.5-cm cyst with high intensity on T2-weighted images without solid component in the stroma of the cervix. Cytological examination and biopsy of the cervix revealed no malignancy. HIK 1083-labeled latex agglutination test was performed preoperatively using watery discharge, resulting in a positive reaction. Therefore, we suspected that the cystic lesion was formed by LEGH and performed a laparotomy. The cervix was markedly enlarged by cytic mass located in the anterior wall of the uterine cervix. The inside of the cyst communicated with the canal of the cervix and the cystic lesion could be removed by oophorocystectomy. The cervix was preserved with normal muscle layer. Microscopic evaluation showed the inner surface of the cyst wall was lined by low columnar cells and clusters of small glands were focally located surrounding dilated duct. Immunohistochemically, the glandular cells showed cytoplasmic immunoreactivity for MUC6 and HIK1083. Thus, we diagnosed the cyst as LEGH. LEGH are usually observed as a multicystic lesion, arranged in floret-like manner with aggregates of small cyst on imaging test. This is the first case of a rare finding of LEGH and we propose a new terminology as cystic lobular endocervical glandular hyperplasia.

ISP-24-11

Clinical outcomes and prognostic factors in 55 patients with uterine sarcoma at a single institution Seok Mo Kim *Chonnam National University, Korea*
Objective This study evaluated clinical outcomes and prognostic factors of patients with uterine sarcoma. **Methods** The retrospective analysis was performed on 55 patients with uterine sarcoma, who had been treated and followed at Chonnam National University Hospital from 2004 to 2015. **Results** The median age of patients was 53 years (range : 27-80) and 60.0% of all was postmenopausal status. The surgery was the first line of treatment for all patients. After the surgery, the adjuvant therapies were given to 37 patients (67.3%), such as chemotherapy to 13, radiation to 11, and chemoradiation to 13. The complete and par-

tial response to treatments were achieved in 43 (78.2%) and one (1.8%) patients. And, the progressive and stable disease were shown in 9 (16.4%) and 2 (3.6%) patients. The 2- and 5- year overall survival (OS) rate were 80.4% and 70.6%. The 2- and 5-year disease free survival (DFS) rate were 69.3% and 49.7%. The multivariate analysis revealed that postmenopausal status ($p=0.026$), elevated preoperative serum CA-125 level ($p=0.001$), histological subtypes ($p<0.05$), lymphovascular space invasion (LVSI) ($p=0.044$), and LN involvement ($p=0.004$) were significantly associated with DFS, while no factor affected OS. **Conclusions** Despite small numbers of UES and LMS, more aggressive subtypes, it seems that the complete surgical resection and following adjuvant therapy has a better outcome. And, menopause, elevated preoperative serum CA-125 level, more aggressive subtypes, LVSI, and LN involvement negatively affect a prognosis.

ISP-25-1

TME-like surgery by vaginal endoscopy in retrograde radical hysterectomy Masato Kita, Yusuke Butsuhara, Takeharu Kido, Hiromi Murata, Tomomi Mizokami, Tomoo Yoshimura, Hidetaka Okada *Kansai Medical University*

Objective We have developed retrograde radical hysterectomy assited by vaginal endoscopic surgery (vaginal Natural Orifice Transluminal Endoscopic Surgery ; V-NOTES) and reported good postoperativeurination function. We reported TME-like anatomical findings of upper vagina and cervix in this operation. **Methods** We performed retrograde radical hysterectomy in 65 cases and observed anatomy of upper vagina and cervix by V-NOTES in 27 cases. **Results** After circumcision of vagina, anterior vaginal wall was easily separated from vesico-uterine fascia and reached to the attaching end of cervix. Venous varix could be observed behind the posterior lobe of vesicouterine ligaments. This could correspond to neuro-vascular bundle and could be landmark to preserve bladder nerve. Recto-vaginal fascia (so-called Denonvillier's fascia) was weak and rectum could be easily separated from vagina and cervix like TME for rectal cancer. Paracolpium including vaginal vessels were cut and separated from vesico-rectal ligament. Uterine vessels, hypogastric nerves and pelvic plexus existed above endopelvic fascia and not damaged by this procedure which performed beneath endopelvic fascia. **Conclusion** By this vaginal endoscopy, upper vagina and cervix could be removed extrafascially like TME without bladder nerve injury.

ISP-25-2

Easy and effective cystoscopy for gynecologists using a 5mm laparoscope with a Nelaton catheter Miyako Sakanaka, Keiko Kohno, Ryota Ichikawa, Yuko Arai, Masato Nishida *National Hospital Organization, Kasumigaura Medical Center*

Objective It has been reported that routine cystoscopy at the end of every laparoscopic hysterectomy is worthwhile. We had used the TUR standard set or the 5mm laparoscope for cystoscopy. But we felt the preparation of the TUR set was troublesome and the 5mm laparoscope alone was not enough for all cases because it does not have function of perfusion. We developed easy, accurate and cost-effective cystoscopy using a 5mm laparoscope with a Nelaton catheter. **Methods** Cystoscopy was performed in 14 patients by using a 5mm laparoscope with a 10 Fr. Nelaton Catheter at the end of TLH in our hospital. At the end of surgery, 5cc of indigo carmine was administered intravenously, and the bladder was inflated with saline solution. Then the 5mm laparoscope is inserted with jelly. When we felt difficult to see blue urine stream through the ureteral orifices, a Nelaton catheter connected with a syringe contained with saline solution was inserted along the scope carefully. When saline solution was flushed toward the ureteral orifices, we could see the stream obviously in all cases. **Results** Although our method does not have function of perfusion, it was enough to inspect inner bladder wall and the blue urine stream. **Conclusion** A Nelaton catheter is cheap and safe tool to insert in the bladder. Cystoscopy with a 5mm laparoscope and a Nelaton catheter is easy, cost-effective and enough to investigate urinary injuries for gynecologists. This method reduces the work of the operating room staff and saves time, too.

ISP-25-3

Laparoscopic approach of ovarian masses during pregnancy Kana Kasai, Takeshi Kato, Yuri Kadota, Kaoru Keyama, Sumika Matsui, Kanako Yoshida, Minoru Irahara *Tokushima University*

Objective Laparoscopic surgery is often applied to ovarian tumor patients during pregnancy. In our facility, for the ovarian masses, laparoscopic surgery is performed after 12 weeks pregnancy when there is no torsion or malignancy. We report laparoscopic approach of ovarian masses during pregnancy. **Methods** Between 2005 and 2016, 37 patients underwent laparoscopic ovarian tumor surgery during pregnancy. We retrospectively evaluated MRI diagnosis, pathological diagnosis, surgery results and pregnancy outcome and compared with the 18 laparotomy cases. In order to reduce the impact on the placental blood and decrease negative affects on the fetus, abdominal air pressure is set to 8mmHg. In addition, the position of the trocars are devised in order not to stimulate the uterus as much as possible. **Results** Of the 37 cases, unilateral was 28 and bilateral was 9 cases, gestational age at the time of surgery was 13.7 weeks (6-16 weeks) and tumor size was 7.0cm. Surgery outcome of 28 cystectomy and 9 adnexectomy were 95 ± 25 minutes operation time, 17 ± 29g bleeding. Postoperative complication or adverse effect on pregnancy was not recognized. Pathological diagnosis was 27 mature cystic teratoma, 2 serous cystadenoma, 2 mucinous cystadenoma, 2 acute abdomen with the corpus luteum cyst and 1 mucinous tumor of border malignancy. MRI concordance rate was 97.2%. **Conclusion** It is necessary to devise to minimize irritation to the uterus in laparoscopic surgery during pregnancy. In laparoscopic surgery, although surgery time was extended, amount of bleeding was small and there was no perioperative complications or perinatal complications.

ISP-25-4

The estimate of the uterine weight via MRI measurement Hiroshi Kuroda, Kazu Ueda, Satoshi Yanagida, Haruka Matsunaga, Seika Nagae, Akari Nakajima, Masaya Tanaka, Ryosuke Saito, Satoshi Funaki, Yoko Nagayoshi, Seiji Isonishi, Aikou Okamoto *The Jikei University School of Medicine*

Objective Generally, the uterine weight is recognized as one of the risk factors in total laparoscopic hysterectomy (TLH), but the strategies to estimate the weight pre-surgically has not been established. The aim of this study is to investigate if the measurements of MRI is useful for estimating the weight of the uterus. **Methods** Retrospective study was performed in 75 cases (leiomyoma 51 cases, adenomyosis : 6 cases, CIN : 4 cases, endometrial hyperplasia : 4 cases, Corpus carcinoma : 10 cases) which underwent TLH in our institutions. We measured and defined the diameters of the uterus in MRI as below ; length from uterine cervix to fundus on sagittal section as Major diameter, the maximum length of uterine anteroposterior diameter which is perpendicular to the Major diameter on sagittal section as Anteroposterior diameter, and the maximum length of uterine lateral diameter on horizontal section as Transverse diameter. We examined the correlation between the product of the Major diameter, Anteroposterior diameter, and Transverse diameter and uterine weight. **Results** The average of uterine weight was

283.1g (62–980). The average of the product of the three diameters was 583.0cm^3 (46.5–1860.9). The product of the three diameters (X) significantly correlated with the uterine weight (Y), regression line : Y=0.4406X+26.197, correlation coefficient (R) = 0.927, standard error (SE) =75.6g. The 95% confidence interval of the uterine weight was 500g : 694.2–1318.0cm^3. **Conclusion** Pre-surgical measurement of the three diameters in MRI is an easy and useful method for estimating the uterine weight.

ISP-25-5

Usefulness of preoperative ultrasonography of umbilical site before first trocar insertion in gynecologic laparoscopic surgeries Kazuaki Nishimura[1], Kaori Hoshino[1], Kazuaki Yoshimura[1], Toru Hachisuka[2] *Wakamatsu Hospital of the University of Occupational and Environmental Health[1], University of Occupational and Environmental Health[2]*

Objective The serious complications of laparoscopic surgeries are vascular and/or intestinal injuries by a first trocar insertion at the umbilicus. The aim of this study is to evaluate preoperative ultrasonography of umbilical site to avoid the complications. **Methods** From January 2015 to April 2016, 224 cases who underwent gynecologic laparoscopic surgeries in our hospital were involved in this study. The ultrasonography was performed after tracheal intubation to observe the structures of the umbilical site and the bowel movement associated with respiration. The distances between the umbilical skin surface and the rectus fascia (subcutaneous fat thickness), and the distance between rectus fascia and the peritoneum (peritoneal fat thickness), were measured. Spearman correlation coefficient between those thickness and body mass index (BMI) were calculated. **Results** The structures of the umbilical site could be observed successfully in all cases. Asymptomatic umbilical hernia was detected in 3 cases preoperatively. The mean subcutaneous fat thickness and peritoneal fat thickness were 7.9 mm and 3.9 mm, respectively. The correlation coefficient of the subcutaneous fat and peritoneal fat thickness with BMI was 0.5 and 0.3, respectively. There was no remarkable association between the peritoneal fat thickness and BMI. **Conclusion** Preoperative ultrasonography of umbilical site is useful to understand the structure of the umbilicus and to perform the first trocar insertion safely.

ISP-25-6

Surgical site infection due to obesity after obstetric/gynecologic surgical procedure : case report and review of a retrospective series of an institution Takako Shimada, Ai Higashijima, Naoko Murakami, Shintaro Morisaki, Ayumi Harada, Kazuaki Ohashi, Atsushi Yoshida, Kiyonori Miura, Hideaki Masuzaki *Nagasaki University Graduate School of Biomedical Sciences*

Objective Surgical site infection : SSI is a common complication that is detected in the obese patients. We report three patients with SSI complicated to gynecological surgery. We also investigated the prevalence of SSI in obese patients (BMI 30 and over) and the clinical characteristics. **Case presentation** Case 1 was 47 years old and BMI was 46.3. Abdominal total hysterectomy, bilateral oophorectomy was performed for mucinous borderline tumor of left ovary. On the 4th postoperative day, fever up and discharge from the wound scar were detected and she was diagnosed SSI. Case 2 was 58 years old and BMI was 30. She was diagnosed endometrial adenocarcinoma, and then total hysterectomy, bilateral oophorectomy, and retroperitoneal lymphadenectomy was performed. On the 7th postoperative day, bleeding from the wound was detected and she was diagnosed SSI. Case 3 was 47 years old and BMI was 38.1. She was diagnosed uterine cervical cancer stage IB1 and abdominal radical hysterectomy, bilateral oophorectomy, and retroperitoneal lymphadenectomy was performed. On the 7th postoperative day, bleeding and surgical wound dehiscence were detected and she was diagnosed SSI. From August 2015 to August 2016, 21 obese patients who had had the surgery for obstetric/gynecologic diseases were detected and three out of 21 (14.3%) cases had been diagnosed SSI. Two out of 3 cases got long-time operation (over 10 hours) and remaining case was BMI 40 and over. **Conclusion** Obesity is confirmed as risk factor for SSI. Especially, obesity with long-time operation and/or BMI 40 and over was the high risk factors for SSI.

ISP-25-7

A diagnostically challenging case of uterine cervical diverticulum mimicking a rudimentary communicating horn of a unicornuate uterus Naho Umezawa[1], Hiroko Fukuoka[1], Azusa Wada[1], Soonna Yun[1], Chifumi Ooyagi[1], Hiroaki Tsubouchi[1], Aya Fukuda[1], Yusuke Tanaka[2], Yutaka Ueda[2], Tateki Tsutsui[1] *Japan Community Healthcare Organization Osaka Hospital[1], Osaka University[2]*

Mullerian anomalies are caused by abnormalities in the development of female genitalia. Depending on the developmental stage at which the abnormality occurs, it can produce various kinds of malformations. In this study, we present a diagnostically challenging case of uterine cervical diverticulum, mimicking a rudimentary communicating horn of a unicornuate uterus. A 48-year-old woman (gravida 2, para 0) with a history of chronic menometrorrhagia was referred to our hospital. Her previous doctor had detected a mass measuring approximately 5 cm in diameter on the right side of her uterus via pelvic magnetic resonance imaging (MRI), but chose to adopt the wait-and-see approach. Vaginal speculum examination and transvaginal ultrasonography at our hospital revealed the patient had uterus bicornuate unicollis. Pelvic MRI indicated clotted blood in the right uterine cavity. The endometrial cytology of each uterine cavity yielded negative findings. Considering the results from the investigations above, we performed total laparoscopic hysterectomy and bilateral salpingectomy with a preoperative diagnosis of a left unicornuate uterus with a rudimentary right-communicating uterine horn. However, pathological examination revealed squamous epithelium on the surface and endocervical glands in the stroma of the right uterine cavity, indicating that the patient had a uterine cervical diverticulum. In conclusion, we report a rare case of a uterine cervical diverticulum. Further, we would like to investigate past case reports to add bibliographic value.

ISP-25-8

Ipsilateral interstitial pregnancy after salpingectomy : two case report Toru Kobayashi, Mari Kitade *Juntendo University Hospital*

The ectopic pregnancy is the famous emergency disease in obstetrics and gynecology department, and it develops at 1–2% of frequency of all pregnancy, and salpingectomy is often selected. However, it is reported that the case of ipsilateral interstitial pregnancy after salpingectomy occur rarely, 0.3–4.2%. We report 2 case of ipsilateral interstitial pregnancy after salpingectomy. Case 1) 38 years old, gravidas 0 para 0. She had experienced laparotomy-right salpingectomy in other Hospital for right ampulla tubal pregnancy. In 5 weeks 3 days, we found sac-like mass by vaginal ultrasonography in the right adnexa area and HCG rose in 5608mIU/ml. So we decided operation under laparoscopy. In abdomen ectopic pregnancy to uterine tube interstitial subdivision after the right salpingectomy and enforce a resection. Case 2) 29 years old, gravidas 0 para 0. She had experienced laparoscopic right salpingectomy in our hospital for right

ampulla tubal pregnancy. In 5 weeks 5 days, She had lower abdominal pain and came to our hospital. By vaginal ultrasonography we found a hematoma-like mass in the right adnexa area.

ISP-25-9

One case that we performed total laparoscopic hysterectomy (TLH) for uterine myoma, and caused rectal insertion of a vaginal delineator tube Kazutaka Kuramoto, Katsuko Egashira, Tomoko Matsushita, Kana Hiasa, Kiyoko Kato *Kyushu University*

We report a case of TLH for uterine myomas and caused rectal injury by operation. A 42-year-old nulligravida woman was referred to our hospital because of anemia and hypermenorrhea. We can examine her vagina with small size Cusco speculum but vaginal introitus was tight. Transvaginal ultrasound and MRI showed uterine myomas, 59*53mm and 39*36mm. We diagnosed anemia and hypermenorrhea due to the uterine myomas. She was treated in oral iron preparations. Because of hypermenorrhea, she decided to have surgery. After four times of GnRHa treatment, we performed TLH. We inserted a vaginal delineator (VAGI pipe ; Hakko Medical, Tokyo, Japan) after cutting of the cardinal ligament to outline the cervicovaginal junction. When we incised anterior fornix of vagina, there was not the VAGI pipe inside. Thus, we continued incising deeply, we detected the VAGI pipe and recognized that we incised posterior fornix and anterior wall of the rectum successively. We performed rectal examination, VAGI pipe was got into rectum through the vaginal wall at the position of 2cm from inlet of vagina. We restored rectum and the vagina and completed surgery. First, repair of anterior rectal wall was performed under laparoscope. Next, transanal repair of anterior rectal wall and transvaginal repair of vaginal wall was performed. Finally, an ileostomy was placed. We noticed the risk of rectal insertion of VAGI pipe, but lack of awareness concerning perforation to rectum. We can find only 1 report about this complication. Because the consequence of perforation is serious, this risk should always be taken into consideration.

ISP-26-1

Six cases of emergency cesarean hysterectomy in which electrothermal bipolar vessel sealing system was used Asako Kumagai, Toshitaka Tanaka, Eri Kitamura, Sachi Sukegawa, Kanako Murata, Yoshiko Murase, Satomi Tanaka, Shotaro Yata, Yuka Yamamoto, Hiroshi Kaneda, Naoki Mitsuhashi *Juntendo University, Shizuoka Hospital*

Background In recent years, the benefits of non-surgical methods such as balloon tamponade and uterine artery embolization for the obstetric massive hemorrhage has been noticed. However, in an emergency, hysterectomy may not be avoided. Obstetric hysterectomy is often decided suddenly, and is difficult in hemostasis. Therefore, the development of the more effective surgical technique is in great demand. In last four years, we have used electrothermal bipolar vessel sealing system (EBVS) for all of the emergency cesarean hysterectomy. We have retrospectively studied the benefits of using this system during the emergency hysterectomy. **Cases** There were six cases of emergency cesarean hysterectomy in our facility between September 2012 and September 2016. EBVS was used in all of the cases. Those six cases include four cases of placenta accreta, one case of atonic bleeding, and one case of placental abruption. The average time and the total blood loss of the six cases were 173minutes and 2709g (including amniotic fluid), respectively. The blood transfusion was given in three cases, which include one of the placenta increta, the atonic bleeding, and the placental abruption. Among these three cases, the atonic bleeding and the placental abruption were diagnosed as obstetric DIC before the surgery. **Conclusion** Because of its accessibility and usability, EBVS is thought to be one of the beneficial instruments for the safer management of the emergency obstetric massive hemorrhage.

ISP-26-2

Clinical and histopathological study on genital acquired lymphangiectasia accompanied by lower limb lymphedema secondary to gynecologic cancer Hisako Hara, Mihara Makoto *Saiseikai Kawaguchi General Hospital*

Objective Sometimes acquired lymphangiectasia accompanies lymphedema. It highly impairs quality of life of the patients. The purpose of this study was to elucidate the clinical pathology and histopathology of acquired lymphangiectasia. **Methods** We examined histopathology of 10 patients (16 biopsies) and lymphoscintigraphic findings of 17 patients. The average age of the patients was 57.2 and 58.8 years, respectively, and all were female with secondary lymphedema. Surgical specimens were fixed in formalin and stained with hematoxylin eosin. Additional immunostaining (podoplanin, CD4, CD8, CD20, etc.) was performed in 6 cases. **Results** In lymphoscintigraphy, we found lymphatic fluid adversely flew into the genital area from the lower limb in 68.2% patients. In histopathological examination, dilation of lymphatic vessels in the papillary dermis was present in all 16 specimens. Ifiltration of iflammatory cells, most of which were lymphocytes, was also observed in the dermis and the epidermis in all cases, even though there were no clinical signs of iflammation. The number lymphocytes was significantly larger in the superficial layer of the dermis than in the deep layer, which may indicate that they oozed out from the dilated lymphatic vessels located in the superficial dermis. CD8+ T cells infiltrated the epidermis in seven of eight specimens. **Conclusion** Lymphatic dilation and constant infiltration of lymphocytes in the dermis and the epidermis were observed, which may have a relation to frequent cellulitis, which is often seen in lymphedema patients. Improving the increased lymphatic inner pressure in both genital and lower limb seemed to be necessary.

ISP-26-3

Gasless single-port laparoscopic-assisted vaginal hysterectomy for large uteri weighing 500g or more Shiori Tsuge, Shotaro Hayashi, Yoshie Teranishi, Sanae Imoto, Hiromi Nakamura, Akihiro Takeda *Gifu Prefectural Tajimi Hospital*

Objective To evaluate the safety and feasibility of gasless transumbilical single-port laparoscopic-assisted vaginal hysterectomy (LAVH) for the management of large uteri weighing 500 g or more. **Methods** We conducted a retrospective comparative study of women with large uteri from 2006 through 2016, each undergoing gasless multi-port or single-port LAVH. Preoperatively, gonadotropin-releasing hormone agonist was administered and autologous blood was donated except for cases requiring immediate surgery. **Results** Of the 650 women managed by multi-port or single-port LAVH, 55 and 67 women each with uteri weighing 500g or more, respectively, were included. In the single-port LAVH group, the median extirpated tissue weight was 652g with a median estimated intraoperative blood loss of 450ml. A significant positive linear correlation was observed between the operative time or estimated blood loss and extirpated uterine weigh. Although excessive bleeding exceeding 1000ml was noted 15 cases, a transfusion of bank blood was not required by using preoperatively donated autologous blood and intraoperative autologous blood salvage and donation. The median surgical duration in the single-port LAVH group was significantly longer than that in the multi-port LAVH group, although no significant differences were noted between the two groups in other surgical outcomes. **Conclusion** Gasless single-port LAVH is a

feasible alternative that can yield similar major surgical outcomes as multi-port LAVH, with potential cosmetic benefit.

ISP-26-4

Comparison between single-port and two-port for the laparoscopic surgery of adnexal masses : Review of a single institution Heng-Cheng Hsu[1], Wen-Chun Chang[1], Chin-Jui Wu[2], Bor-Ching Sheu[1] *College of Medicine, National Taiwan University, Taiwan[1], Division of Gynecology, Taoyuan General Hospital, Ministry of Health and Welfare, Taiwan[2]*

Objective To compare the tumor sizes, feasibility, operative time, blood loss, and pathology in patients with adnexal lesions receiving single-port or two-port laparoscopic surgery. **Study design** 350 patients with adnexal masses who had laparoscopic surgery between 2011 and 2014 done by two surgeons in a single institution were enrolled. Patients who had a second surgery were excluded from the study. **Results** The mean size of the tumors was 8.07cm in single-port surgery and the mean size of those from 2-port was 7.18cm. The mean time of single-port surgery was 61.0 minutes and the mean time of two-port surgeries was 71.8 minutes. The mean age of patients receiving oophorectomy was 46 and the mean age of those that had oophorocystectomy was 32.1. The average tumor size in single-port surgery who had oophorocystectomy was 6.83 cm and those who had oophorectomy was 9.40 cm. The mean time who had oophorocystectomy was 68 minutes and those who had oophorectomy was 57.3 minutes. Most of the pathologies were endometrioma and the second most pathology was dermoid cyst. **Conclusion** Single-port laparoscopic surgery is feasible under careful selection for patients with adnexal lesions.

ISP-26-5

Blood transfusion in elective abdominal gynecologic surgery Dittakarn Boriboonhirunsarn, Patama Chaopothong, Titima Jirasawas *Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

Objectives To evaluate the rate of blood use and evaluate various transfusion indices in elective gynecologic surgery. **Methods** A total of 260 women scheduled for elective gynecologic surgery were enrolled. Various surgery-related data were collected including data of blood request and actual blood use. Incidence of blood transfusion and other indices were estimated including cross match to transfusion ratio (C/T ratio), transfusion index (TI), and transfusion probability (%T). **Results** Majority of cases had benign uterine pathology (42.7%), and 27.3% had gynecologic malignancies. Blood requests were type and screen in 60.8%. Almost half of the surgeries were performed by staff (46.9%) and hysterectomy was the most common procedure (62.3%). The overall rate of actual blood use was 11.5%. The rate was 5.1% among type and screen cases, and 21.6% in cross matching cases. Blood use was significantly more common among gynecologic malignancy operations than others. Overall C/T ratio was 4.27, TI was 0.23, and %T was 23%, which indicated over-ordering of blood. Inappropriate blood ordering was observed among patients with uterine pathology and gynecologic malignancy cases ; patients operated on by fellow and staff ; and those with hysterectomy with/without adnexal surgery and oncologic procedures. **Conclusion** The rate of blood use was 11.5% in elective gynecologic surgery. Various indices showed that blood use is still inefficient and needs some improvements.

ISP-26-6

Comparison of the Outcome with Robotic-Assisted Laparoscopic Myomectomy and Laparoscopic Myomectomy Li Yun Chou[1], Bor Ching Sheu[2], Wen Chun Chang[2] *Taiwan Adventist Hospital, Taiwan[1], National Taiwan University Hospital, Taiwan[2]*

Objectives This study aimed at comparing short term outcomes of patients who underwent robotic assisted laparoscopic myomectomy (RM) and laparoscopic myomectomy (LM). **Method** Prospective data including 21 consecutive patients who underwent RM with the da Vinci surgical system and 50 patients who underwent LM were recorded. Patients' demographics, fibroid characteristics, operative time, estimated blood loss (EBL), length of hospital stay, conversion to laparotomy and operative complications were collected in both groups. Ultrasound was obtained preoperatively and postoperatively (one month, three months, and six months) to check the myoma wound. **Results** Mean operative time for the RM vs. LM was 182 ± 40 min vs. 113 ± 40 min, $p < 0.001$. Mean number of myoma for the RM vs. LM 3.2 ± 2.4 vs. 1.9 ± 1.2, $p=0.003$. No significant differences were noted between RM versus LM for hospital stay and EBL. The size, weight and location of myomas removed for RM vs. LM were similar. None of the cases in both groups required conversion to laparotomy. Four patients (4/50, 8%) in LM group with intramural myoma (4/21, 19%) had hematoma at one month sonography follow up. Three hematoma spontaneously resolved at 3rd month, and one resolved at 9th month postoperatively. **Conclusion** RM needs more operative time than LM, which may be due to more myomas removed in RM. RM has easier suturing and access and is suggested for intramural myoma to prevent postoperative wound hematoma, thus improving wound healing and avoiding future uterine rupture during pregnancy.

ISP-26-7

LAPAROSCOPIC SURGERY IN WOMEN WITH ACUTE ABDOMEN PAIN Jyoti Chaubey, Parveen Ruby, Saily Sahu, Sanjay Chaubey, Agarwal B P *St. Jude's Hospital, India*

Gynecologic emergencies are majority four diseases ectopic gestation torsion of adnexa rupture of ovarian tumor and ovarian bleeding. Diagnostic modalities are inconclusive some time and laparoparotomy was main option of treatment. Laparoscopy was used to confirm the findings of the imaging modalities and therepeutic option. Laparoscopic management of acute abdomen was performed in 98 cases during a period of 5 years. Majority of cases were of ectopic gestation. Thirteen cases were of twisted adnexa and one case of ovarian bleeding was there. Laparoscopy is a good option for confirmation of diagnosis and therepeutic measure in case of acute abdomen of gynecological emergencies.

ISP-26-8

New application of PlasmaKinetics Sealer in vaginal routes during laparoscopic-assisted surgeries for benign and malignant gynecologic disease : Better choice? Yi-An Tu[1], Chin-Jui Wu[1], Wen-Chun Chang[1,2], Bor-Ching Sheu[1,2] *National Taiwan University Hospital, Taiwan[1], Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taiwan[2]*

OBJECTIVE The bipolar electrosurgical device (PlasmaKinetics Sealer ; Olympus, Japan), uses plasma kinetic technology to deliver a high current and very low voltage to the tissue. A series of rapid pulses with a cooling phase during coagulation allows decrement of lateral thermal spread and tissue sticking. It has been reported that vessel sealing with the pulsed bipolar system is more effective than with clips, suture, or staples. The purpose of this study was to determine whether the pulsed bipolar system can safely and effectively replace conventional sutures in vaginal parts of surgical manipulation in laparoscopic-assisted vaginal hysterectomy. **METHOD** We retrospectively reviewed medical records of 71 women who underwent laparo-

scopic-assisted vaginal hysterectomy (LAVH) for benign gynecologic disease or laparoscopic (LSC) staging for malignant condition between Jun. 2014 and Oct. 2016. Fifty-one women received LAVH or LSC staging using the conventional sutures and another 20 using the pulsed bipolar system. **RESULTS** No significant differences between the 2 groups were observed in terms of body mass index, myoma volume, uterine mass, and the history of previous abdominal surgery. In trend analysis, we found the mean blood loss and operation time were decreased in the pulsed bipolar system group. None of the surgeries were required to be converted to laparotomy. No significant differences were found in intraoperative or postoperative complications between the groups. **CONCLUSION** The pulsed bipolar system has some advantages over the conventional sutures, and therefore, may offer a better alternative option for patients during vaginal manipulation in LAVH or LSC staging.

ISP-27-1

Strategy for repeated assisted reproductive technology failures associated with hydrosalpinx Shozo Kurotsuchi *Tokoname City Hospital*

Objective This retrospective study aimed to evaluate the reproductive outcomes of infertile patients who underwent laparoscopic surgery for hydrosalpinx and propose a strategy for repeated assisted reproductive technology failures (r-ART-f) associated with hydrosalpinx. **Methods** From 2010 to 2014, 32 infertile patients with bilateral tubal obstruction were included in this study. Among these, nine patients underwent laparoscopic surgery because of r-ART-f (seven salpingectomies and two salpingostomies). The clinical records of the patients who conceived after surgery were investigated. **Results** The severity of hydrosalpinx of salpingectomy included four patients with > 25-mm diameter of hydrosalpinx and three with <25-mm diameter, whereas all that of salpingostomy were vaginal ultrasound scan (US)-non-visible. In patients with r-ART-f, all patients who underwent salpingectomy had recurrent implantation failures with high quality blastocysts (HQB), while one was recurrent implantation failure with HQB and the other difficulty of acquirement of HQB in salpingostomy cases. **Case1** A 35-year-old nulliparous woman with severe hydrosalpinx diagnosed by not only hysterosalpingography (HSG) but US. The patient failed to conceived repeatedly, despite HQB were transfered. Salpingectomy was performed. The patient conceived in the first blastocyst transfer after surgery. **Case2** A 26-year-old nulliparous woman failed to conceived repeatedly in ART. HQB were not obtained in the past three cycles of ART. Hydrosalpinx was diagnosed as mild degree because it was not visible in US but only in HSG. The patient conceived spontaneously two months after salpingostomy. **Conclusion** The therapeutic strategies must be decided in consideration of both the severity of hydrosalpinx and the type of r-ART-f.

ISP-27-2

Analysis of endoscopic surgery-assisted reproductive technology hybrid therapy for infertile women of late reproductive age or diminished ovarian reserve with uterine tumour Keiji Kuroda[1], Mari Kitade[1], Jun Kumakiri[1], Makoto Jinushi[1], Yuki Ujihira[1], Rie Ozaki[1], Yuko Ikemoto[1], Koji Nakagawa[2], Rikikazu Sugiyama[2], Satoru Takeda[1] *Juntendo University Faculty of Medicine[1], Sugiyama Ladies Clinic[2]*

Objective For infertile women of late reproductive age with uterine tumor, it is a debatable whether infertility treatment or surgery should be the first choice. We first reported successful cases of combination treatment of endoscopic surgery and ART, as "surgery-assisted reproductive technology (ART) hybrid therapy" in 2009. We show our recent data of hybrid therapy.

Methods We gained informed consent of hybrid therapy for infertile patients of late reproductive age or diminished ovarian reserve with uterine myomas in 2014-2015. The patients underwent ART for cryopreservation of embryos preoperatively and reproductive surgery. And we transferred warmed embryos into the uterus after post-operative contraceptive interval. **Results** Eighteen women underwent surgery-ART hybrid therapy at an average age of 39.9 ± 3.0 years and AMH level of 2.0 ± 2.0 ng/ml. Two women still try to collect pre-operative frozen embryos and one woman acquired no embryo and gave up conceiving. The other 15 women underwent 2.5 ± 1.1 times of oocyte retrieval and cryopreserved 3.7 ± 2.3 embryos pre-operatively. Out of 15 patients who were operated, 4 women are in post-operative contraceptive period and 11 underwent 18 times of embryo transfer. Two women delivered babies and 2 women are ongoing pregnancy. Seven women resulted in implantation failure or miscarriage. The 4 women who succeeded in hybrid therapy had significantly larger number of cryopreserved embryos comparing with the 7 women of hybrid therapy failure. **Conclusion** Sufficient frozen embryos are needed for successful of "surgery-ART hybrid therapy".

ISP-27-3

Negative impact of adenomyosis on blood level of AMH Tomoki Tanaka, Yasushi Hirota, Hirofumi Haraguchi, Mitsunori Matsuo, Takehiro Hiraoka, Shun Akaeda, Miyuki Harada, Tetsuya Hirata, Kaori Koga, Osamu Hiraike, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo*

Objective Adenomyosis is often accompanied by menstruation-related symptoms and infertility. However, it remains unclear how adenomyosis influences on fertility, especially on ovarian reserve. In the current study, we investigated blood levels of anti-mullerian hormone (AMH) in women with and without adenomyosis to clarify the impact of adenomyosis on ovarian reserve. **Methods** This study was approved by the ethics committee in our institution. Fifteen women who had symptomatic adenomyosis diagnosed by MRI, and 27 infertile women with male factor who did not have apparent adenomyosis were included in this study. Age, serum AMH levels, and the presence or absence of endometrioma, which are known factors related to ovarian reserve, were searched through the review of medical records. Women with medical history of ovarian surgery as well as PCOS were excluded. Multivariate analysis was performed using linear regression analysis to assess the role of variables : adenomyosis, age and endometrioma. **Results** The multivariate analysis showed that advanced age and the presence of adenomyosis were correlated with reduced blood levels of AMH (p= 0.015 and 0.010, respectively). **Conclusion** Our results suggest that adenomyosis may affect ovarian reserve independently of age and endometrioma, and these findings may be helpful for adenomyosis patients who wish to conceive.

ISP-27-4

Nationwide survey on attitude toward social egg freezing : social influence on women's empowerment and increase in the average age of childbirth Mikiya Nakatsuka *Okayama University*

Objective Demands for social egg freezing have been increased recently in Japan. However, the wishes and problem consciousness of social egg freezing have not been surveyed among Japanese. **Methods** We performed nationwide self-administered questionnaire survey on social egg freezing from February to May in 2016 after approval of institutional review board and informed consent. We obtained 1,248 responses (response rate : 15.8%). **Results** Respondents voted "agreement"(27.5%) and "conditional agreement"(28.2%) to social egg freezing. Respon-

dents considered it as "a kind of insurance against infertility caused by aging" (69.6%), "women's empowerment" (64.9%), or "countermeasures to the falling birthrate" (63.3%). However, tkey also concerned about "increase of high-risk birth" (85.9%), "increase in the average age of marriage" (72.2%), or "Young son or daughter has to care for old parents" (56.8%). Respondents felt affirmative to subsidy from the private company to an employee who wishes social egg freezing (57.9%). They considered it as "career support" (64.5%), "good corporate image" (57.3%), "increase in unmarried or the average age of marriage" (67.7%), or "restraint of job-changing" (45.2%). Respondents felt affirmative to subsidy from the local government (62.7%). They considered it as "countermeasures to the falling birthrate" (70.1%), "women's empowerment" (61.4%), "good city image" (55.8%), "increase in unmarried or the average age of marriage" (60.1%), "wasting the city money" (36.5%), or "demand to have children" (25.9%). **Conclusion** Approximately 56% of respondents agreed social egg freezing. However, they also concerned about negative aspects of them. Further discussion for guideline of social egg freezing is necessary.

ISP-27-5

Japanese semen donor perspective for knowing rights of DI offspring Tomomi Kutsuna, Naoaki Kuji, Tomoya Hasegawa, Keiko Ueno, Shigeatu Takamizawa, Michirou Yushima, Hiroe Ito, Keiichi Isaka *Tokyo Medical University*

Objective Although donor insemination (DI) is performed totally anonymously in Japan now, some offspring who were born from DI is claiming the rights to know their genetic origin. However, there are so few information about Japanese donor's perspectives about the knowing rights of offspring. Here, we present one Japanese donor's perspectives. **Methods** The donor, over 60 years old now, was interviewed by four questioners privately. **Results** He had donated his sperm in his 20th. Donation was not compensated, but he donated because family building should be so important in infertile couples. At that time, he thought that family tie should be founded by intimate relationship during every-day living, rather than genetic bond, since he himself were nurtured by several female relatives after his own mother passed away. Now, he recognized the importance of genetic information, and willing to disclose his information if the offspring who was born from his donation needs it. In his view, it should be necessary to establish third party institution which organize and arrange the encounter of donor and offspring. Although his wife was comfortable for him after knowing his donation recently, she is reluctant for his coming-out as donor in public, since she is anxious about the misunderstandings and bad feelings from the public. **Conclusion** There should be some Japanese donors who are willing to disclose their information to the offspring. However, they needs some assistance by third party for encountering with offspring, and the serious attention should be paid to views and opinion of donor's own family.

ISP-27-6

Comparison of the effectiveness of clomiphene citrate versus letrozole for mild IVF in poor respoders Akiko Takashima, Naoki Takeshita, Mayumi Urita, Tomohiro Adachi, Izumi Sasaki, Kei Yokokawa, Ayami Yokoyama, Toshihiko Kinoshita *Toho University Medical Center Sakura Hospital*

Objective The management of poor responders remains a challenge in IVF techniques. Our objective was to evaluate the effectiveness of clomiphene citrate (CC) vs. letrozlole (L) alone induction protocol for poor responders in IVF cycles. **Methods** Retrospective observational study included cycles with CC and L alone induction protocols of 254 poor responders from August 2013-July 2016.136 cases in the CC and 118 cases in the L groups, based on receiving CC 50 mg/day or L 2.5 mg/day, beginning on day 3 of the cycle and continued until the day of hCG. This group was compared with a randomly-selected. Single frozen embryo transfer were performed. Written informed consent was obtained from all patients. This study was approved by the ethical review board. **Results** There was no significant difference the two groups regarding age, BMI, infertility period, AFC, basal FSH and AMH levels. Mean E2 level on the day of hCG injection was significantly higher and endometrium was thinner in the CC group when compared to the L group but other cycle characteristics were similar in both groups. No significant differences were observed with respect to the number, the quality of the oocytes retrieved. The rates of MII oocytes, fertilization, blastocyst retrieval, good-quality blastocyst retrieval, clinical pregnancy were same in two groups. **Conclusion** The number and quality of the oocytes retrieved, fertilization rates, following vitrification-warmed pregnancy rate per transfer were similar in both groups. Further analysis is necessary to elucidate the optimal ovarian condition for induction protocol, and implantation as well as pregnancy outcomes.

ISP-27-7

In vitro maturation of immature human oocytes retrieved from non-stimulated ovaries resected from patients with gynecologic cancer and from intraoperative non-stimulated ovaries in patients undergoing surgery for non-cancer indications Hiromitsu Shirasawa, Yukiyo Kumazawa, Wataru Sato, Natsuki Ono, Hideya Kodama, Yukihiro Terada *Akita University*

Objective There have been no published studies comparing the in vitro maturation (IVM) of immature oocytes retrieved from resected non-stimulated ovaries and from intraoperative non-stimulated ovaries. The aim of this study is to compare the results of IVM between these two groups. **Methods** We retrieved oocytes from ovaries resected from five patients with endometrioid adenocarcinoma (resection group). During surgery for nucleation of a benign ovarian tumor, we aspirated the non-stimulated ovaries of three patients who desired oocyte collection (intraoperative group). We cultured the immature oocytes with an IVM media kit for 24-48 hours. We cryopreserved mature oocytes and performed intracytoplasmic sperm injection (ICSI) for the intraoperative group only. **Results** The average age of resection and intraoperative group was 39.8 ± 2.2 and 34.0 ± 7.9 years, respectively. On average 5.4 ± 6.2 and 2.0 ± 1.0 oocytes were retrieved from the resection and intraoperative groups, respectively. The percentage of oocytes that reached meiosis II after IVM (MII rate) was 88.2% and 66.7% in the resection and intraoperative groups. In the intraoperative group, one mature oocyte was cryopreserved. Of the three mature oocytes that underwent ICSI, one was fertilized. There were no significant differences in all variables examined. **Conclusion** Despite the lack of ovarian stimulation related to IVM and fertilization, the MII rate for both groups was satisfactory given past reports. It may be useful to collect immature oocytes during surgery to preserve fertility for patients undergoing ovarian nucleation if patients desire additional oocytes collection. And, collecting oocytes from resected ovaries can be useful for research on eggs in various stages of maturation.

ISP-27-8

Serum progesterone level in the early pregnancy after the frozen embryo transfer Yuri Yamamoto[1], Akira Kuwahara[1], Kiyohito Yano[1], Takeshi Iwasa[1], Toshiya Matsuzaki[1], Minoru Irahara[1], Kenji Hinokio[2] *Tokushima University[1], Shikoku Medical Center for Children and Adults[2]*

Objective We objected to examine the validity of hormone re-

placement quantity and the supplement period by comparing serum progesterone (P) level of hormone replacement therapy frozen thawed embryo transfer (HRT-FET) with natural cycle frozen thawed embryo transfer (N-FET). **Methods** The cases that got pregnant with FET and agreed our study from May 2015 to July 2016 were measured serum P level for every one week during pregnancy 3w6d to 8w6d weeks. In HRT-FET cycle, we used estradiol patch and chlormadinone ester acetate until 4w6d, estradiol patch and vaginal P supplementation (300mg/day) or IM P supplementation (50mg/day) until 7w6d, and only dydrogesterone until 8w6d. **Results** The object was 23 HRT-FET cases (15 IM P cases, 8 vaginal P cases) and 3 N-FET cases. Only one case was the miscarriage in HRT-FET. Each serum P level from 3w6d to 8w6d in HRT-FET were 0.2±0.1, 0.2±0.1, 15.8±6.0, 18.3±7.1, 23.7±9.5, 18.0±10.4ng/ml, and in N-FET were 17.4±6.6, 22.2±6.9, 16.6±0.1, 18.1±4.5, 20.4±6.9, 21.3±7.6 ng/ml. We found no statistical differences between both groups after 5w6d. **Conclusion** The P level after 5w6d was equal to N-FET in HRT-FET, and it was suggested that the dose and period of P supplementation in HRT-FET was proper.

ISP-28-1

Comparison of reproductive outcome in azoospermic men undergoing intracytoplasmic sperm injection with epididymal and testicular sperm Ryota Suganuma[1], Satoshi Suzuki[1], Miki Oohara[1], Akiko Yamaguchi[1], Hiromi Komiya[1], Toshifumi Takahashi[2], Hideki Mizunuma[2], Keiya Fujimori[1] *Fukushima Medical University[1], Fukushima Medical University, Fukushima Medical Center for Children and Women[2]*

Objective Previous findings have suggested that clinical relevant sperm DNA damage may occur at the post-testicular level. And some investigator reported that percutaneous epididymal sperm aspiration (PESA) is caused higher post-surgical damage than testicular sperm extraction (TESE) for azoospermic men. Our study evaluated reproductive outcomes following intracytoplasmic sperm injection (ICSI) cycles using epididymal and testicular sperm. **Methods** Patients with azoospermia, in the absence of identifiable female factor infertility, who had previously failed one or more ICSI cycles performed using epididymal sperm, and who had decided to undergo TESE at our hospital between 2010 and 2015, were identified for inclusion in this retrospective cohort study. The differences in the clinical outcomes of ICSI using TESE (T-ICSI) or PESA (P-ICSI) were evaluated. The main outcome measures were fertilization rates, embryo development rates and pregnancy rates. **Results** A total of 4 patients with azoospermia who underwent a total of 8 T-ICSI cycles and 13 P-ICSI cycles. Male hormonal analysis (FSH, LH and Testosterone) showed that there were no harmful effects after both surgery (PESA and TESE) in all patients. A comparison between T-ICSI versus P-ICSI revealed significantly higher fertilization rate (90% vs. 56%), higher embryo development rate (Blastocyst formation rate 48% vs. 24%) and higher pregnancy rate (31% vs. 8% per embryo transfer). **Conclusion** It is postulated that spermatozoa are subjected to post-testicular damage during sperm transport. In selected patients with azoospermia, the use of testicular spermatozoa for ICSI should be considered at their first treatment.

ISP-28-2

Limited benefit of electing to freeze all embryos for later transfer in the time-lapse confirmed single embryo transfer program Hisao Ando, Ryosuke Uekusa, Atsushi Kunishima, Seiko Matsuo, Satoru Katsuki, Kei Fujita, Atsushi Yabuki, Kazuhisa Kitami, Yoshiki Ikeda, Kota Umemura, Mayumi Okada, Michiyasu Kawai *Toyohashi Municipal Hospital*

Objective Freeze-all policy is a novel approach to improving IVF/ICSI outcome based on that controlled ovarian stimulation may have a negative effect on the receptivity of the endometrium for embryo implantation. However, overall benefits and limitations of the new strategy have not been elucidated. **Methods** Single embryo transfer was mandatory. Embryo selection was based on time-lapse cinematography. Conventional freeze-all cycles for avoiding ovarian hyperstimulation syndrome or poor endometrial receptivity were excluded for this study. We set up the freeze-all suggestion (FAS) index. We also set up the freeze-all consideration (FAC) index. Both indices are expressed as a percentage of the denominator of the cycle number of successful or clinical pregnancy following fresh embryo transfer (FET) and that of unsuccessful FET followed by frozen-thawed embryo transfer (TET). The numerator of FAS and FAC index is the cycle number of unsuccessful FET followed by successful and overall TET, respectively. **Results** FAS and FAC index in women 35 years old and over (481 cycles) was 17.2 and 63.8, respectively. FAS and FAC index in women younger than 35 (415 cycles) was 20.2 and 54.9, respectively. FAS and FAC index in women with peak estradiol concentration 3,500 pg/ml or more (162 cycles) was 27.7 and 71.6, respectively. FAS and FAC index in women undergoing GnRH agonist/antagonist (509/287 cycles) was 22.8/13.2 and 61.5/60.3, respectively. **Conclusion** The benefit of freeze-all policy was limited. FET should be considered with reference to our new indices.

ISP-28-3

Childhood growth and development at 6 years of age among children born from infertility treatments Yasufumi Ooishi[1], Kohta Suzuki[2], Naoaki Kuji[1], Keiichi Isaka[1] *Tokyo Medical University[1], Aichi Medical University, Department of Health and Psychosocial Medicine[2]*

Objective This study aimed to estimate the difference in childhood growth and development in singleton babies conceived by infertility treatments such as in vitro fertilisation (IVF) with fresh embryos, IVF with frozen embryos, other infertility treatments, and natural conception. **Methods** A multicenter retrospective cohort study was conducted which included 3,509 singleton babies. Parents of these singleton babies had received infertility treatment from 1 January 2008 to 31 December 2008. Naturally conceived singleton babies were born between 1 October 2008 and 30 November 2009. In 2015, the data of their growth and development (KIDS developmental scale) at 6 years of age were obtained by questionnaire. Weight, height, body mass index (BMI) and the score of KIDS scale were compared between each treatment group by analysis of variance. **Results** Finally, the number of participants of follow-up survey was 1,830 (52.2%). In the children born from IVF, weight and height were significantly larger than these in the children born from natural conception although there was no significant difference of BMI between each group. On the other hand, there was no significant difference of KIDS score between each treatment group. **Conclusion** Although it is necessary to consider the effect of selection bias in each group, no significant adverse effect of infertility treatment on childhood growth and development.

ISP-28-4

Spontaneous/mild ovarian stimulation for *in vitro* fertilization after fertility-preserving treatment for patients with endometrial cancer Yoshimasa Kawarai, Akira Mitsuhashi, Hiroki Sonehara, Asuka Sato, Sachi Morimoto, Hiromi Kanetani, Maki Fujita, Hiroshi Ishikawa, Makio Shozu *Chiba University*

Objective We previously reported that a combination of metformin and progestin successfully reduced relapse rate after fertility-preserving treatment for endometrial cancer (EC). Assisted reproductive technology (ART) is recommended for

prompt conception after remission of fertility-preserving treatment in patients with endometrial cancer ; however, the optimum protocol for ART is still unclear. **Methods** We retrospectively analyzed the ovulation induction methods, pregnancy rate, and recurrence rate after remission of fertility-preserving treatment in patients with EC who were treated with medroxyprogesterone acetate plus metformin in our hospital from 2008 to 2015. **Results** Twenty-four patients (median age, 34 years) were included. All patients continued to receive metformin after remission. Twenty-three patients began ART with spontaneous/mild ovarian stimulation (S/MOS) (within the spontaneous cycle or with clomiphene citrate [CC] or aromatase inhibitor). The remaining one patient underwent ovarian stimulation with follicle-stimulating hormone (FSH)-human chorionic gonadotropin (hCG). Fourteen patients became pregnant (pregnancy rate : 58.3%). Eleven patients gave live birth ; nine of them achieved pregnancy by S/MOS alone, while one patient failed to achieve pregnancy by S/MOS. Therefore, the method was changed to GnRH agonist protocol ; one patient who had an adverse event due to CC underwent ovarian stimulation with FSH+hCG. Four patients showed recurrence of EC (recurrence rate : 13.8%) at the time of analysis. **Conclusion** ART by S/MOS showed favorable pregnancy rates after fertility-preserving treatment in patients with EC. In addition, S/MOS method prevented the exposure of patients with EC to high blood estradiol levels, which may account for the reduced recurrence rate after remission of fertility-preserving treatment.

ISP-28-5

Comparison of estrogen profiles among different controlled ovarian hyper-stimulations during IVF treatment revealed that excess E_2 level alone could not be predictive for IVF failure Jun Kawagoe, Hideki Igarashi, Koki Matsuo, Satoko Suzuki, Isao Takehara, Jun Matsukawa, Satoru Nagase *Yamagata University, School of Medicine*

Objective Some studies have reported that excess estrogen (E_2) level and mid-luteal decline of E_2 may cause the failure of IVF treatment, whereas no report has shown the comparison of those values among controlled ovarian hyper-stimulations (COHs). This study is to reveal the differences of E_2 dynamics among different COHs and compare their effects on IVF success. **Methods** A retrospective study was designed covering 687 patients aged ＜41 years undergoing IVF-ET/intracytoplasmic sperm injection (ICSI) cycles. Levels of E_2 at hCG administration (peak E_2) and luteal day 7 (mid-luteal E_2), P_4 at luteal day7 (mid-luteal P_4), and other factors were measured and compared among four different COHs ; Clomiphen citrate (CC), FSH + antagonist (Antagonist), GnRHa long (Long), and GnRHa short (Short) (n=59, 137, 451, and 47, respectively). Approval for the study was obtained from the ethics committee. **Results** Antagonist (30.65%) and Long (32.15%) protocols showed higher implantation rate than CC (19.23%) and Short (17.02%), though there were no statistical differences. Long protocol showed statistically higher peak E_2 and bigger decline E_2 ratio (peak E_2/mid-luteal E_2). Antagonist protocol showed statistically higher mid-luteal E_2. Mid-luteal E_2/P_4 ratio did not show significant differences. Endometrial (EM) thickness, retrieval oocytes number, and fertilization ratio were also significantly high in Antagonist and Long versus CC and Short protocols. **Conclusion** Though Antagonist and Long protocols have higher E_2 levels, their implantation ratio were better than other protocols. Therefore, E_2 values alone does not appear the predictive for failure of IVF.

ISP-28-6

The occurrence of multinucleated embryos after intra-cytoplasmic sperm injection (ICSI) treatment may be prevented by the administration of prednisolone Sagiri Taguchi, Miyako Funabiki, Masako Karita, Yoshihiro Tada, Terumi Hayashi, Yuri Iwaki, Yoshitaka Nakamura *Oak Clinic*

A 38-year-old woman with infertility visited our clinic in November 2013. She received seven intra-cytoplasmic sperm injection (ICSI) treatments at our clinic, and prior to each, she was administered clomifene (4 tablets per day for 5 days) and human menopausal gonadotropin and 0.25 mg cetrotide (cetrorelix acetate for injection). Although calcium ionophore treatment was administered after ICSI treatment, many of embryos were multinucleated embryos (e.g., 3PN) which could not be transferred. Additionally, she was positive for anti-centromere antibody. Under the speculation that the existence of antibody relate to the multinucleated embryos and it can be suppressed by prednisolone, prior to the eighth round of ICSI treatment, she was administered prednisolone (5 mg per day for 14 days) as well as clomifene (4 tablets per day for 5 days), human menopausal gonadotropin, and 0.25 mg cetrotide. Informed consents were obtained for the treatment. As a result, all of embryos had two pronuclei on the day after ICSI, and all of them were cryopreserved. One of those four embryos (2PN) was later used for blastocyst transfer, and clinical pregnancy was confirmed by the observation of a gestational sac (GS) in July 2016. With the result of the case, the occurrence of multinucleated embryos after ICSI treatment may have been prevented by the administration of prednisolone. In conclusion, the administration of prednisolone before ICSI treatment may be useful for generating normal embryos for infertile women with a positive anti-centromere antibody. Additional studies in the near future are needed to confirm these findings.

ISP-28-7

Monozigotic pregnancy after sigle blastocyst transfer Yuko Ikemoto, Keiji Kuroda, Asako Ochiai, Shinichiro Ikuma, Yuki Ujihira, Makoto Jinushi, Ai Takamizu, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Juntendo University*

Introduction Monozygotic multiple pregnancy after in vitro fertilization and embryo transfer (IVF-ET) occurs very rare, about 0.01-0.02% per ET in Japan. We report an extremely rare case of monozygotic triplets after single blastocyst transfer. **Case report** A 37-year-old nulliparous woman underwent IVF-ET because of bilateral tubal obstruction and oligozoospermia. Five oocytes were collected after ovarian stimulation with clomiphene citrate and recombinant FSH, and two blastocysts were cryopreserved on 5th day following intracytoplasmic sperm injection (ICSI). The patient underwent ultrasound guided aspiration of bilateral hydrosalpinx fluid and one warmed and complete hatched blastocyst transfer (Gardner classification, grade 6BA) after laser assisted hatching and culture using hyaluronan rich media during hormone replacement cycle. We recognized implantation with serum hCG level on 4 weeks 2 days of gestation and diagnosed monozygotic triplets on 11 weeks of pregnancy. Unfortunately all embryos ended in miscarriage on 13 weeks. **Discussion** The incidence of monozygotic multiple pregnancy after IVF-ET is still poorly understood. However some literature reported the association with artificial manipulation of oocytes or embryos including ICSI, assisted hatching, embryo biopsy, blastocyst culture due to inner cell mass splitting. In this case, under the impact of several manipulations, the inner cell mass might be separated after hatching from zona pellucida.

ISP-28-8

Infertility and associated abdominal tuberculosis a major cause in developing countries Sanjay Chaubey, Jyoti Chaube, Agarwal Chandra Mohan, Mahendra Bhusari, Rubey Parveen,

Shaily Sahu *Division of MAS. St. Jude's Hospital, India*
Chronic abdominal pain is a common problem associated with infertility in our region. Abdominal tuberculosis is prevalent in this part of central India. biological and radiological investigations were inconclusive. Diagnostic laparoscopy was performed in 98 patients. laparoscopic findings were analysed. A majority of infertility patients were having abdominal tuberculosis. Chromopertubation revealed tubal blokage in 58 patients. Turbid colour fluid in 88 patients. Tubercles were present in 19 patients. Adhesions were seen in 56 patients. Abdominal tuberculosis is a common association with infertility in our part of region.

ISP-29-1

Screening for thanatophoric dysplasia with sonographic determination of the biparietal diameter–to–femur length ratio Liangcheng Wang[1], Kazunori Baba[1], Yukiko Mikami[1], Yasushi Takai[1], Masahiro Saitou[1], Isao Horiuchi[2], Ryo Konno[2], Kenjiro Takagi[2], Hiroyuki Seki[1] *Center for Maternal, Fetal and Neonatal Medicine, Saitama Medical Center, Saitama Medical University[1], Saitama Medical Center, Jichi Medical University[2]*
Objective The aim of the study was to determine whether the biparietal diameter/femur length ratio (BPD/FL) can be used to detect thanatophoric dysplasia in the first trimester of pregnancy. **Methods** We experienced 9 cases of thanatophoric dysplasia from 2009 to 2016, and 13 reported cases diagnosed based on molecular analysis were included. All sonographic measurement records were extracted and reviewed, and the BPD/FL ratio was calculated for each gestational week. In addition, 10,293 routine fetal biometry measurements from 1,395 cases of patients without skeletal dysplasia were compared. **Results** The BPD/FL ratio in the control group decreased to less than 3 prior to gestational week 13, and to less than 2 prior to week 18. Of the 33 ratios obtained from 22 cases of thanatophoric dysplasia, none was in the control range. **Conclusion** The BPD/FL ratio may be used to detect an extreme outlier such as thanatophoric dysplasia since first trimester.

ISP-29-2

Risk factors of recurrent placental abruption (PA) Natsuki Nagashima, Seisuke Sayama, Rieko Shitara, Toshio Nakayama, Takayuki Iriyama, Atsushi Komatsu, Takeshi Nagamatsu, Yutaka Osuga, Tomoyuki Fujii *The University of Tokyo Hospital*
Objective Recurrence of placental abruption (PA) is a big concern in the management of pregnant women with a history of PA. Perinatal management to avoid PA recurrence or to improve fetomaternal outcome is not established in such women. This study aimed to find out clinical risk factors of recurrent PA and to improve knowledge contributing to better perinatal management. **Methods** This study was conducted under the approval of our institutional ethics committee. Reviewing the delivery cases in our hospital from January 2006 to December 2015, we found 24 cases which had a history of PA in the preceding pregnancy. In those cases, the perinatal data of the previous and the last pregnancy were extracted including maternal complications, delivery modes, gestational weeks of delivery, and neonatal outcome. **Results** Recurrent PA was observed in 4 out of the 24 cases (17%). Symptoms of pregnancy-induced hypertension (PIH) was significantly related to the recurrence of PA (p=0.03). Recurrent PA occurred in 3 out of 6 women with PIH in ongoing pregnancy, whereas 1 out of 18 without PIH. The fetal growth in the recurrent group tend to be poorer than that in the non-recurrent group ; −0.86SD and −0.36SD, respectively (p =0.07). **Conclusion** Our findings propose that vigilant management is necessary in women with a history of PA when PIH and restricted fetal growth are observed in ongoing pregnancy.

ISP-29-3

Obstetric outcome of Jehovah's Witnesses : a single-institution experience Mie Tanaka, Shinya Matsuzaki, Aiko Kakigano, Yasuto Kinose, Tadashi Iwamiya, Kazuya Mimura, Keiichi Kumasawa, Masayuki Endo, Tadashi Kimura *Osaka University*
Objective To retrospectively review the obstetric outcomes of Jehovah's Witnesses and determine the treatment management of Jehovah's Witnesses' deliveries **Methods** We reviewed the obstetric outcomes of Jehovah's Witnesses during a 16-year period from January 2001 to August 2016 in our institution. **Results** During the study period, our institution had 9,542 deliveries, which included 73 deliveries of Jehovah's Witnesses. Of these, 47 cases were vaginal deliveries, four cases were vacuum deliveries, and 22 cases were cesarean delivery. Blood loss during delivery exceeded 1,000 ml in 14 cases and 2,000 ml in three cases. The maximum blood loss recorded was 4,343 ml. The causes of massive hemorrhage were atonic bleeding (two cases) and placental abruption (one case). We perfomed hysterectomy in two cases, administered fibrinogen in two, and recombinant factor VIIa in one. As a result, we could control postpartum hemorrhage, and no maternal death occurred. **Conclusion** Jehovah's Witnesses' deliveries are high-risk deliveries because postpartum hemorrhage without transfusion could easily cause maternal death. Patients and their families should be sufficiently counseled about the risk of death caused by refusing transfusions, and the drugs and treatments permitted by their organization should be confirmed. When massive bleeding occurs, it is necessary to provide fibrinogen or recombinant factor VIIa and rapidly proceed to hysterectomy depending on the amount of blood loss. It is possible to treat Jehovah's Witnesses' deliveries in the institutions that can counsel them enough about the risk and follow the processes as above.

ISP-29-4

Comparison of non-invasive prenatal testing related data from one institution in Tokyo with national data in Japan Madoka Horiya[1], Osamu Samura[1], Takuma Sato[1], Akiko Konishi[1], Norimichi Yamamura[1], Tomona Matsuoka[1], Momoko Inoue[1], Michiko Miya[1], Taizan Kamide[1], Hiroaki Aoki[1], Tomohiro Tanemoto[2], Aikou Okamoto[1] *The Jikei University School of Medicine[1], Eastern Chiba Medical Center[2]*
Objective To analyze the data of patient who comes for our "Genetic counseling program for non-invasive prenatal testing" at the university hospital with the national data of the NIPT Consortium for comparison of patients statistical data statics. **Methods** The medical records of pregnant women who received genetic counseling between December 2013 and December 2015 were reviewed. **Results** From the 272 women who received genetic counseling, NIPT was performed in 263 cases. Another one woman received only amniocentesis, and the eight women did not receive any prenatal chromosome test. The mean [range] age was 38.3 [28 -46] years, the mean gestational age at the time of testing was 12 [10 -17] weeks. 13 women [4.9%] were recipient of artificial insemination and 72 women [27.3%] underwent in vitro fertilization. The characteristics of the pregnant woman who received NIPT were similar to the national data in Japan. Of the 263 women tested, two [0.76%] had positive results, 260 had negative results, and one [0.38%] had results that were not reportable at the first test. Of the two positive women who underwent amniocentesis, chromosome abnormalities of trisomy 21 were confirmed. The women decided to terminate the pregnancy. Perinatal outcome of the women who received negative results were as follow, two cases with intrauterine death, four cases with termination of the pregnancy. 254 women delivered. No infant has trisomy 13, 18 and 21. Seven infants had congenital disease. **Conclusion** This study describes the finding of NIPT in

our hospital. These results were congruent with the national trend of NIPT in Japan.

ISP-29-5

The obstetrical outcome of over 40-years-old dichorionic diamniotic twin pregnant women after oocyte donation
Chuyu Hayashi, Erina Kato, Hiromitsu Azuma, Takehiro Nakao, Kaori Shinya, Hideki Takahashi, Takuo Nakayama, Takahiro Nakajima, Takayuki Matsuno, Go Ichikawa, Fumihisa Chishima, Kei Kawana *Nihon University*

Objective There has been reported to be no difference in the obstetrical outcome of dichorionic diamniotic twin (D-D twin) cases between spontaneous pregnancy and IVF-ET pregnancy. The obstetrical outcome of oocyte donation was different from IVF using autologous embryo. Here we investigated the obstetrical outcome of over 40-years-old D-D twin pregnancies after oocyte donation comparing with that of D-D twin pregnancies through IVF using autologous embryo. **Methods** Over 40-years-old D-D twin pregnant women managed in a perinatal center during 2008.1-2015.5 were enrolled with written informed consent. Among them, five pregnancies after oocyte donation (donation group) were compared with five pregnancies with IVF using autologous embryo (IVF group). Maternal background, gestational weeks, delivery, perinatal complication, and neonatal data were investigated retrospectively for each group. **Results** Although there was a trend that maternal age of donation group was higher than IVF group (47±4.28 vs 42±2.70), it was not significant. All of donation group were born by emergent cesarean-section. Newborn's weight of donation group was significantly smaller than that of IVF group (1495±278 g vs 2473.5±364 g $p<0.05$). All newborns of donation group were taken care in NICU. Among the newborns of donation group, more than a half of newborns were less than 2000g. **Conclusion** Among over 40-years-old pregnant women, D-D twin pregnancies after IVF-ET using donor eggs have a higher risk for perinatal care compared with IVF using autologous embryo. Information concerning obstetrical and neonatal risk is important for couples considering oocyte donation.

ISP-29-6

Placenta accreta is common condition in women aged over 45 years who conceived by in vitro fertilization
Etsuko Kajimoto, Shinya Matsuzaki, Aiko Okada, Takao Owa, Hiroko Tanaka, Yukiko Shimazu, Aiko Kakigano, Kazuya Mimura, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

Objective Placenta previa and a previous cesarean section are risk factors for placenta accreta. Recently, advanced maternal age and in vitro fertilization (IVF) have also been reported as risk factors. This study aimed to investigate the risk factors of placenta accreta. **Methods** We retrospectively investigated women with placenta accreta during January 2008-December 2015. Placenta accreta was confirmed by histological examination. Maternal backgrounds were retrieved from the hospital database. **Results** During the study period, we managed 4,199 deliveries, including those of 38 (0.9%) women with placenta accreta. Medical history was not significantly different between the IVF and non-IVF groups. Placenta accreta occurred in 2.4% and 0.66% cases of IVF and non-IVF groups, respectively ($p<0.01$). Although incidence of placenta previa and previous cesarean section was lower in the IVF group, the rate of placenta accreta was higher in IVF group than in non-IVF group. Five of 13 women aged >45 years with IVF pregnancy harbored a donor oocyte. Surprisingly, three (23.1%) of 13 women aged >45 years with neither placenta previa nor previous cesarean section who conceived by IVF developed placenta accreta in the uterine corpus, but the rate in women aged <45 years was 0.7% ($p<0.01$). No woman (>45 years with IVF pregnancy) was diagnosed with placenta accreta antenatally. **Conclusion** Women aged >45 years with IVF pregnancies, including those without placenta previa and a previous cesarean section, are at a high risk of placenta accreta.

ISP-29-7

The perinatal outcomes of pregnancy in women with heart disease in our hospital and towards the future.
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Objective It has been increasing the number of pregnancy in women with heart disease due to improving the prognosis of heart disease. We discussed the outcome of pregnancy with heart disease in our hospital. **Methods** Sixty cases after the exception of 21 cases with only arrhythmia were examined from 2004 to 2016 in our hospital on the institutional review board approval. **Results** NIHA classification I degrees is 56 cases, II degrees in 4 patients. Cesarean section was performed in 18 cases were (emergency 12 cases) including 5 cases due to the internal maternal adaptation. In vaginal delivery, 24 of 42 patients had underwent a painless delivery by epidural anesthesia. Preterm birth was 11 cases, and the emergency Caesarean Section at 28 weeks at NRFS by maternal hemorrhagic shock in a pregnancy with the post Fontan surgery. **Conclusion** Result of almost pregnancies with heart disease had uneventful course, and it was possible to vaginal delivery without outbreak of the cardiac performance. We must cooperate closely with cardiologist about the pregnancy and delivery management while considering to be the original safe perinatal management of strict follow-up of cardiac function, cardiovascular internal medicine at higher medical facilities. A lot of cases with adult congenital heart disease are referred to our hospital including the post Fontan operation which is very high risk for preterm birth and fetal growth restriction. We'll also report on a change in the current state of the fetus heart disease case in our hospital, and the role of the adult congenital heart disease center.

ISP-29-8

Usefulness of fetal cardiac assessment for management of monochorionic-diamniotic twin pregnancies
Yasuhiro Utsuno, Tetsuji Odagiri, Akiyoshi Kanagawa, Megumi Mizusaki, Hiroyuki Yamazaki, Yuriko Ooishi, Minako Hakoyama, Toshiaki Yoshida, Kenrokurou Mitsube, Mio Taketazu *Hokkaido P.W.F.A.C. Asahikawa-Kosei General Hospital*

Introduction Twin-twin transfusion syndrome (TTTS), a life-threatening complication in monochorionic-diamniotic (MD) twin pregnancies, is generally managed based on Quintero staging system. However, even when the MD twin do not met TTTS criteria by Quintero staging system, they can complicate cardiac disturbance, which often makes the neonatal management difficult. Recently, TTTS staging systems combined with fetal cardiac assessment have become introduced to manage MD twin pregnancies in some institutions. We reported our experience of the utility of fetal cardiac assessment for management of MD twin pregnancies. **Method** Since April 2015, 15 MD twin pregnancies were enrolled in the fetal cardiac examination program at our hospital. In this program, atrioventricular valvular regurgitation, atrioventricular flow waveforms, the left ventricular Tei index, umbilical blood flow patterns, pericardial effusion, and fetal myocardial thickening were examined. Pregnancies were managed based on Quintero staging system and

fetal cardiac examination program. Neonatal outcomes under this management were evaluated. **Results** None of 15 pregnancies met Quintero criteria. Two pregnancies were terminated because of fetal cardiac dysfunction and bigger babies in these pregnancies complicated heart failure required special treatment including the inotropic support. None of other babies in 15 pregnancies complicated cardiac disturbance nor needed inotropic support. Two pregnancies diagnosed as selective IUGR and discordant twin did not associate cardiac disturbance before and after birth. There was one pregnancy diagnosed with twin anemia–polycythemia sequence after birth. **Conclusion** In MD twin pregnancies, fetal cardiac assessment may be useful to determine the appropriate timing of delivery before the fetal status deterioration.

ISP-29-9

Hemostatic effect of Bakri balloon for primary postpartum hemorrhage：Single institute's experience of 75 patients Manabu Ogoyama, Hironori Takahashi, Mami Kobayashi, Shiho Nagayama, Kayo Takahashi, Hirotada Suzuki, Yosuke Baba, Tomoyuki Kuwata, Rie Usui, Akihide Ooguchi, Shigeki Matsubara *Jichi Medical University*

Objective To determine the hemostatic effect of Bakri balloon (balloon) for primary postpartum hemorrhage (PPH). **Methods** Study subjects consisted of 75 patients in whom balloon was inserted for primary PPH in this institute. <Success> vs. <failure> was defined as：hemostasis (+) by balloon vs. hemostasis (−) followed by additional procedures (hysterectomy, transarterial embolization, etc), respectively. **Results** 1) Indications：atonic bleeding (n=34：45%), placenta previa (PP) (n=32：43%), and miscellaneous (inversion, retained placenta, abruption). 2) Insertion timing：in almost all PP (30/32), balloon was inserted from hysterotomy, with abdominal traction stitch and holding the cervix employed to prevent balloon prolapse. 3) Balloon prolapse：of 75, it occurred in 4, and, thus, the following number/percentage was based on 71 (75−4) without balloon prolapse. 4) Success rate：success in 66 (93%：66/71). Failure in 5：PP (n=2), uterine inversion (n=2), and atonic bleeding (n=1). 5) Data confined to PP：Patients with clinical placenta accreta (PA) (−) (n=27) vs.(+) (n=4) achieved hemostasis in 100% (27/27) vs. 50% (2/4), respectively (p=0.013). 6) Clinical PA：Of 8 with clinical PA (+) (including non−PP), 3 (37.5%) ended in <failure>. 7) One patient with suspected amniotic fluid embolism (DIC−preceding type) ended in <failure>. **Conclusion** Balloon achieved hemostasis in approximately 90% of patients. Abdominal traction stitch and holding the cervix may maintain the balloon position and increase its effect. Failure occurred in clinical PA and amniotic fluid embolism. Although balloon is effective hemostatic procedure, patient's selection may be needed.

ISP-29-10

Incidence and risk factors for postpartum hemorrhage among transvaginal delivery at tertiary perinatal medical facility in Japan Tatsuya Fukami, Maki Goto, Haruhiko Kondou, Fuyuki Eguchi, Hiroshi Tsujioka *ASO Iizuka Hospital*

Objective Postpartum hemorrhage (PPH) remains a leading cause of maternal deaths in Japan as well as worldwide. It is important to understand the relative contributions of different risk factors for PPH. We assessed the incidence of, and risk factors for postpartum hemorrhage among transvaginal delivery cases. **Methods** Between June 2013 and July 2016, a prospective cohort study was conducted at tertiary perinatal medical facility. Women were administered a questionnaire to ascertain risk factors for postpartum hemorrhage, defined as a blood loss of 1,000 mls or more, and assessed using a calibrated under−buttocks drape at childbirth. We constructed multivariable logistic regression models for the variables associated with PPH. The analysis was restricted to vaginal deliveries. We adjusted for clustering at confounding factors. **Results** Among the 1,920 women, the cesarean section, stillbirth, multiple pregnancy and missing data cases were eliminated. Finally we analyzed 1,068 cases of transvaginal delivery in singleton pregnancy. The incidence of postpartum hemorrhage was 8.7%, and of severe postpartum hemorrhage (1,500 mls or more) was 2.1%. Risk factors for postpartum hemorrhage among the deliveries were：fetal macrosomia ＞4,000 g, Pregnancy induced hypertension, pregnancy after assisted reproductive technology, severe vaginal or perineal laceration, weight gain ＞15 Kg during pregnancy. Over 15 Kg weight gain significant increase the incidence of PPH compared with less than 10 Kg weight gain during pregnancy. Body mass index at non−pregnant status does not affect the PPH. **Conclusion** The risk factors identified could be addressed by extra vigilance during labor and preparedness for PPH management in all women giving birth.

ISP-29-11

Uterine necrosis after uterine artery embolization Yasuko Sano, Jun Takeda, Chihiro Hirai, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Juntendo University*

Objective Uterine necrosis is known as a severe complication of Uterine artery embolization (UAE). However, the precise incidence of uterine necrosis following UAE is not known. This time, we retrospectively evaluated MRI images after UAE to clarify the uterine ischemia. **Methods** Cases performed UAE for the management of pregnancy−related hemorrhage or threatened hemorrhage status were obtained in a single hospital from 2009−2015. MRI images of uterine myometrium after UAE, UAE related complications, maternal background, and clinical course were evaluated. **Results** Sixteen cases had received UAE during the periods. Enhanced MRI scanning following UAE were operated in 8 cases (50%). Absence or decrease of enhancement in the myometrium after intravenous injection of gadolinium on MRI were recognized in 4 cases (25%), and 3 cases were lack of enhancement on mid−posterior wall of uterine fundus. One of those case was diagnosed as uterine rupture during operative hysteroscopy for intrauterine synechia 15 months after the UAE. Within 4 cases of decreased enhancement, 2 cases felt hypomenorrhea, but rests were asymptomatic. Asherman's syndrome was found in 3 cases (18%) within the 16 cases. No pregnant cases after UAE were found at the present. **Conclusion** Though uterine necrosis was not proven pathologically, enhanced MRI images showed that ischemia was recognized in high incidence. Thus, UAE should be chosen with full consideration, and MRI evaluation would be useful for managing the risk.

ISP-29-12

SPONTANEOUS RUPTURE OF UTERINE ARTERY IN PREGNANCY：A CASE REPORT Michelle Malabanan[1], Marietta Sapaula[1,2] *St. Luke's Medical Center, Philippines[1], St. Luke's Medical Center, Global City, Philippines[2]*

Spontaneous rupture of utero−ovarian vessels during pregnancy is a rare but dramatic and life threatening complication. It is associated with high maternal and fetal mortality. Etiology remains unknown however, hypotheses have been postulated including effects of pregnancy on utero−ovarian vessels, presence of adhesions, and history of endometriosis has been described and will be discussed in this paper. Due to high maternal and fetal mortality, a rapid recognition together with prompt surgical intervention and supportive medical treatment are essential to achieve a favorable outcome for both mother and child. We present a case of A.M. a 38−year−old Gravida 3 Para 1 (1−0−1−1), who came in at the emergency room for sudden abdominal pain

at 31–32 weeks age of gestation. Upon examination, noted sudden hypotension, pallor, tender abdomen and fetal bradycardia. Assessment at this time was Abruptio placenta hence, an Emergency Cesarean Section was done which revealed a hemoperitoneum of 2600 ml and a ruptured left uterine artery, delivered to a live preterm baby girl, transverse presentation with Apgar score of 0, 6, 7, birth weight of 1860g appropriate for gestational age and underwent uterine artery ligation.

ISP-29-13

CHALLENGES IN REDUCING HIV/AIDS IN JAPAN
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Melaka Manipal Medical College, Malaysia
Objective The population of Japan in the year 2016 is 126,573,481. In the year 2013, a total of 15,812 HIV infection and 7,203 AIDS cases were reported. **Method** This is the traditional retrospective study of the reports of the UNGASS, UNAIDS, AIDS council and other pertaining reports of both the countries **Results** There were 1106 cases of HIV reported in the year 2013. Among this 780 cases (70.50%) were men sex with men (MSM), 194 cases were (17.50%) heterosexual, 2 cases were (0.18%), due to injection drug use IDU and 1 case was (0.095) due to mother – to–child vertical transmission. Sexual transmission accounts to 88.10% of HIV. and 77.5% the cases are within 20–44 years of age group. MSM is the biggest threat in Japan. The HIV prevalence among them is projected to increase from current 2% to 10% in the next 30 years. Sexual behaviour of younger generation, stigma and discrimination need serious attention. 89.5% of the infected patients are males. More than 30% of people newly diagnosed With HIV infection had already progressed with advanced stages of AIDS **Conclusion** The magnitude of sexually transmitted infections is very much under represented. Diversification of sexual behaviour, poor use of condom, most at risk population, stigma and discrimination, emerging vulnerable population, migration, poor notification and inadequate screening are the major problems Health education, safe sex promotion, Provider Initiated Testing and Counselling (PITC), intensifying the screening programme, medical care provision and promoting research are the required forward steps.

ISP-30-1

18–HEPE and resolvin E3, metabolic substances of eicosapentaenoic acid, prevent LPS–induced preterm birth through inhibition of proinflammatory cytokines in the uteroplacental unit
Eri Inoue, Takeshi Nagamatsu, Mari Hoya, Aki Hara, Takayuki Iriyama, Atsushi Komatsu, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*
Objective Eicosapentaenoic acid (EPA) is a representative omega–3 polyunsaturated fatty acid (PUFA) which opposes proinflammatory actions of omega–6 PUFA–derived eicosanoids. Previous works demonstrated that EPA–rich meal suppressed lipopolysaccharide (LPS)–induced preterm birth in mice. This study aimed to clarify this mechanism, focusing on omega–3 PUFA metabolites, 18–HEPE and its downstream product, resolvin E3 (RevE3). **Methods** Preterm birth was induced by transcervical LPS injection at day 15 pc. RevE3 was injected twice at the same time of LPS administration and at 6 hr later. 18–HEPE was injected once at 24 hr prior to LPS administration. The incidence of preterm birth was assessed. The mRNA expression levels for inflammatory cytokines in the uteroplacental unit were measured by real–time PCR. Additionally, histological changes in the placenta was examined. **Results** Preterm birth rate was significantly reduced by RevE3 administration (56%, p=0.04) and completely by 18–HEPE (0%, p< 0.001) compared with the control (88%). Significant inhibition of the LPS–induced up–regulation for TNFα, IL6, MIP2, and KC mRNA was detected after RevE3 and 18–HEPE administrations in the placenta and after RevE3 administration in the uterine myometrium. In the placental histology, regression of spongiotrophoblast and labyrinth layers caused by LPS–induced inflammation was diminished in the pregnant mice rescued by 18–HEPE and RevE3. **Conclusion** Omega–3 metabolites suppressed the production of inflammatory cytokines in the uteroplacental unit and reduced placental damage, which may lead to the prevention of preterm birth caused by LPS.

ISP-30-2

Retrospective study of pregnant women complicated with prior preterm birth
Kazufumi Haino, Masayuki Yamaguchi, Koichi Takakuwa, Takayuki Enomoto *Niigata University Medical and Dental Hospital*
Objective The aim of this study was to evaluate the risk factor of recurrent preterm birth in women complicated with prior spontaneous PTB. **Methods** This was the retrospective study of pregnant women with prior spontaneous PTB delivered at our hospital during the 10–year period of Jan 2006 to Dec 2015. Spontaneous PTB was defined as a birth less than 37 weeks of gestation due to onset of labor or preterm premature rupture of membranes. Exclusion criteria was multiple gestation, still birth, inaccurate gestational age, and unavailability of data. We extracted the clinical data from our hospital medical records and database. Statistical analysis was performed by chi–square test, t–test, Mann–Whitney U test. **Results** A total of 90 cases were included. The rate of total recurrent PTB less than 37 week was 42.2%. In particular, the rate of recurrent spontaneous PTB was 35.6% (32/90). There were no significant differences between recurrent and nonrecurrent PTB groups in Body Mass Index (P= 0.056), pregnancy by ART (P=0.361), uterine anomaly (P=0.587), and cervical surgery (P=0.052). The rates of cigarette use (P= 0.042) and received artificial abortions (P=0.039) were significantly higher in recurrent PTB group than nonrecurrent group. **Conclusion** Prior spontaneous PTB was reaffirmed as high–risk pregnancy group of PTB. Further investigation was needed to reveal the precise risk factor of recurrent spontaneous PTB.

ISP-30-3

Clinical feature of pregnancy following cervical conization
Hiroshi Kawamura, Koji Nishijima, Chiyo Tamamura, Toshimichi Oonuma, Kazumi Kurata, Akiko Shinagawa, Jin Takahashi, Yoko Chino, Makoto Orisaka, Tetsuji Kurokawa, Yoshio Yoshida *Fukui University*
Objective To clarify the clinical feature of pregnancy with history of conization for cervical intraepithelial neoplasia (CIN), especially the correlation between the surgical procedure and pregnancy outcome. **Methods** This is a retrospective study of pregnancy with history of conization and managed in our hospital between January 2007 and September 2016. Cases performed conizations during the pregnancy were excluded. Perisurgical and perinatal information was evaluated. **Results** During the study period, 17 pregnancies (15 pregnant women) had history of conization. Two were excluded because of performed procedures during the pregnancies. Among 15 subjects, one lead to spontaneous abortion (SA) on 1st trimester, two extremely preterm deliveries, and eleven term deliveries. One pregnancy was ongoing following two times conizations. The indication for conization was all CIN3. About surgical methods at conization, two were done by cold knife ; one was leading to SA and the other was extremely preterm delivery, and one by Loop Electrosurgical Excision Procedure, which was lead to term delivery. The others were all done by harmonic scalpel ; one of them was complicated with preterm premature rupture of membrane (pPROM) and lead to extremely preterm delivery. Cervical cer-

clages were performed on four of 13 cases and delivered at term except for one ongoing case. **Conclusion** About pregnancies following conizations, relatively favorable outcomes were obtained in our hospital. The case treated by cold knife for CIN should be noticed for extremely preterm delivery even if it was not complicated by pPROM.

ISP-30-4

The presence of pPROM and delivery before 29 weeks of gestation were independent risk for poor perinatal outcome in preterm labor patients with and without pPROM before 31 weeks of gestation Noriko Yoneda, Satoshi Yoneda, Kaori Fukuda, Masanori Yoshie, Arihiro Shiozaki, Shigeru Saito *University of Toyama*

Objective To determine the poor perinatal prognosis factors in women with pPROM (preterm PROM) and without pPROM (non-pPROM) before 31 weeks of gestation. **Methods** Retrospective cohort study in preterm labor patients with 1) pPROM, 2) non-pPROM and 3) all patients at 22-31 weeks of gestation. The primary poor outcome was neonatal death and composite severe neonatal morbidity including IVH>grade 3, PVL, NEC, sepsis, and CLD type 3 and 3'. This study was conducted under the approval of the institutional review board of our institution. **Results** 1) In patients with pPROM, the prevalence of poor outcome infants was 45.2% (19/42). Delivery before 29 weeks of gestation ($p=0.007$) and fetal tachycardia>155bpm ($p=0.01$) were risk for poor outcome. 2) In non-pPROM patients, the prevalence of poor outcome infants was significantly lower than those of pPROM (10.1% (9/89), $p<0.0001$). Delivery before 31weeks of gestation ($p=0.001$), onset-to delivery interval<17days ($p=0.004$) and polymicrobial amniotic fluid infection with mycoplasma/ureaplasma and other bacteria ($p=0.0003$) were risk for poor outcome. 3) The presence of pPROM in women with poor outcome infants was significantly higher than those with good outcome infants, respectively (19/28 (67.9%) vs 23/103 (22.3%), $p<0.0001$). Logistic regression analyses demonstrated that the presence of pPROM and delivery weeks before 29 weeks of gestation were independent risk of the poor perinatal prognosis. **Conclusion** The presence of pPROM and delivery before 29 weeks of gestation were independent risk factors of poor perinatal prognosis in preterm labor patients before 31 weeks of gestation.

ISP-30-5

Vaginal *Ureaplasma* species coexist with *Lactobacillus iners* in women with spontaneous preterm labor Yuko Matsuda[1], Daiki Ogishima[1], Satoru Takeda[2] *Juntendo University Nerima Hospital[1], Juntendo University[2]*

Objective Intra-amniotic infection with *Ureaplasma* species has been associated with the production of cytokines and is believed to cause serious complications such as preterm labor (PL) and preterm premature rupture of membranes. Our previous studies showed that *Lactobacillus crispatus*, *L. iners*, and *L. gasseri* are predominant species in the vaginal microbiota of pregnant women. In this study, we investigated the relevance of vaginal *Ureaplasma* spp. and the coexistence between *Ureaplasma* species and other microorganisms. **Methods** After obtaining informed consent, vaginal samples were collected from 27 women with PL by swabbing. A comprehensive analysis of the vaginal microbiota was performed in PL cases and samples from 21 pregnant women without PL as a control using pyrosequencing. Additionally, the *Ureaplasma* species in each sample were determined by nested PCR using specific primers. **Results** *Ureaplasma* species were detected in 59% of subjects with PL and the detection rate was significantly higher than that in women without PL. The vaginal microbial composition of the samples containing *Ureaplasma* species primarily comprised *Lactobacillus* species. In subjects with PL with a predominance of *Ureaplasma* species in the microbiota, *L. iners* coexisted at a higher frequency than other Lactobacillus species, whereas in *Ureaplasma* species-negative subjects, *L. crispatus* was identified. **Conclusion** This study suggests that colonization of *Ureaplasma* species may be associated with the particular species of *Lactobacillus* that is also present. Therefore, the composition of the vaginal microbiota is involved in the development of perinatal complications. (This study was performed in collaboration with Dr. Sugita at Meiji Pharmaceutial University.)

ISP-30-6

Progesterone prevents preterm birth by inhibition of uterine contractions in mice with chronic dental *Porphyromonas gingivalis* infection Satoshi Urabe[1], Hiroshi Miyoshi[1], Yuko Teraoka[1], Haruhisa Konishi[1], Mutsumi Miyauchi[2], Takashi Takata[2], Yoshiki Kudo[1] *Hiroshima University[1], Department of Oral and Maxillofacial Pathobiology, Hiroshima University[2]*

Objective Progesterone (P4) is thought to be essential to maintain pregnancy and has been used in the prevention of preterm birth. We previously reported that mice with dental *Porphyromonas gingivalis* infection (*P.g* mice) underwent preterm birth and were useful as a chronic inflammation-induced preterm birth model. The purpose of this study was to evaluate the effects of P4 on uterine contractions in this model. **Methods** *P.g* mice were injected subcutaneously with 1 mg of P4 daily from gestational days 15.5~18.5 (*P.g* + P4). We examined the expression of the oxytocin receptor in the myometrium on day 18 of gestation using real-time polymerase chain reaction in *P.g* mice (*P.g*) and P4-injected mice (*P.g* + P4). Uterine contraction was recorded using a tissue organ bath system. **Results** No preterm birth was observed in *P.g* + P4 mice. The mRNA levels of oxytocin receptor were lower by 73% in *P.g* + P4 mice compared with that in *P.g* mice. The intensity of spontaneous uterine contractions was suppressed by 40% in *P.g* + P4 mice. The EC50 in concentration-response curves for oxytocin was 1.3 nM in *P.g* mice and 2.2 nM in *P.g* + P4 mice, demonstrating that sensitivity to oxytocin was markedly decreased by P4 treatment. **Conclusion** Progesterone prevented preterm birth by suppression of oxytocin receptor expression and inhibition of uterine contractions.

ISP-30-7

Clinical significance of inflammatory biomarkers in the amniotic fluid for evaluation of chorioamnionitis Sota Takahashi, Masatoshi Saito, Hirotaka Hamada, Tetsuro Hoshiai, Hidekazu Nishigori, Nobuo Yaegashi *Tohoku University Hospital*

Objective The aim of current study was to determine the predictive values of inflammatory biomarkers (interleukin-6 ; IL-6, interleukin-8 ; IL-8, and tumor necrosis factor-α ; TNF-α) in the amniotic fluid obtained by amniocentesis against histological chorioamnionitis and funisitis, and against adverse neonatal outcomes in subclinicalchorioamnionitic patients. **Methods** The present study was retrospective case-control study. 26 singleton pregnant women (23-35 weeks of gestation) suspected chorioamnionitis and their infants was eligible. We collected their amniotic fluid by amniocentesis and measured threeinflammatory biomarkers, IL6, IL8, and TNF-alpha ; with cut-off value 17,000 pg/ml, 12400 pg/ml, and 30 pg/ml, respectively. Exceeding the cut-off value, we basically induced delivery (including Caesarian section). We analyzed relationship between the results of amniotic inflammatory markers and histological chorioamnionitis and funisitis, and adverse neonatal outcomes in subclinicalchorioamnionitic patients. **Results** Clear correlation was observed between the placental histology (Blanc's classifi-

cation) and inflammatory markers. However, there was not a significant correlation between maternal WBC/CRP and amniotic inflammatory markers. **Conclusion** This data shows that inflammatory biomarkers in the amniotic fluid by amniocentesis are useful and authentic tools for evaluating subclinical chorioamnionitis.

ISP-30-8

Dental infection of *Porphyromonas gingivalis* induces preterm birth through Galectin-3 Mutsumi Miyauchi[1], Satoshi Urabe[2], Haruhisa Konishi[2], Yuko Teraoka[2], Hiroshi Miyoshi[2], Yoshiki Kudo[2], Takashi Takata[1] *Department of Oral and Maxillofacial Pathobiology, Hiroshima University[1], Hiroshima University[2]*

Objective We recently reported that odontogenic infection of *Porphyromonas gingivalis (Pg)*, a periodontal pathogen, induced preterm birth (PB), in which upregulation of Galectin-3 (Gal-3), an immune regulator, was evident. The aim of this study is to clarify the critical role of Gal-3 in PB caused by *Pg*-infection. **Methods** Female mice were infected with Pg from the pulp. Mating was started at 6w post-infection when slight chronic systemic inflammation was established. At gd10 and 13, Gal-3 inhibitor (IGal) was intraperitoneally applied to a half of the animals with *Pg*-infection. The gd was recorded. In gd15 placenta, cytokines and Gal-3 expression and *Pg*-localization were examined immunohistochemically. Amniotic fluid and serum were collected and Gal-3 level of them were analyzed. Uninfected mice were used as negative control (NC). HTR-8 (a placental cell line) was used to assess the effects of *Pg*-LPS, Gal-3 and IGal on cytokine-expression. **Results** *Pg* group showed 2d of PB ($p<0.01$). Interestingly *Pg* was detected in *Pg*-infected placenta. The amnion epithelium, trophoblasts and endothelial cells were degenerative. Moreover, Gal-3 is significantly upregulated in placenta, amniotic fluid and serum in comparison with NC. The immuno-expression of COX-2 and TNF-α increased in *Pg*-infected placenta. IGal prevented PB caused by *Pg*-infection. *Pg*-LPS upregulated the expression of COX-2, TNF-α and Gal-3. Moreover, Gal-3 increased expressions of them, whereas IGal reduced their expression. **Conclusion** Dentally infected *Pg* reaches placenta through blood circulation and induces PB by upregulating COX-2 and TNF-α via Gal-3 production in placenta.

ISP-30-9

Management of Premature Preterm Rupture of the Membranes between 28 and 34 weeks and perinatal outcomes Yuto Maeda, Aya Matsubayashi, Baku Nakakita, Asuka Sakiyama, Nobutaka Hayashi, Fumimasa Kobayashi, Ruriko Oyama, Noriko Ootake, Hiroyuki Tomita, Kazuhiko Uematsu, Takuya Aoki, Shinya Yoshioka *Kobe City Medical Center General Hospital*

Objective In patients with preterm premature rupture of the membranes (PPROM), we have adopted three different management policies. This study evaluated perinatal outcomes under those policies. **Methods** Between July 2011 and September 2016, 77 patients with spontaneous PPROM between 28 and 34weeks of gestation were admitted in our hospital. We retrospectively extracted the data from the medical charts. Our management policies were classified into three groups as follows : in Group1 patients were managed expectantly with tocolysis. Termination was considered when infection was clinically suspected ; in Group2 patients were managed expectantly with or without tocolysis until corticosteroid was administered. Induction was considered if labor did not progress spontaneously ; in Group3, an immediate cesarean section was performed if termination was necessary at admission. **Results** The numbers of patients were 12 in Group1, 44 in Group2 and 17 in Group3, respectively. The median gestational age (IQR group1 223-235days ; group2 215-232 days, group3 214-230 days) and the median latency from PPROM to delivery were longer in Group1 (IQR group1 6-12.5days ; group2 1-3 days). There were neither stillbirth nor neonatal death. The incidence of neonatal morbidities, including neonatal sepsis and respiratory distress syndrome, was not significantly different between Group1 and Group2. Neonates of mothers in Group3 had an increased rate of any mechanical ventilation >24h than neonates of mothers in Group1 (relative risk [RR] 0.53, 95% CI 0.30-0.95 ; p=0.01). **Conclusion** In the absence of overt signs of infection or fetal compromise, expectant management with tocolysis might extend gestational age without increased neonatal morbidities in pregnant women with ruptured membranes.

ISP-30-10

Longitudinal Lifestyle Monitoring Reveals Associations between Series of Lifelogs and Preterm Birth Daisuke Ochi[1], Takafumi Yamauchi[1], Yuki Harada[2], Riu Yamashita[3], Osamu Tanabe[2], Nobuo Yaegashi[4], Masao Nagasaki[2], Junichi Sugawara[5] *NTT DOCOMO, INC. / Tohoku University[1], Tohoku University[2], Tohoku University[3], Tohoku University[4], Tohoku University[5]*

Objective Over 200,000 pregnant women each year are affected by pregnancy related disorders, including preterm birth (PTB) in Japan. They are caused by a complex interaction of genetic and environmental factors such as lifestyle and living environment. We have designed a prospective cohort study "Maternity Log Study" to investigate unrevealed mechanisms of those disorders. **Methods** 280 Participants were recruited by written informed consent from Sep 2015 to Aug 2016. We collected daily lifelogs of physiological data (body weight, blood pressure, pulse rate, steps, body temperature, duration of sleep) and symptoms (morning sickness, abdominal pain, uterine contraction, stool) as well as blood samplings at several points throughout pregnancy. We investigated association of series of lifelogs and PTB. **Results** Longitudinal lifestyle monitoring revealed that several different patterns in vital information in pregnancy related complications. As a result, pulse rate in the morning at 25 weeks of gestation significantly different between control and PTB (77.5 ± 9.3 vs 88.4 ± 11.2 bpm, $p<0.001$). **Conclusion** In the present study, for the first time, longitudinal lifelog information was collected using series of devices throughout pregnancy. Daily maternal pulse rate monitoring might be one of predictive markers for preterm birth. Wearable monitoring devices specific for pregnant women are expected to develop in the near future.

ISP-30-11

Glucocorticoid can weaken fetal membranes in pregnant mice Hikaru Kiyokawa[1], Haruta Mogami[1], Mai Sato[1], Hiroshi Takai[1], Kaoru Kawasaki[1], Fumitomo Nishimura[2], Yoshitsugu Chigusa[1], Eiji Kondoh[1], Noriomi Matsumura[1], Ikuo Konishi[3] *Kyoto University Graduate School of Medicine[1], Kyoto Katsura Hospital[2], National Hospital Organization Kyoto Medical Center[3]*

Objective Maternal stress increases the risk of preterm delivery and preterm premature rupture of membranes (pPROM), and psychological stresses increases serum levels of glucocorticoid. Here, we investigated the effect of glucocorticoid on fetal membranes in vivo and in vitro by analyzing collagen metabolism and production of prostaglandin E2 (PGE2). **Methods** Corticosteron 40 mg/kg/day was subcutaneously injected to pregnant mice daily from 12.5 dpc to 18.5 dpc. Fetal membrane was collected at 18.5 dpc. Thickness of fetal membrane was measured under microscope after Trichrome stain. Primary human amniotic mesenchymal cells were incubated with hydrocorti-

sone for 24 hours. Gene expressions were analyzed by quantitative RT-PCR, and PGE2 production and MMP9 activity were measured by ELISA and FRET respectively. **Results** In glucocorticoid injected mice, amniotic mesenchymal layer was thinner and had less collagen content than those in control mice (2.9 ±0.3μm vs 1.4±0.1μm, P<0.05). mRNA levels of collagen genes, *Col1a1*, *Col1a2* and *Col3a1* were decreased (×2.6**, ×1.4*, ×2.6**, respectively, *P<0.05, **P<0.01), whereas *cyclooxygenase-2* (*COX2*) and *MMP9* mRNA levels (×3.7**, ×2.9*, respectively, *P<0.05, **P<0.01) as well as PGE2 and MMP9 activity were significantly increased (×1.7, ×1.6, respectively, P<0.05) in glucocorticoid injected mice. In human amnion mesenchymal cells, glucocorticoid increased *MMP2*, *MMP9*, and *COX2* and mRNA levels (×1.9, ×2.3, ×2.2, P<0.01). **Conclusion** Glucocorticoid weakened amnion by inhibition of collagen synthesis and up-regulation of collagen degradation as well as PGE2 synthesis, which would contribute to the onset of preterm delivery and pPROM by maternal stresses.

ISP-30-12

Pregnancy and neonatal outcomes of Group B Streptococcus agalactiae (GBS) infection in preterm birth Yae Heun Lee, Suk Young Kim, Sun Young Jung, Ju Young Kim *College of Medicine, Gachon University, Korea*

Purpose The aim of this study was to examine whether GBS was associated with subsequent preterm delivery and neonatal outcome. **Method** This study design is retrospective cross-sectional study. Maternal and neonatal outcomes were examined among singleton pregnant woman with preterm delivery (from 24+0 weeks to 36+6 weeks) who underwent GBS-analysis (n=230) during this pregnancy. Data were reviewed between January 2015 to June 2016 in Gil hospital. We compared with maternal, neonatal, obstetrical factor between GBS infected and non-infected pregnant women and we evaluated efficacy of screening test in GBS culture. **Result** There were 157 singleton pregnant women under study, of whom 18 pregnant woman were confirmed GBS infection during this pregnancy. Maternal, neonatal, obstetrical factor remained independently associated with GBS infection in pregnacy. **Conclusion** GBS infection in preterm birth did not have adverse obstetrical and neonataloutcomes. But constant attention and studies on GBS infection which is knownas a major cause of neonatal sepsis and pneumonia are needed.

ISP-31-1

LPAR3 signaling is possibly involved in the clearance of oxidative stress in preeclamptic placenta Tatsuya Fujii[1], Takeshi Nagamatsu[1], Mayuko Ichikawa[1], Takayuki Iriyama[1], Atsushi Komatsu[1], Kei Kawana[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *The University of Tokyo[1], Nihon University[2]*

Objective Lysophosphatidic acid (LPA) is a new class lipid mediator. Among six LPA specific receptors (LPARs), LPAR3 is predominantly expressed in reproductive organs. This study aimed to elucidate the involvement of LPAR3 signaling in oxidative stress clearance in the placenta and its possible association with the pathogenesis of preeclampsia (PE) **Methods** This study was conducted under the approval of the ethics committee. Term placental samples were collected form preeclamptic women (n=24) and uncomplicated pregnant women (n=18). The expression of LPARs was examined by Western blotting and immunohistochemistry. The impact of LPAR3 stimulation on oxidative stress-related genes expression were investigated in a trophoblast-like HTR-8/SVneo (HTR) cells transfected with LPAR3. The regulatory mechanisms of LPAR3 in response to oxidative stress were investigated in in vitro experiments **Results** Among six LPA receptors, only LPAR3 were significantly elevated at mRNA and protein levels in the PE placentas compared to normal placentas (p<0.05). Immunohistochemistry revealed that LPAR3-specific staining in syncytiotrophoblast was stronger in the PE placentas compared with the normal placentas. LPAR3 stimulation in transfected HTR cells induced a series of heat shock protein genes which are known to play an essential role in oxidative stress clearance. In addition, oxidative stress by hydrogen peroxide enhanced LPAR3 mRNA expression in HTR cells **Conclusion** Our findings suggest that LPAR3 signaling could be involved in oxidative stress clearance in the placenta. The enhanced LPAR3 expression in PE placenta might be a compensatory response to aberrant accumulation of oxidative stress which is known as an etiological factor of PE.

ISP-31-2

Metformin attenuates Endoplasmic Reticulum stress and induces up-regulation of PlGF mRNA in human villous-like trophoblastic BeWo cells Masahiro Suzuki, Masahito Mizuuchi, Tsuyoshi Baba, Shinichi Ishioka, Tsuyoshi Saitou *Sapporo Medical University*

Objective It is known that maternal circulating concentrations of placental growth factor (PlGF) are lower in the early stages of pregnancy in pre-eclamptic patients. Our lab previously demonstrated that placental endoplasmic reticulum (ER) stress negatively regulate PlGF transcription via one of the ER stress response pathway, PERK pathway in villous-like trophoblastic BeWo cells. ER stress plays an important role in the pathogenesis of diabetes and heart disease. There are several reports that metformin -a widely used oral comorbidity of type 2 diabetes- attributes to suppression of ER stress. Recently, it is reported that metformin significantly reduces the pathogenesis of preeclampsia on clinical data. In this study, we investigated the effect of metformin to ER stress and PlGF in vitro. **Methods** We used the human choriocarcinoma cell line, BeWo for analysing the effect of metformin and/or thapsigargin. Thapsigargin is chemical ER stress inducer. We performed qPCR to measure mRNA levels and Western blots to compare protein levels. **Results** Thapsigargin negatively regulated the transcription of PlGF mRNA. Conversely, metformin positively regulates PlGF mRNA in dose dependent. The administration of thapsigargin and metformin showed significant up-regulation of PlGF mRNA compared with thapsigargin only. Western Blotting analysis showed the reduction of phosphorylation of eukaryotic initiation factor 2α (p-eIF2α) protein level under the administration of thapsigargin and metformin compared with thapsigargin only. **Conclusion** These results showed metformin positively regulated PlGF by attenuating ER stress in villous-like trophoblastic cells. This study support that metformin might be a new therapeutic agent for preeclampsia.

ISP-31-3

Prediction of PIH using CAVI (Cardio Ankle Vascular Index) Masako Sawada, Tomomi Kotani, Masataka Nomoto, Yukako Iitani, Yoshinori Moriyama, Mayo Miura, Yumiko Ito, Shima Hirako, Kenji Imai, Tomoko Nakano, Hiroyuki Tsuda, Fumitaka Kikkawa *Nagoya University*

Objective PIH (Pregnancy Induced Hypertension) is a major complication of pregnancy, which attacks 5-10% of pregnant women. Despite its morbidity and mortality, prediction of this disease is difficult. CAVI (Cardio Ankle Vascular Index) is an arterial wall stiffness parameter. PIH is associated with increased arterial stiffness, so we investigate the Association of PIH and CAVI which can be measured at bedside. **Methods** Between November 2009 and March 2016, pregnant women who received prenatal care in our hospital and obtained the consent from all participates in this study. The CAVI were measured

and their clinical data was collected. We classified into 2nd and 3rd trimester, and statistical analyses were performed with EZR. **Results** The pregnant women who were measured CAVI of 2nd and 3rd trimester were 152 and 191 respectively. 16 (10.5%) and 27 (14%) women developed PIH. No woman developed eclampsia and HELLP syndrome. CAVI was related to age, PIH, thyroid disease, and parity. For the 2nd trimester model and the 3rd trimester model of CAVI, the AUCs were 0.68 and 0.69 and the cutoff points derived from the AUC curve were 7.40 (0.98, 0.31) and 7.15 (0.88, 0.56). Because there are few women whose CAVI is 7.4 or higher in 2nd trimester, we set the cutoff point at 6.3 (0.75, 0.493), median of normal women. Odds ratio of 2nd and 3rd trimester adjusted for age, BMI before pregnancy, parity, and smoking was 5.54 (95%CI, 1.24–24.80, p=0.025) and 10.40 (95%CI, 3.83–28.30, p＜0.0001). **Conclusion** A CAVI of 6.3 or higher in 2nd trimester can be used to predict the PIH development.

ISP-31-4

Circulating levels of chromosome 19 miRNA cluster microRNAs in pregnant women with pre-clampcia, gestational hypertension and chronic hypertension Yuko Murakami, Kiyonori Miura, Ai Higashijima, Naoki Fuchi, Yuri Hasegawa, Atsushi Yoshida, Masanori Kaneuchi, Hideaki Masuzaki *Nagasaki University Graduate School of Biomedical Sciences*

Objective We have previously reported normal ranges of the circulating levels of chromosome 19 miRNA cluster (C19MC) during pregnancy. The aim to this study is to investigate whether circulating level of C19MC in maternal plasma could detect pre-eclampcia (PE), gestational hypertension (GH) and chronic hypertension (CH) by using normal ranges of the circulating levels of C19MC during pregnancy. **Methods** All samples were obtained after receiving written informed consent and the study protocol was approved by the Institutional Review Board for Ethical, Legal, and Social Issues of our University. We collected maternal blood samples from 34 pregnant women (PE group ; n=19, GE group ; n=4 and CH group ; n=11). The circulating levels of C19MC microRNAs (miR-515-3p, miR-517a, miR-517c and miR-518b) were measured by real-time quantitative PCR. **Results** The circulating levels of all four C19MC microRNAs in maternal plasma were increased in PE, GE, and CH group compared with the normal ranges. The circulating miR-517c levels in 14 pregnant women with PE, two pregnant women with GE and nine pregnant women with CH ware plotted outside of upper limit of normal range. **Conclusion** Normal ranges of the circulating C19MC levels, which we have developed previously, were useful to detect pregnant women with pre-eclampcia, gestational hypertension and chronic hypertension.

ISP-31-5

Change in microRNA expression in preeclamptic maternal blood : Sixty such microRNA detected by microarray analysis (3D-Gene chip) with global normalization Hironori Takahashi[1], Manabu Ogoyama[1], Shiho Nagayama[1], Yoichi Ishida[1], Hirotada Suzuki[1], Yosuke Baba[1], Tomoyuki Kuwata[1], Rie Usui[1], Toshihiro Takizawa[2], Akihide Ooguchi[1], Shigeki Matsubara[1] *Jichi Medical University[1], Nippon Medical School[2]*

Objective MicroRNA (miRNA), a non-coding RNA, regulates a target messenger RNA. Since some placenta-associated miRNAs are involved in trophoblast invasion and since abnormal trophoblast invasion underlies the pathogenesis of preeclampsia (PE), we hypothesized that expression of miRNA in maternal blood may increase or decrease between preeclampsia (PE) (+) vs.(-). If so, some such miRNAs may become candidates of maternal serum marker of preeclampsia. **Methods** After obtaining informed consent and Ethics Committee approval, RNA was extracted from maternal plasma in 5 women with early-onset PE and those with 5 controls (PE (-)) during 27-29 weeks. The expressions of 2,565 miRNAs was compared between PE (+) vs.(-) by microarray-based expression analysis, i.e., 3D-Gene miRNA Oligo chip version 21 (Toray, Tokyo, Japan). For normalization, we adopted global normalization, with the median of the signal intensity adjusted to 25. **Results** Of 2,565 miRNAs, 418 were detected in maternal blood from all 10 women. Sixty miRNAs significantly increased or decreased in PE (+) compared with PE (-), namely, with 52 miRNAs (e.g., miR-6895-5p, -3918, -4792, -30c-1-3p, -4435, -4459) up-regulated and with 8 miRNAs (miR-451a, -8059, -4258, -4634, -4638-3p, -342-5p, -6787-5p, -4708-3p) down-regulated in PE (+). Of these 60, 30 miRNAs have not been reported in NCBI database (PubMed). **Conclusion** Global normalization employed here is easy and reproducible, and, thus may become a potential candidate for miRNA normalization. Expression of some maternal circulating miRNA increased or decreased in PE, of which 30 were newly demonstrated here. These miRNAs may become candidates of a novel biomarker of PE.

ISP-31-6

Usefulness of the urinary L-FABP diagnoses acute kidney injury in preeclampsia Atsushi Tajima, Aya Ootsuka, Hanako Kasahara, Akari Koizumi, Rie Seyama, Shun Masaoka, Youko Tsuzuki, Yasuka Miyakuni, Chikako Suzuki, Iwaho Kikuchi, Michio Nojima, Koyo Yoshida *Juntendo University Urayasu Hospital*

Objective Acute kidney injury (AKI) is considered to be the state that was not able to maintain constancy of the body fluid by acute renal function disorder. The causes of AKI were invasion of surgery, massive bleeding, and during pregnancy, preeclampsia, HELLP syndrome, postpartum hemorrhage became the cause of AKI. In preeclampsia, the patients frequently received a renal tubular injury, and sometimes the renal function disorder continued.Recently many biomarkers were developed for AKI. Urinary L-FABP (uL-FABP) was an early predictive biomarker of renal tubular injury. We evaluated whether uL-FABP was usefulness for diagnosis of AKI. **Methods** We enrolled 28 cases with preeclampsia, managed in our hospital during January 2014 and December 2015, and medical record was used, retrospectively. Preeclampsia was diagnosed by JSOG guideline, and AKI was diagnosed by KDIGO-AKI guideline. The uL-FABP considered the above 8.4ug/g/Cr was positive. **Results** 9 of 28 cases were diagnosed AKI and 14 of 28 were positive uL-FABP. 8 of 9 of AKI patients were positive uL-FABP. 4 of 28 cases had proteinuria after delivery until one month, and 3 of 4 cases were positive uL-FABP. In 14 uL-FABP positive cases, one case complicated placenta abruption, and 2 cases complicated HELLP syndrome. None of the patients died and underwent a hemodialysis. **Conclusion** In preeclampsia uL-FABP could diagnose AKI patients. The uL-FABP positive patients tend to have serious complications. We thought that uL-FABP was effective for a diagnosis of AKI for the patient of preeclampsia.

ISP-31-7

Biomarker Discovery for Preeclampsia by Newly Established Global Metabolomic Technology Yasuhiro Kurosawa[1], Maiko Wagata[2], Kaori Suenaga[3], Hiroshi Chisaka[4], Hirotaka Hamada[1], Michiyo Kurakata[1], Tetsuro Hoshiai[1], Hidekazu Nishigori[1], Masatoshi Saito[1], Nobuo Yaegashi[1], Junichi Sugawara[2] *Tohoku University[1], Division of Feto-Maternal Medical Science, Tohoku Medical Megabank Organization, Tohoku University[2], Hachinohe City Hospital[3], SS Lady's Clinic[4]*

Objective Global metabolomics (G-Met) is a cutting edge technology to discover biomarkers for various diseases. However, the quality of metabolomics largely depends on the instrumentation and protocol for normalization. In this study, we applied a newly established protocol for G-Met to elucidate dynamic metabolomic changes in plasma from preeclamptic patients. **Methods** Retrospective case control study was conducted using plasma samples corrected between 2008 to 2011. Protocol was approved by ethics committee in our hospital (a tertiary referral perinatal center in the north part of Japan). Test subjects consisted of 10 patients with normal pregnancies, 9 and 5 patients with preeclampsia and gestational hypertension, respectively. Plasma samples were processed by UHPLC-QTOF/MS and LC-FTMS analysis and data normalization was performed using automated liquid-handling system and quality markers to compensate intra- and inter-batch differences. Multivariate and statistical analysis was performed by principal component analysis and feature extraction by S-plot. Analysis software (Quantbolome). **Results** We obtained 5,272 plasma metabolites with relative quantification data from all samples. 254 potential biomarker candidates were extracted by multivariate analysis between preeclampsia and normal pregnancies, such as Carnitines, uric acid, and diacylglycerol. **Conclusion** In the present study, we discovered potential biomarker candidates for preeclampsia by newly established metabolomic systems. Targeted metabolomics should be conducted for the validation of candidates in a large-scale cohort study.

ISP-31-8

Quantitative analyses for the serum peptides and their clinical utility for pregnancy induced hypertension Kensuke Hamamura[1], Yoshihiko Araki[2], Michio Nojima[2], Koyo Yoshida[2], Satoru Takeda[1] *Juntendo University Hospital[1], Juntando University Urayasu Hospital[2]*

Objective For clinical application, the aim of this study was to develop simple quantitative methods for serum peptides as biomarker (DBM)-candidates for pregnancy induced hypertension (PIH). Using the system established, we evaluated the potential utility of these peptides for the diagnosis of PIH **Methods** Among DBM candidates previously we identified, three peptide fragments, kininogen-$1_{439-456}$ (PDA039), kininogen-$1_{438-456}$ (PDA044) and cysteinyl α2-HS-glycoprotein$_{341-367}$ (PDA071) were examined in this study. Using polyclonal antibodies specific for each peptide, suitable conditions for the sandwich ELISA system of PDA039/044 were investigated. In the case of PDA071, liquid chromatography coupled with multiple reaction monitoring mass spectrometry (LC-MRM/MS) system was investigated for the peptide quantitation due to problems of antibody production for the peptide. Using the established methods, serum samples from PIH patients and paired serum samples from 23/33-week healthy pregnant women were analyzed. **Results** The optimum quantitative conditions for the three peptides were established for PDA039/044 (ELISA) or PDA071 (LC-MRM/MS). The serum PDA044/071 concentration showed no statistical change between PIH and healthy pregnant groups, whereas the PDA039 was significantly increased in the patients' serum. Furthermore, the three-dimensional plotting and Jackknifed classification matrix with PDA039/044/071 peptides showed satisfactory diagnostic precision for PIH patients. **Conclusion** The quantitation methods for PDA039/044/071 were successfully established for clinical application. Although single quantitation of PDA039 confirmed its clinical utility as a DBM, multi-dimensional analysis using these three peptides exhibited higher diagnostic accuracy for PIH.

ISP-31-9

Impaired autophagy and transthyretin protein aggregation in preeclampsia Akitoshi Nakashima, Tae Kusabiraki, Aiko Aoki, Tomoko Shima, Osamu Yoshino, Shigeru Saito *University of Toyama*

Objective Transthyretin (TTR), a transporter of thyroxine and retinol, is aggregated in human placentas, and the aggregated TTR induces preeclampsia-like features in the humanized mouse model. It is, however, unknown how TTR aggregates in trophoblasts. The purpose of this study is to clarify the correlation between TTR aggregation and autophagy, which maintains homeostasis. **Methods** The third trimester trophoblasts cell line, TCL-1 cells, and human hepatoma cell line, HepG2 cells, which express TTR, and autophagy-defect EVT cell line were used. Aggregated proteins were verified with proteostat dye staining. Some chemical inhibitors were used as follows ; chloroquine (CHQ) for inhibiting lysosome-autophagosome fusion, and 3-methyladenine for autophagy inhibition. **Results** Three-methyladenine or chloroquine enhanced TTR expression in TCL-1 cells as well as HepG2 cells, suggesting that inhibition of autophagy contributes to aggregation of TTR. CHQ also induced protein aggregation, which included TTR, in HepG2 cells. Immunocytochemistry analysis also showed that a part of TTR aggregates were co-localized with p62, a substrate of autophagy, in HepG2 cells treated with CHQ. Protein aggregation was seen in trophoblast cells treated with hypoxia, which is recognized in preeclampsia, for 72 hours as well as CHQ. In addition, protein aggregation was also seen in autophagy-deficient trophoblast cells. Western blotting showed that the expression of TTR aggregation was higher in autophagy-defect cells than in autophagy-normal cells, and was more abundant under hypoxia than normoxia in the cells. **Conclusion** TTR aggregation is enhanced by autophagy inhibition in placenta, resulting in preeclampsia like the mouse model.

ISP-31-10

Analysis of Temporal and longitudinal life-logs to predict pregnancy induced hypertension Takafumi Yamauchi[1], Daisuke Ochi[1], Yuki Harada[2], Riu Yamashita[2], Osamu Tanabe[2], Nobuo Yaegashi[2], Masao Nagasaki[2], Junichi Sugawara[2] *NTT DOCOMO, INC. / Tohoku University[1], Tohoku University[2]*

Objective A major issue in perinatal medicine is that personalized protocols for predicting or preventing various pregnancy related diseases have not yet been established. Those diseases are caused by a complex interaction of genetic factors and acquired environmental factors such as lifestyle and living environment, however, little is known about precise mechanisms of interaction. **Methods** We have designed a prospective cohort study "maternity-log study". In this study, pregnant women are recruited in the first trimester or second of pregnancy under satisfactory informed consent (n=280). Participants upload daily life-logs including hours of sleep, fecal conditions, body weight, and blood pressure. Furthermore, we collected specimens such as blood, saliva, and urine for omics analysis. In this present study, we investigated statistical differences of life-logs between pregnancy induced hypertension (PIH) group and control group. **Results** We observed significant differences in several life-logs among two groups. As a result, PIH group showed increased number of awaking at night before 24 weeks of gestation. Next, we constructed PIH prediction model using several life-logs uploaded among gestational 20-23 weeks and assessed the performance by plots of the classifiers' receiver operator characteristic (ROC). The area under the ROC curve (AUC) is approximately 0.7. **Conclusion** By integrated analysis of life-logs during pregnancy, we found candidate life-logs markers for PIH. In further exploration, "maternity-log study" would pro-

duce more knowledge about predicting or preventing various diseases related to pregnancy.

ISP-32-1

Labor progression analysis based on "angle of progression" in perineal ultrasound Naoya Akiba[1], Takeshi Nagamatsu[3], Rieko Shitara[3], Toshio Nakayama[3], Takayuki Iriyama[3], Atsushi Komatsu[3], Ken Sakamaki[2], Koichi Kobayashi[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Tokyo Yamate Medical Center[2], Faculty of Medicine, The University of Tokyo[3]*

Objective Perineal ultrasound (PU) is a new modality in the assessment of labor progression. This study aimed to create a standard labor progression curve for primiparous women based on the parameters measured by PU. We also aimed to clarify the difference in the temporal transition of PU parameters between spontaneous delivery and operative delivery. **Methods** This study was conducted under the approval of our institutional ethical committee. Labor progression was assessed by PU in 31 primiparous women (15 spontaneous deliveries, 8 instrumental deliveries and 8 cesarean sections) in term singleton pregnancy with cephalic presentation. Immediately after labor onset, the assessment by PU together with digital examination was repeatedly performed every one to two hours until delivery. Angle of progression (AoP), progression distance, head direction and midline angle were measured by PU. **Results** Among the parameters, AoP showed the strongest correlation with stations in digital examination and the time to delivery. In the standard curve created by the data of spontaneous deliveries, AoP change rate was about 9 degree/hr during the period of 4 to 6 hr to delivery and the rate was accelerated up to 15 degree/hr in the final 2 hr to delivery. Temporal alteration of AoP was sluggish when it reached near 140 degrees in the women necessitating operative deliveries. **Conclusion** Considering interobserver variability in digital examination, AoP is expected to be more objective approach for assessing labor progression. AoP might be a useful PU parameter to determine the timing of medical intervention in protracted labor.

ISP-32-2

Relation between level of edema and light scattering signal for the brain in a hypoxic ischemic encephalopathy model rat Sakiko Kinoshita, Takeshi Nagamatsu, Takayuki Iriyama, Atsushi Komatsu, Yutaka Osuga, Tomoyuki Fujii *Graduate School of Medicine, The University of Tokyo*

Objective Fifteen percent of cerebral palsy is attributed to hypoxic ischemic encephalopathy (HIE) in labor. However, the precise diagnostic method of HIE has not yet been established. In our previous study, we performed diffuse reflectance measurements for the brain in an HIE model rat, and found that light scattering signal reflecting morphological changes of the cells significantly decreased under the hypoxic state. In this study, we investigated the correlation between the level of brain edema and light scattering signals. **Methods** Seven days old rats were anesthetized using isoflurane and underwent left carotid artery ligation. subsequently the rats were exposed to 8% oxygen for 135 minutes at 37°. In this model, only the ligation side of the brain was pathologically proven to cause HIE. Time courses of diffuse reflectance signals of the brain through the skull were measured, and total hemoglobin, oxygen saturation and light scattering level (scattering amplitude) were quantified based on inverse Monte Carlo simulation. Water contents of the brain were evaluated by the dry and wet method and light scattering amplitudes were composed. **Results** There was a strong negative correlation between the light scattering amplitudes measured 30 minutes before the end of hypoxia and water contents of the brain tissue. However, significant changes related to HIE was not seen in blood sampling. **Conclusion** We found a significant correlation between light scattering amplitudes and the level of edema for the brain in this HIE model, suggesting the usefulness of the light scattering signals for diagnosis or prediction of HIE.

ISP-32-3

Clinical parameters at 20 weeks of gestation associated with successful rate of spontaneous vaginal delivery Tomona Fujikawa[1], Mari Ichinose[1], Hitomi Furuya[1], Toshio Nakayama[1], Takayuki Iriyama[1], Atsushi Komatsu[1], Takeshi Nagamatsu[1], Yutaka Osuga[2], Tomoyuki Fujii[2] *Faculty of Medicine, The University of Tokyo[1], Graduate School of Medicine, The University of Tokyo[2]*

Objective Risk assessment of pregnant women is critical for the safety of perinatal management. This study aimed to clarify the clinical parameters at 20 wks associated with the delivery outcome and to get a clue to the better risk assessment. **Methods** This study was conducted under the IRB approval of our facility. Study subjects were 199 women (128 primipara and 71 multipara) assessed as "low risk" in our hospital from Jan. to July, 2016. The criteria of "low risk" was without the followings at 20 wks, major obstetrical and non-obstetrical complications, fetal anomaly, twins, and prior cesarean delivery and prior severe obstetrical complications. The variables associated with the successful rate of spontaneous vaginal delivery (SVD) were determined among the clinical parameters at 20 wks (age, prepregnancy BMI, height, body weight gain, systolic blood pressure, diastolic blood pressure (dBP), EFW) by multivariable logistic regression analysis. **Results** Rates of SVD were 61% in the primiparous and 92% in the multiparous. In the primiparous, maternal age (odds ratio=0.91, 95% CI=0.84–0.98, p=0.031) and dBP (odds ratio=0.94, 95% CI=0.89–0.98, p=0.012) at 20 wks were significantly associated with the SVD rate. Major indications of operative deliveries in primiparous group were NRFS and protracted delivery. No significant parameter was detected in multiparous women. **Conclusion** Risk assessment based on maternal age and dBP at 20 wks of gestation could contribute to the prediction of SVD.

ISP-32-4

A study to define "the appropriate limit" for second stage of labor with anesthetic care Hiromi Aoi, Kensuke Hamamura, Saki Ito, Koran Ri, Yasuko Sano, Jun Takeda, Tadayoshi Uesato, Izumi Suzuki, Chihiro Hirai, Shintaro Makino, Atsuo Itakura, Satoru Takeda *Juntendo Medical University*

Objective The objectives of this study were to quantitate the chance of without operative delivery for duration of second stage were exceeded and to compare both maternal and neonatal risks for deliveries in a historical cohort manner. **Methods** The objectives of this study were to quantitate the chance of without operative delivery for duration of second stage were exceeded and to compare both maternal and neonatal risks for deliveries in a historical cohort manner. **Results** Vaginal non operative delivery rates occurred in 51.9% and 54.7%, (group A vs. group B), respectively. No statistical differences were recognized between two groups. The incidence of postpartum hemorrhage were significantly higher in group B (3.2% vs. 14.2%). There were no significant differences in neonatal asphyxia. **Conclusion** In this cohort study, no remarkable rise of vaginal non operative delivery was seen by exceeding the definition of prolonged second stage, whereas such exceeding was associated with increased postpartum hemorrhage. Exceeding the second stage of labor with anesthesia beyond 3 hours may be inappropriate.

ISP-32-5

Effect of maternal age on delivery outcome Rina Sakurai, Koichiro Kido, Shigenari Namai, Rintaro Kishimoto, Koichi Umezawa, Yasuhiro Matsumoto, Haruko Hiraike, Masahiro Shiba, Shunsuke Nakagawa, Yukifumi Sasamori, Eiji Ryo, Takuya Ayabe *Teikyo University*

Objective We tried to elucidate if maternal age has any effect on way of delivery, i.e. vaginal delivery (VD) and caesarean section (CS), and bleeding amount (BA). **Methods** 727 nulliparous singleton vertex deliveries chosen from 2,483 deliveries from 2012 through 2015 at our hospital were analyzed retrospectively based on the medical records. Statistical analysis were performed on R statistical language. Informed consent for data analysis were obtained as Japan Society of Obstetrics and Gynecology registry protocols. **Results** Vaginal delivery rate (VDR) decreased with age significantly. VDR=−6.6406age + 93.499 t=−7.12 (p (ex.) p＜0.01). In caesarean deliveries, bleeding amount (BA) did not fluctuate with age. In VD, BA did not increase with maternal age linearly. Instead, BA decreased with age under thirty years of age but not significantly. In VD over thirty years of age, BA increased with age significantly. BA= 7.92age+450.97 t=1.92 ((ex.) p＜0.05). **Conclusion** Decreased VDR with age was brought by increased emergent CS. From the indications of emergent CS such as weak pain or labor arrest, decreased reserve for labor with aging was suspected. Though relatively smaller numbers of younger pregnancies before twenty-years of age might have affected the result, decreasing tendency with age under thirty and increase with age over thirty in BA of VD suggested the existence of some optimal age (s) for delivery in terms of bleeding.

ISP-32-6

Pin-hole amniotomy to reduce obstetrical complications of polyhydramnios : A 5-year experience at single institution Yoko Kawanishi[1], Masayuki Endo[1], Yasuto Kinose[1], Tadashi Iwamiya[1], Shinya Matsuzaki[1], Kazuya Mimura[1], Keiichi Kumasawa[1], Shinsuke Koyama[2], Takuji Tomimatsu[1], Tadashi Kimura[1] *Osaka University Hospital[1], Osaka Rosai Hospital[2]*

Objective Polyhydramnios can be associated with obstetrical complications such as placental abruption or cord prolapse at rupture of membranes (ROM), and postpartum hemorrhage. In our institute, we have used a procedure called "pin-hole amniotomy"to avoid complications associated with ROM. We retrospectively assessed the outcome of pin-hole amniotomy. **Methods** Clinical data of patients with polyhydramnios, from April 2011 to July 2016, was collected retrospectively. In the early active phase of labor, before spontaneous ROM, patients underwent pin-hole amniotomy using an amnioscope and a 26-gauge needle to make several tiny holes on the amniotic sac. **Results** Nineteen cases underwent pin-hole amniotomy. The average amniotic fluid index was 29.8 (20-40). There were 3 cases of idiopathic polyhydramnios, and 16 cases complicated with fetal congenital abnormalities including 8 of bowel obstruction, 4 of cardiac malformation, 1 of fetal hydrops, 1 of hydorocephaly with achondroplasia, and 1 of macrocephaly. There were also 6 cases of chromosomal abnormalities ; 3 of trisomy 21 and 3 of trisomy 18. Among 17 cases with live born babies, 12 delivered vaginally and 5 cases underwent emergent cesarean section. Two cases of trisomy 18 became IUFD during labor. There was no case of placental abruption or cord prolapse. Average maternal bleeding was 592ml (140-1500ml) and no one needed transfusion. Average Apgar score at 1 minutes/5 minutes was 6.65 (0-9) /7.59 (0-9) and umbilical artery pH was 7.26 (6.78-7.43) except cases of IUFD. **Conclusion** With pin-hole amniotomy, there was no case with severe complications associated with ROM. This procedure should be considered to manage polyhydramnios in labor.

ISP-32-7

Postoperative infection with different suture threads Tatsuo Masuda, Shinya Matsuzaki, Yasuto Kinose, Yuri Matsumoto, Tadashi Iwamiya, Kazuya Mimura, Keichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura *Osaka University Hospital*

Objective To assess infectious complications of cesarean section using different suture threads. **Methods** We retrospectively investigated the rate of complications after cesarean sections performed from April 2009 to March 2016. Factors attributed to those complications were analyzed using SPSS Statistics version 2.2. **Results** During the study period, there were 398 emergent and 415 planned cesarean sections. After excluding cases with hysterectomy and/or compression sutures, 154 emergent cases and 179 planned cases utilized P-dioxanone (PDS™ II Poly Monofil ; P) for uterine suture, and the 225 emergent cases and 211 planned cases used VICRYL™ (V). There were 18 cases of endometritis (11.69%) in emergent cases that used P (EP) and 16 cases of endometritis (7.11%) in emergent cases that used V (EV). On the other hand, there were 16 cases of endometritis (8.94%) in planned cases that used P (PP) for uterine suture and 26 cases of endometritis (12.32%) in planned cases that used V (PV). The mean duration of cesarean section was 64.08, 61.36, 72.58 and 75.35 minutes in EP, EV, PE and PV, respectively. The mean blood loss was 861, 910, 993 and 937 ml in EP, EV, PE and PV, respectively. Neither types of suture threads, operation time nor blood loss attain to statistically significant difference or association between infectious complications. **Conclusion** The theoretical benefit of using monofilament thread to reduce infection was not observed in our study.

ISP-32-8

Outcomes of non-vertex second twins, following vertex delivery of first twins Satsuki Hosokawa, Junko Nakagawa, Michiko Watanabe, Manabu Yamada, Yasuyo Kasai, Michiko Kido, Akito Miyauchi, Kazumichi Andoh *Japanese Red Cross Medical Center*

Objective In attempted vaginal delivery of twin, cesarean section is occasionally needed after vaginal birth of first twin due to malposition and/or distress of second twin, especially in non-vertex second twin. We analyzed factors influencing delivery outcomes of non-vertex second twin. **Methods** We analyzed 108 twin pregnancies after 33 weeks gestation of which the first twins were delivered vaginally at our hospital from 2006 to 2015. We compared triads of which non-vertex second twins were delivered vaginally with those of which non-vertex second were delivered by cesarean about their age, parity, infertility, chorionicity, gestational age, labor induction, fetal position, total body weight of twins, method of the first twin delivery, duration of labor, fetal distress, admission, and Apgar score. **Results** 86 cases (group A) were delivered vaginally, and 22 cases (group B) were delivered by cesarean. Risk factors for cesarean are fetal distress of the first twins, dystocia, non-breech position of the second twins. Average durations of labor of the first twin are 7hr and 5min in A group and 9hr and 12min in B group. There is no significant difference in admission rate, Apgar score, and UmApH. Additionally there is no difference in blood loss between two groups ; both groups required no autologous blood transfusion. **Conclusion** Fetal distress of the first twins, dystocia, and non-breech position of the second twins are the risk factors of cesarean section of non-vertex second twin. On vaginal delivery of non-vertex second twins, precise observation of lowest part of second twins during delivery and evaluation of labor progression are important.

ISP-32-9

Fetal bradycardia lead by a tetanic uterine contraction during epidural anesthesia for painless delivery Hiromi Nihei, Takahiro Yamashita, Hirotaka Nishida, Haruka Mitsui, Eri Inoue, Tomoko Shinohara, Minoru Nakabayashi, Yukiko Kawana, Yoshiharu Takeda, Tomoko Adachi, Takashi Okai, Masao Nakabayashi *Aiiku Hospital*

Objective A weak labor is known to be a side effect of painless delivery. However, when opioids are administered as anesthetic agents, it is reported that a tetanic uterine contraction may occur, which leads to fetal bradycardia. In this study, we surveyed the character of the bradycardia and its effect on the course of the labor. **Methods** We analyzed retrospectively the chart of the all 243 cases who chose epidural anesthesia for painless delivery between April and August in 2016 in our hospital. The severe variable or prolonged deceleration within 30 minutes after the administration of the anesthetic agents were picked up and analyzed. **Results** In 10 cases, fetal bradycardia were observed and suspected as being associated with epidural anesthesia. In seven cases, fentanyl and ropivacaine were administered as bolus before the deceleration, and in three cases only ropivacaine were administered. Nine cases were administered fentanyl as bolus and/or continuously. The tetanic uterine contraction was identified in five cases. In the other five cases, it was difficult to evaluate the existence of the tetanic contraction because of the change of the maternal position. Normal blood pressure was recorded just after the recovery from the deceleration. In all the 10 cases, the fetal heart rate recovered and finally the healthy newborns were delivered. **Conclusion** The fetal bradycardia associated with epidural anesthetic were observed in up to 4.1% (10/243) of the painless delivery. The tetanic uterine contraction was confirmed in half of them.

ISP-33-1

Evaluation of Kielland Forceps on fetal malrotation Jun Takeda, Shintaro Makino, Yasuko Sano, Chihiro Hirai, Atsuo Itakura, Satoru Takeda *Juntendo University Faculty of Medicine*

Objective Malrotation of the fetal head is the most common indication for second-stage caesarean section. Kielland forceps (KF) are used for rotational assisted vaginal delivery, but remain controversial having undergone a significant reduction of caesarean section without increasing the complications. As the number of transverse arrest increases with the painless delivery, we have been using KF after simulation training of KF. To evaluate the feasibility of introducing KF in obstetrical practice, we retrospectively analyzed medical records in a single teaching hospital. **Methods** Parturient attempted KF at term with singleton cephalic position were obtained from February to September of 2016. As a control group, cases of occiput transverse position delivered using Naegele forceps (NF) from 2014 to 2015 were identified. The outcomes analyzed as operational features, and maternal and neonatal morbidity. Statistical analysis was performed by chi square and Student t test. Statistical significance was defined when $p<0.05$. **Results** Fifteen women were eligible during the study period, and no differences were found in maternal characteristics. All the cases attempted KF resulted in successful vaginal delivery. The types of the forceps did not show influence on bleeding, counts of extraction, Apgar scores, and umbilical cord pH. Forceps marks on eyes and central of the faces were significantly higher in NF groups ($p<0.05$). No case of severe perineal lacerations was recognized in KF group. **Conclusion** Newly introduction of KF with careful consideration may be associated with high successful delivery rate without increasing the morbidity.

ISP-33-2

Teamwork-focused interprofessional simulation training reduces the decision-to-delivery interval for emergency cesarean section. Mayumi Morizane, Masashi Deguchi, Kenji Tanimura, Shinya Tairaku, Yoko Maesawa, Noriyuki Morimoto, Satoko Morikami, Hideto Yamada *Kobe University*

Objective Emergency cesarean section (ECS) is performed when the life of the pregnant woman and/or fetus is considered at risk. It is not easy to accomplish a decision-to-delivery interval (DDI) within a 30-minutes time frame as widely recommended for ECS. This report demonstrates how we improved our DDI. **Methods** To introduce "ECS protocol" to achieve a 20-minutes DDI, the working group was formed to analyze and improve component parts of the ECS process. The group consisted of an obstetrician, two midwives, an anesthetist, two operating room nurses and a neonatologist. The DDI was the main outcome measure. Relevant data were collected from the ECS case files between October 2013 and September 2016. **Results** We established the designated code to indicate ECS after standardizing the terminology of ECS among the ECS providers. The interprofessional team training courses has been held every 2-3 months since May 2014. A total of three courses of team training assuming a day or night shift time zone were held before the official introduction of "ECS protocol" in October 2014. Over time, multiple small changes in the protocol were made during this preliminary period. Six and 20 ECSs were performed before and after introduction of "ECS protocol", respectively. The median DDI of ECS was dropped from 49 (20-111) to 11 (6-47) minutes. The proportion of ECS achieved a 20-minutes DDI was higher in the second year (7/8) than the first year (9/12) after introduction of "ECS protocol". **Conclusion** Interprofessional team training may contribute to reduce the DDI.

ISP-33-3

The effect of simulation training to shorten the decision-to-delivery interval for emergent cesarean section on maternal and neonatal outcome Yukako Iitani, Hiroyuki Tsuda, Masataka Nomoto, Mayo Miura, Yumiko Ito, Yoshinori Moriyama, Shima Hirako, Masako Sawada, Kenji Imai, Tomoko Nakano, Tomomi Kotani, Fumitaka Kikkawa *Nagoya University*

Objective To make decision-to-delivery interval (DDI) shorter, we started simulation training for extremely emergent cesarean section on March, 2014. We evaluate the effect of simulation training on maternal and neonatal outcomes. **Methods** In this retrospective study we divided participants into two groups. Pre-training group : from November, 2011 to March, 2014. Post-training group : from April, 2014 to August, 2016. The primary outcome was the time of DDI. The secondary outcome was umbilical arterial blood pH levels, Apgar score, maternal operative complications. **Results** A total of 45 patients had emergent cesarean section (Pre-training group : 15 patients, Post-training group : 30 patients). Pre-training group : 4 cases of placenta abruption, 8 NRFS, 3 others. Post-training group : 6 placenta abruption, 19 NRFS, 5 others. Average DDI times : 22.67 (11-45) and 15.5 (8-27) minutes ($p=0.010$). Time required to enter the operation room : 10.9 and 6.6 minutes ($p=0.003$) ; time to start surgery : 8.5 and 6.7 ($p=0.032$) ; delivery time : 3.1 and 2.5 ($p=0.118$). Average umbilical arterial blood pH level : 7.15 (6.82-7.39) and 7.28 (7.10-7.37) ($p=0.021$). In both groups, we didn't have any complications such as damage to other organs, postoperative infection and ileus. **Conclusion** Introduction of a simulation training to shorten the DDI for emergent cesarean section was associated with neonatal outcomes such as umbilical cord pH. Simulation training could make medical staffs recognize the importance of how to carry the pregnant woman to the operation room quickly.

ISP-33-4

Two cases of postpartum vaginal laceration treated by transcatheter arterial embolization Shintaro Sakate, Yumi Araki, Masaki Sekine, Mio Hanaoka, Takashi Kodama *Higashihiroshima Medical Center*

The vaginal lacerations sometimes cause puerperal hematomas and rarely postpartum hemorrhage (PPH). Here we present two cases of postpartum vaginal laceration who performed transcatheter arterial embolization (TAE). Case 1 : A 28-year-old woman, primipara, was transferred to our hospital because of PPH after the delivery of a 3470 g female infant vaginally. We found a vaginal laceration on the left side of vagina and a little bleeding from the laceration and the total hemorrhage volume at that time was about 2000 g. As the blood examination before operation showed severe blood coagulation disorder, after giving a blood transfusion we performed the operation. We couldn't stop bleeding surgically, we decided to perform TAE. Active extravasation of contrast medium was seen from a peripheral branch of the left pudendal artery and we embolized it with porous gelatin particles and microcoils. Then the bleeding decreased and she was discharged from our hospital on postoperative day 10. Case 2 : A 21-year-old woman, primipara, had given vaginal birth to a 2858 g male infant by the labor augmentation. We found about 5cm-sized vaginal hematoma on the left side of vagina and it continuously bled from the underlying tissues. As the operation room was occupied, we decided to perform TAE. Extravasations from a blanch of the left internal pudendal artery was shown by pelvic angiography and we embolized it with porous gelatin particles. These cases suggest the effectiveness of TAE in cases of postpartum vaginal laceration in the situations where surgical hemostasis is difficult.

ISP-33-5

Incidence of intrapartum abnormal fetal heart rate pattern Kanittha Boonchuan, Kanokwaroon Watananirun, Dittakarn Boriboonhirunsarn *Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

Objectives To determine the incidence of intrapartum abnormal fetal heart rate (FHR) pattern in women delivering at Siriraj Hospital. Factors associated with abnormal FHR pattern and pregnancy outcomes were evaluated. **Methods** A total of 900 pregnant women were enrolled. Baseline characteristics, obstetric, labor and delivery data were collected. Incidence of intrapartum abnormality of FHR pattern was determined, according to NUCHD classification. Comparisons were made between those with and without abnormal FHR pattern to evaluate possible associated factors. **Results** Mean age was 29.1 years, majority was nulliparous (55.7%), and mean gestational age at delivery was 38.1 weeks. Incidence of abnormal FHR pattern was 30.7% (30.3% and 0.4% in NICHD category 2 and 3 respectively). Among these, 46.6% and 39.7% occurred in active and deceleration phase of labor, respectively. Univariate analysis showed that rate of abnormal FHR pattern was more common among nulliparous women (RR 1.22, 95% CI 1.0-1.5, p=0.045). Other factors were not significantly associated with abnormal FHR pattern. However, no significant independent associated factor was determined from multivariate analysis. Overall, cesarean section rate was significantly less in women with abnormal FHR pattern compared to others (28.9% vs. 42.2%, $p<0.001$), and only 19.1% required emergency cesarean section from the condition. Birth asphyxia was significantly more common among those with abnormal FHR pattern (7.2% vs. 3.7%, p=0.016). **Conclusion** Incidence of intrapartum abnormal FHR pattern was 30.7% and 19.1% required emergency cesarean section. No significant independent associated factor was determined. The condition significantly increased the risk of birth asphyxia.

ISP-33-6

Decision-to-delivery interval in emergency cesarean section Khemanat Khemworapong, Nalat Sompagdee, Dittakarn Boriboonhirunsarn *Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

Objectives To determine the decision-to-delivery interval (DDI) in emergency cesarean delivery and associated factors. **Methods** A total of 431 pregnant women who were indicated for emergency cesarean delivery were enrolled. The patient demographic data and clinical information were collected. The timing of process after decision and pregnancy outcomes were evaluated. **Results** Mean age was 30 years, and 59.4% were nulliparous. Mean gestational age at delivery was 37.9 weeks. The indications for cesarean section were CPD in 27.4%, and non-reassuring FHR in 14.8%. The decision was made during normal office hour in 33.2%. Median decision-to-operating room, decision-to-incision, and decision-to-delivery intervals were 45, 70 and 82 minutes, respectively. Only 3.5% of patients had a DDI less than 30 minutes, while 52.2% had a DDI>75 minutes. During after office hours, every time interval was significantly shorter and 4.9% had a DDI $\leq$30 minutes compared to 0.7% in normal office hours (p=0.001). Compared to other indications for cesarean delivery, time intervals were significantly shorter in those with non-reassuring FHR, and DDI $\leq$30 minutes was achieved in 18.8% vs. 0.8% ($p<0.001$). Shortest DDI was observed among those with non-reassuring FHR during after office hours. Neonatal outcomes were comparable between different DDIs. **Conclusion** Only 3.5% of emergency cesarean delivery had a DDI 30 minutes (median 82 minutes). Significant shorter time intervals were observed in those with non-FHR and during after office hours.

ISP-33-7

Amnioinfusion for Irreducible Shoulder Presentation in a Dead Fetus : A Case Report Sameer Hamadeh, Bishr Addas, Nasreen Hamadeh, Jessica Rahman, M.S Rahman *King Fahd Hospital of the University. University of Dammam, Saudi Arabia*

Shoulder presentation in labor is an obstetric emergency that might lead to catastrophic complications. The mode of delivery is hysterectomy, if it occur in the late second trimester and beyond. We present a patient in labor at 24 weeks gestation with irreducible shoulder presentation. Hysterotomy was avoided by using transcervical amnioinfusion. Few cases published in the literature have reported the use of anesthesia to achieve reduction of shoulder presentation (1),(2),(3). This is the first case report to our knowledge where amnioinfusion was successfully used to dislodge an irreducible shoulder to permit internal podalic version and breech extraction, thereby avoiding hysterotomy. **Conclusion & recommendations** The effectiveness of transcervical amnioinfusion in reducing the shoulder presentation in order to avoid abdominal delivery has been described. We support this method management in irreducible shoulder presentation, when all other recommended methods fails, especially with dead, premature fetus in labor. Transcervical amnioinfusion can also be performed as the first line treatment in order to avoid the need of anaesthesia, its possible complications or when the time matters.

ISP-33-8

Accidentally rt ovarian vein thrombosis presenting as postpartum retroperitoneal hematoma Sa Jin Kim, Jae Eun Shin *Catholic University Bucheon St. Mary Hospital, Korea*

Ovarian vein thrombosis (OVT) is an extremely rare but life-threatening complication of the postpartum period. It has also been associated with other conditions, such as pelvic inflamma-

tory disease, malignancy, sepsis, inflammatory bowel disease, and recent pelvic or abdominal surgery. It is critical to recognize and treat this condition as early as possible to avoid the potential complications of the thrombosis and adverse sequelae such as infection and sepsis. POVT must be considered in the differential diagnosis of postpartum acute abdomen. We hereby present a case on a 25–year–old woman who developed an massive perivesical and retroperitoneal hematoma as acute abdomen after spontaneous vaginal delivery. Computed tomography of the abdomen and pelvis revealed right ovarian vein thrombosis due to infrarenal IVC compression. The patient was treated with anticoagulant therapy and responded well.

ISP-34-1

Cytological and virological disappearance in CO_2 laser vaporization for the patients with cervical intraepithelial neoplasia 2 Mizuki Uenaka, Yasuhiko Ebina, Hitomi Imafuku, Kaho Suzuki, Yoshiya Miyahara, Hideto Yamada *Kobe University*

Objective The most effective treatment for grade 2 cervical intraepithelial neoplasia (CIN2) is controversial. This study was performed to evaluate the disappearance of cytological and virological factors of CIN2 after CO_2 laser vaporization. **Methods** Patients with CIN2 who were either positive for high-risk human papillomavirus (HPV) or had the lesion for >6 months were evaluated. Sixteen patients underwent CO_2 laser vaporization from March 2013 to December 2015. The patients were followed up using Pap tests and HPV genotyping. All patients provided written informed consent. The patients' median age was 34 years (range, 21–41 years), and the median follow-up duration was 15 months (range, 6–36 months). The rates of the normalization of cytology, high-risk HPV disappearance, and pathological recurrence (CIN2–3) were analyzed. Abnormal cytology was defined as detection of atypical cells on atypical squamous cells of undetermined signification. **Results** The cytological normalization rate after 3 months was 62.5%, and the HPV disappearance rate was 30.8%. The HPV disappearance rate in patients with super-high-risk HPV (types 16, 18, 31, 33, 35, 52, and 58) and in patients with other types of high-risk HPV were 43.8% and 75.0%, respectively. Similarly, the HPV disappearance rate in patients with multiple and single infections were 16.7% and 42.9%, respectively. The pathological recurrence rate after 2 years was 35.0%. Pathological recurrence rate after 2 years was 35.0%. **Conclusion** Divergence was found between the cytological normalization rate and HPV disappearance rate 3 months after laser vaporization. Additional research is needed to determine whether persistence of HPV is correlated with the long-term clinical course.

ISP-34-2

Phase II study to investigate the efficacy and safety of CO_2 laser vaporization followed by HPV prophylactic human papillomavirus vaccine for cervical intraepithelial neoplasia in single institution Kouichiro Kawano, Teruyuki Yoshimitsu, Hiroki Nasu, Ken Matsukuma, Atsumu Terada, Shin Nishio, Naotake Tsuda, Kimio Ushijima *Kurume University, School of Medicine*

Objective Primary endpoint of this study is to investigate if bivalent prophylactic human papillomavirus (HPV) vaccine after CO_2 laser vaporization improve the cumulative 2-year recurrence rate of cervical intraepithelial neoplasia (CIN). Secondary endpoint is the recurrence rate of HPV16/18 related CIN, infection rate of HPV16/18 after vaporization, and adverse response of HPV vaccine. **Methods** Between October 2011 and March 2014, women with CIN who were going to undergo vaporization were enrolled in this study. Bivalent prophylactic HPV vaccine was given three times after vaporization. Patients were followed up to 24 months after vaporization. HPV genotyping was conducted before and after 6, 12, and 24months of vaporization. Sample size was calculated as 59 cases when the cumulative 2-year recurrence rate was estimated to be 25% which is equal to our historical data and threshold was estimated to be 15%. This study was approved by institutional review board. **Results** Fifty-nine patients were enrolled in this study. Four patients withdrew consent before vaccination. Cumulative 2-year recurrence rate of entire or HPV16/18 related CIN were 13.4% (95% CI : 6.1–26.8%) or 18.2% (95%CI : 9.7–31.4%), respectively. Postoperative HPV infection was observed in 37.3% (HPV16/18 : 25.0%, other type : 37.1%, p=0.327). New HPV16/18 infection was not observed after vaporization. Grade 3 or worse than Grade 3 of adverse response of HPV vaccine was not observed. **Conclusion** This study did not indicate to reduce the recurrence of CIN. Recurrence rate did not differ among HPV type. Severe adverse response of HPV vaccine was not observed.

ISP-34-3

Human papillomavirus genotypes identified in high-grade CIN and invasive cervical cancer in Japanese women Jinichi Sakamoto, Takeo Shibata, Yasuhiro Oosaka, Satoko Fujita, Hiroaki Takagi, Toshiyuki Sasagawa *Kanazawa Medical University*

Objective To elucidate all HPV genotypes likely to induce cervical cancer in Japan, we examined HPV genotypes infected with CIN and cervical cancer in Japanese women. **Methods** Totally 912 CIN and 358 cervical cancer patients were evaluated, after agreement to use their clinical samples. HPV genotype was determined using cervical cell samples for CIN and tissue samples for cervical cancer with Genosearch-31, Roche Linear Array and LCR-E7-PCR tests. **Results** For CIN, 373 of 912 cases were infected with a single HPV type. Among them, 12 of 13 high-risk (13HR) HPV types (except for HPV-45) and probable high-risk (Probable HR) HPV types (HPV-53, 66, 67, 82) were identified in CIN-2 or CIN-3 cases. The prevalence of single type infection of 13 HR was 90%, 84%, 98% in CIN1, CIN2, CIN3, respectively. On the other hand, 279 cervical cancer cases had single type HPV infection with 12 of 13HR-HPV (except for HPV-35) and Probable HR-HPV (HPV-53, 67, 69, 70). The prevalence of HPV-16 or 18 in cervical cancer decreased according to older age, whereas opposite trend was observed in relatively lower-risk types within 13HR (Lower-risk HR) (HPV-39, 51, 56, 59, 68). **Conclusion** Not only 13HR-HPV but also Probable HR-HPV like HPV-53, 66, 67, 69, 70, 82 might be oncogenic in Japanese women. Among 13 HR types, age-distribution pattern suggests that cancer develops earlier by HPV-16 or 18 than Lower-risk HR types. Further investigation is needed to clarify difference in behavior between Lower-risk HR and Probable-HR.

ISP-34-4

Investigation of relationship between HPV infection, cervical cytological abnormality and sexual activity in Niigata Manako Yamaguchi[1], Masayuki Sekine[1], Risa Kudou[1], Sosuke Adachi[1], Yutaka Ueda[2], Tomomi Takata[2], Akiko Okazawa[2], Yusuke Tanaka[2], Asami Yagi[2], Takayuki Enomoto[1] *Niigata University[1], Osaka University[2]*

Objective Our aim is to investigate the relationship between HPV infection, cytological abnormality and sexual activity by each generation and then quest for the effective cervical cancer prevention in Japanese young women. **Methods** We recruited 20–30, 34–35 and 40–41 years old females from the public cervical cancer screening program from April 2014 to March, 2016 in Niigata. Pap smear and HPV test were performed and questionnaires about sexual behavior were conducted. HPV test was performed using HCII and TM HPV kit. We divided 20–30 years women into three groups : early 20s (20–22 years), middle 20s (23–26 years), and late 20s (27–30 years). **Results** HPV test were performed at 4596 registrants and 4086 women replied to the questionnaire among them. The infection rate of high risk HPV was 12.8%, 18.6%, 13.0%, 7.1% and 7.2% in early 20s, middle 20s, late 20s, 34–35 and 40–41 years, respectively. The infection rate of HPV16/18 and the rate of cytological abnormality (ASC-US or worse) were highest in middle 20s, 3.3% and 7.8%, respectively. The average of the sexual debut age was 17.9, 18.7, and 19.7 in 20–30 years, 34–35 years and 40–41years, respectively. The HPV infection rate was significantly correlated with the age of sexual debut (p<0.001), especially the rate was 23.7% in 15 years or younger of the age. **Conclusion** The HPV infection

rate in Niigata was relatively low compared with other area in Japan, and younger sexual debut-age was strongly associated with high HPV infection rate. Therefore, we should recognize importance of resumption of vaccination and sex education to the younger generation.

ISP-34-5

Utility of cytology and HR-HPV test for detection of recurrence of cervical intraepithelial neoplasia (CIN) lesions after cervical laser vaporization Azumi Miyauchi, Takashi Iwata, Naohiko Saiki, Tomoko Iijima, Yukako Suga, Hiroshi Nishio, Masaru Nakamura, Shigenori Hayashi, Tohru Morisada, Kyoko Tanaka, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective The aim of this study was to examine the utility of initial postoperative cytology and HR-HPV test for detection of recurrence of CIN lesions after laser vaporization. **Methods** The subjects were 92 patients with CIN2/3 who underwent laser vaporization from April 2013 to November 2015 at our hospital. Cytology was performed every 4-6 months postoperatively and the mean observation period was 18 months (range : 10-32 months). Histology was performed immediately if cytologic diagnosis is HSIL or ASC-H. Following LSIL or ASC-US, histology was performed if abnormal cytology was repeated twice. CIN2 or higher in histology was defined as recurrence. HR-HPV tests were performed simultaneously with initial postoperative cytology. The study was conducted after approval of the institutional ethics committee. Patients gave informed consent. **Results** The results of initial postoperative cytology of 92 patents were NILM : 56, ASC-US : 7, ASC-H : 3, LSIL : 7, and HSIL : 19. The rate of abnormal cytology was 39.1% (36/92). HR-HPV was detected in 40 cases (43.5%) postoperatively. 16 patients were recurred during the observation period. In initial postoperative cytology, the sensitivity and specificity were 93.8% and 72.3% for detection of recurrence with abnormal cytology, 81.2% and 64.4% for HR-HPV-positive cases. In double negative (normal cytology and HPV-negative) cases, there were no recurrence during the observation period. **Conclusion** Initial postoperative cytology had high sensitivity for detection of recurrence after laser vaporization. For normal cytology and HPV-negative cases, a combination of cytology and HR-HPV test is useful for prediction of non-recurrence and that is likely to improve risk assessment after laser vaporization.

ISP-34-6

Pregnancy outcome of women with cervical intraepithelial neoplasia 3 after cervical laser conization Akiko Uchida, Yasuhiko Ebina, Yuka Murata, Hitomi Imafuku, Kaho Suzuki, Yoshiya Miyahara, Hideto Yamada *Kobe University Hospital*

Objective Shallow laser conization was performed for reproductive-aged women with cervical intraepithelial neoplasia (CIN) 3. The aim of this study was to evaluate the subsequent pregnancy outcome of women who had undergone the surgery. **Methods** A total of 154 women with CIN3 were treated by laser conization between 2010 and 2014. Subsequent 24 pregnancies of 22 women ended in 1 induced abortion, 1 ectopic pregnancy, 5 spontaneous abortions and 17 live births in median 31 (range, 2-72) months of an observation period. The 17 pregnancies with live births were enrolled with informed consent in this study. The maternal age was 31 (25-40) years old. An association between pregnancy outcome and conization height was evaluate using Mann-Whitney U test. **Results** Gestational weeks (GW) at delivery were 38 (28-41) GW. The 23.5% (4/17) of the pregnancies ended in preterm delivery (PD). One pregnancy ended in 28 GW due to severe PIH, one in 34 GW due to preterm PROM, and two in 36 GW. Five women were admitted for threatened labor. Conization height in women who ended in PD (13.5mm ; 10-19mm) was not different from that in full-term delivery (14mm ; 11-20mm) (p=0.69). **Conclusion** The conization height were not associated with risks of PD in women with shallow laser conization.

ISP-34-7

The impact of HPV genotypes in prognosis of advanced cervical cancer Mamiko Onuki[1], Koji Matsumoto[1], Yuri Tenjimbayashi[2], Sari Nakao[2], Manabu Sakurai[2], Hiroyuki Ochi[2], Takeo Minaguchi[2], Hiroyuki Yoshikawa[3], Toyomi Satoh[2] *Showa University School of Medicine[1], Faculty of Medicine, University of Tsukuba[2], Ibaraki Prefectural Central Hospital[3]*

Objective The impact of HPV type on survival of invasive cervical cancer (ICC) is less evidenced compared with the influence of HPV type on progression to CIN3. The aim of this study is to address the prognostic impact of HPV types. **Methods** We analyzed clinical data from 137 women that were treated for ICC in a single institute for eight years. This study was approved by ethics committee in the institute and informed consent was obtained by all of the patients. **Results** ccording to HPV genotyping results, the study subjects were divided into three groups : HPV16-positive (n=59), HPV18-positive (n=33) and HPV16/18-negative ICC (Non-HPV16/18, n=45). HPV genotypes did not correlate with FIGO stage (P=0.25). In women with FIGO stage I-II diseases, 5-year overall survival rate (5y-OS) was similar among HPV genotypes ; 92.1% for HPV16, 100% for HPV 18 and 96.4% for Non-HPV16/18 (P=0.70). In women with FIGO stage III-IV tumors, however, 5y-OS was 73.7% for HPV16, 45.7% for HPV18 and 53.6% for Non-HPV16/18 ; a significant difference was observed between HPV16-positive and HPV16-negative ICC (73.7% vs. 52.7%, P=0.04). In a multivariate analysis including FIGO stage, histology and age, women with HPV 16-positive ICC were more likely to have a better prognosis in PFS (relative risk 0.62, 95%CI 0.40-0.94, P=0.02). **Conclusion** These data suggested that HPV16 positivity may be a favorable prognostic factor in advanced stage ICC, implying higher radiosensitivity in HPV16-positive ICC. A further study is under way to clarify the mechanism by which HPV genotypes may contribute to biological characterization of cervical cancer.

ISP-34-8

The assessment of cervical cancer screening using the cotesting with cervical cytology and high-risk human papillomavirus testing in Fukui prefecture Tetsuji Kurokawa, Akiko Shinagawa, Yoko Chino, Yoshio Yoshida *University of Fukui*

Objective The high incidence and mortality rates of cervical cancer in young women are big social problem in Japan. However, the HPV vaccination rate is very low. In such situation, cervical cancer screening using cytology has played an important role for detecting early cervical cancer and the improvement has been expected. The objective of this Fukui Cervical Cancer Screening (FCCS) study was to determine whether the induction of HPV testing is a beneficial method for cervical cancer screening in Japan. **Methods** A total of 7585 women aged 25 years or older undergoing routine screening were enrolled. All women underwent liquid-based cytology and HPV testing. Women with abnormal cytology regardless of high-risk HPV (hrHPV) status, women with positive hrHPV regardless of cytology results, and some women randomly selected from normal cytology and negative hrHPV testing were referred for colposcopy. **Results** Of 7585 cytological results, 96.7% were normal cytology and 3.3% were abnormal cytology. The overall prevalence of hrHPV was 6.8%. The estimated sensitivity for CIN2 or worse of cytology alone and contesting with cytology and HPV testing (cotesting) was 65.9% and 100.0%, respectively. **Conclusion** The FCCS study found that the prevalence of hrHPV was

significantly lower than the U.S. in almost all age groups. This study also is the first report about the sensitivity of cytology for the detection of CIN2 or worse in a Japanese cervical cancer screening. Furthermore, this study suggests that induction of HPV testing is a beneficial method in Japan.

ISP-34-9

Human papillomavirus type 68 may has a causal role in development of stratified mucin-producing intraepithelial lesion : a case report Shiho Fukui[1], Shunsuke Nakagawa[1], Naoko Iimura[1], Ranka Kanda[1], Takayuki Ichinose[1], Shigeki Takeshita[1], Yuko Sasajima[2], Takuya Ayabe[1] *Teikyo University School of Medicine[1], Department of Pathology, Teikyo University School of Medicine[2]*

Stratified mucin-producing intraepithelial lesion (SMILE) is uncommon precursor lesion of the uterine cervix. SMILE is characterized by stratified immature epithelial cells displaying varying quantities of intracytoplasmic mucin throughout the epithelial layer. Human papillomavirus (HPV) is thought to be relevant to development of SMILE based on its positive staining of p16. Here, we show the evidence to support the relevance of HPV to development of SMILE using in-situ hybridization. We experienced a case of SMILE with human papillomavirus (HPV) infection. A 30-year old patient had her routine uterine cervical cancer screening, and her Pap smear showed the possibility of the existence of atypical glandular cells. Colposcopic examination revealed coexistence of atypical glandular lesion and squamous lesion. Pathological analysis showed she has SMILE and low-grade CIN lesion on her cervix. HPV typing showed her lesion is positive for type 52 and 68 infection. She underwent conization of the uterine cervix. Her SMILE lesion was positive for p16 and Mib-1 (Ki67) throughout the epithelial cell layer. We analyzed the lesion for in-situ hybridization using specific probe for HPV type 52 and 68. The basal and parabasal SMILE cells showed strong positive signal by the specific probe for HPV type 68, but not for type 52. Our data support the possibility that HPV type 68 infection in the reserved cells leads to undifferentiated growth of infected cells throughout the epithelial cell layer and development of SMILE lesion.

ISP-34-10

Cervical cancer screening with liquid-based cytology in women with intellectual disabilities Hiroyuki Hashimoto *Sakai City Medical Support Center for Severely Handicapped Children & Persons*

Objective To evaluate the use of liquid-based cytology in cervical cytology in women with intellectual disabilities for the presence of endocervical cell and abnormalities, with the use of speculum or blind technique. **Methods** Retrospective review of charts for 29 women with intellectual disabilities from May 2016 to August 2016 for data on success in pelvic examination, pathology results of the cervical cytology. Institutional ethical committee approved this study. **Results** Of the 29 women with intellectual disabilities, the average age was 55.0 years (range 28-76). On the pelvic examination, 24 (82.8%) cases were completed and cervical cytology was collected with standard speculum examination. 5 (17.2%) could not be completed and a blind vaginal smear was obtained. 7 (24.1%) contained endocervical cells. The presence of endocervical cell with speculum was 20.8% and was 40.0% with blind technique. No cytological abnormalities were detected. **Conclusion** Cervical cytology with liquid-based cytology in women with intellectual disabilities provides an overall rate of endocervical cells of approximately 21%-40% depending on the technique used. Although these results are lower than that of the general population, the blind technique with liquid-based cytology is a reasonable alternative for intellectually disabled women with difficult pelvic examinations.

ISP-34-11

Analyses of atypical glandular cells on cervical cytology : histopathology and follow-up outcome Tetsuya Kawaguchi, Hitomi Imafuku, Kaho Suzuki, Yoshiya Miyahara, Yasuhiko Ebina, Hideto Yamada *Kobe University*

Objective The aim of this study was to evaluate the histopathology and the follow-up outcome of women who had atypical glandular cells (AGC) on cervical cytology. **Methods** Forty-seven women with AGC who underwent colposcopic and histopathologic evaluation between January 2013 and December 2015 were reviewed. Written informed consent was obtained. The age of women was median 46 (range, 29-80) years old. The follow-up outcomes of women with benign histopathologic results were also assessed. Chi-square test or Fishers exact test was used. **Results** Cancer was diagnosed in 23 women (49%) with AGC ; 17 with invasive diseases (cervical adenocarcinoma 7, endometrial cancer 9, ovarian cancer 1) and 6 with preinvasive diseases (AIS 3, CIN3 2, atypical endometrial hyperplasia 1). The detection rate of invasive diseases in menopausal women (76%) was significantly higher than those in pre-menopausal women (13% ; $p<0.01$). On the other hand, in a median of 16 months (range 6-34) follow-up period, 3 out of 14 women had pathological abnormality ; 1 with endometrial cancer, 1 with LEGH and 1 with CIN3. The rate of pathological abnormality in menopausal women (75%) was higher than those in pre-menopausal women (0% ; $p<0.01$). **Conclusion** AGC was clinically important due to the high prevalence of underlying preinvasive and invasive diseases. Menopausal women with AGC had particularly high risk of gynecologic malignancies.

ISP-35-1

Baseline risk of recurrence in stage I-II endometrial carcinoma Yae Takehara, Mayu Yunokawa, Yutaka Yoneoka, Mayumi Kobayashi, Kenta Takahashi, Takafumi Tsukada, Keisei Tate, Hanako Shimizu, Takashi Uehara, Mitsuya Ishikawa, Shunichi Ikeda, Tomoyasu Kato *National Cancer Center Hospital*

Objective Though there are no evidences that postoperative therapy improves overall survival in stage I-II endometrial carcinoma, many women receive adjuvant therapy such as radiation or chemotherapy. This study aimed to examine the effectiveness of post-operative therapy to investigate the baseline risk of recurrence after complete resection without any adjuvant therapies. **Methods** Three hundred seventy four patients with stage I-II endometrial carcinoma who underwent operation without postoperative therapy between January 2005 and December 2011 were retrospectively reviewed and the risk of recurrence and prognosis were assessed. Risk classifications were performed according to European Society for Medical Oncology (ESMO) clinical practice guidelines and Japanese guideline written by Japan Society of Gynecologic Oncology Group. Informed consent was obtained from all patients. **Results** Three hundred eleven patients were evaluable. Five-year recurrence rates by ESMO and Japanese were 2.6%/3.1% in low-risk, 9.2%/6.6% in intermediate-risk and 13.5%/13.8% in high-risk group (P =.003 and .015, respectively). High-risk group had worse overall survival (OS) compared with low- and intermediate-risk groups (5-year OS, low : 97.9%/97.6%, intermediate : 97.9%/98.8% and high : 89.5%/87.5%, P=.003 and .008, respectively). Independent predictive factors of recurrence were age over 60 years, type 2 (estrogen-independent) and peritoneal cytology. **Conclusion** ESMO and Japanese risk classification similarly stratify the baseline risk of recurrence. Patients with stage I-II endometrial carcinoma, especially low- and intermediate-risk diseases, had

low recurrence rate and favorable OS, and the benefit of postoperative therapy might be small.

ISP-35-2

Adnexal metastasis is a poor prognostic factor in endometrial cancer with lymph node metastasis Hidenori Machino[1], Katsutoshi Oda[1], Takahide Arimoto[1], Kenbun Sone[1], Michihiro Tanikawa[1], Mayuyo Mori[1], Kazunori Nagasaka[1], Katsuyuki Adachi[1], Yoko Matsumoto[1], Kei Kawana[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Graduate School of Medicine, The University of Tokyo[1], Nihon University[2]*

Objective Lymph node metastasis is one of the major poor prognostic factors in endometrial cancer. The aim of this study is to clarify prognostic factors for stage III/IV endometrial cancer in the presence or absence of lymph node metastasis. **Methods** A total of 119 patients with FIGO stage III/IV (IIIa；n=31, IIIb；n=7, IIIc；n=60, and IV；n=21) endometrial cancer were retrospectively studied under informed consent and approval of our institutional ethics committee. All patients underwent surgical treatment and adjuvant chemotherapy between 2000 and 2015. Lymph node metastasis (pN1) was positive in 66 patients (55%). Median follow-up period was 51 months. Statistical analyses were performed by Kaplan-Meier method, Log-Rank test and Cox proportional hazards model. **Results** Among 119 patients, age (HR 1.33, p=0.012), tumor grade (HR 1.93, p=0.044) and distant metastasis (HR 2.86, p=0.004) were associated with poor progression-free survival (PFS), but adnexal metastasis, lymph node metastasis, myometrial invasion and peritoneal cytology were not. However, poor prognostic factors for PFS in pN1 patients were adnexal metastasis (HR 6.90, p＜0.0001) and distant metastasis (HR 5.84, p=0.002), although age, tumor grade, myometrial invasion and peritoneal cytology were not significantly associated. Adnexal metastasis (HR 8.94, p=0.0002) was shown to be an independent poor prognostic factor by multivariate analysis. Adnexal metastasis was also a prognostic factor for poor overall survival (p=0.035) in pN1 patients. **Conclusion** Prognostic impact of adnexal metastasis is suggested to be contradictory between the node-positive (pN1) and node-negative groups. Concurrent metastasis to the ovary (s) and lymph nodes may reflect the biological aggressiveness in endometrial cancer.

ISP-35-3

Evaluation of effectiveness in sentinel node navigation surgery to high-risk endometrial cancer patients by cervical injection method Asami Toki, Hitoshi Niikura, Satoshi Okamoto, Shoko Sakurada, Chiaki Hashimoto, Ai Otsuki, Tomoyuki Nagai, Michiko Kaiho, Hideki Tokunaga, Masafumi Toyoshima, Muneaki Shimada, Nobuo Yaegashi *Tohoku University Hospital*

Objective The aim of this study was to verify the safety of cervical injection for determination of sentinel lymph node (SLN) in patients with high-risk (myometrial invasion ＞1/2, histology：serous/clear cell/group3 endometrioid adenocarcinoma) endometrial cancer (EC). **Methods** From February 2009 to July 2016, 40 patients with high-risk EC underwent SLN mapping through cervical Radio-isotope and dye injection prior to systematic pelvic and para-aortic lymphadenectomy. We analyzed removed SLNs with ultrastaging method. **Results** One or more SLNs could be detected 38/40 (95%) patients. All SLNs existed in pelvis. Lymph node metastasis could be detected 10/38 (26.3%). They could be classified to five patterns. A (2/10)：SLN (+)/non-sentinel pelvic lymph node (PLN) (-)/para-aortic lymph node (PAN) (-), B (2/10)：SLN (-)/PLN (+)/PAN (-), C (1/10)：SLN (+) /PLN (+) /PAN (-), D (3/10)：SLN (+)/PLN (-)/PAN (+), E (2/10)：SLN (+)/PLN (+)/PAN (+). In group B, metastasis was detected at macroscopic swelling PLN, and SLN could be detected only at the counter side. **Conclusion** The following attention was necessary to perform cervical injection method safety. We should perform additional para-aortic lymphadenectomy in the case with only one positive LN examined by ultrastaging method. Moreover, we must remove the swelling LNs, and perform side-specific pelvic lymphadenectomy at the no mapping side, as shown in the National Comprehensive Caner Network guideline for cervical cancer.

ISP-35-4

The impact of p53 in predicting clinical outcome of type II endometrial carcinoma：a retrospective analysis Atsushi Fusegi, Akiko Furusawa, Noriko Ooshima, Mikayo Toba, Kimio Wakana, Masakazu Terauchi, Satoshi Obayashi, Naoyuki Miyasaka *Tokyo Medical and Dental University*

Objective Although immunohistochemical staining of p53 is commonly used to characterize endometrial carcinoma, the relationship between p53 expression and prognosis of the patient with type ii endometrial carcinoma remains uncertain. This study aimed to evaluate the prognostic significance of p53 expression. **Methods** The patients with type ii endometrial carcinoma who underwent hysterectomy at our institution during 2000-2015 were studied. The cases with incomplete surgery or with both uterine and ovarian lesion of the same histological subtype were excluded, and 50 cases were enrolled in this study. The patients were divided into two groups based on the p 53 expression i.e. aberrant or normal, and progression free survival (PFS) and overall survival (OS) were compared using Kaplan-Meier method with log-rank test. Multivariate analysis was also performed with cancer stage and histological subtypes by the COX proportional hazards model. P-value＜0.05 was regarded as significant. **Results** The median age of the patients was 62 years old (range：37-87). The median follow-up period was 66 months (range：1-190). PFS in the p53 aberrant group (n=17) was significantly worse than that in the p53 normal group (n=33) (p=0.045), while OS in them was not significantly different. Multivariate analysis revealed that aberrant p53 expression was an independent prognostic factor of worse PFS (HR 0.254- 95%CI：0.073 to 0.875, p=0.03). **Conclusion** Our study showed that the patients with aberrant p53 expression were independently associated with worse PFS in type ii endometrial carcinoma. These finding suggested that p53 expression could become a prognostic indicator of endometrial carcinoma.

ISP-35-5

Risk factors of recurrence and lymph node metastasis in pT1 endometrial cancer (EMC) Yoko Nagayoshi, Kyosuke Yamada, Takako Kiyokawa, Takafumi Kuroda, Ryusuke Kaya, Yasushi Iida, Kazu Ueda, Motoaki Saito, Nozomu Yanaihara, Aikou Okamoto *The Jikei University School of Medicine*

Objective The purpose of this study was to investigate the risk factors of recurrence in EMC confined to the uterus and the significance of microcystic elongated and fragmented pattern of myometrial invasion (MELF) in pT1 EMC. **Methods** We conducted a retrospective study of 215 patients pathologically diagnosed as pT1 pN0 (Group I) or pT1 pN1 (Group II) EMC between 2009 and 2015 at our hospital. We reviewed the following factors：patients age, histological type, grade, stage, peritoneal cytology, lymphovascular space invasion (LVSI), and presence of MELF. **Results** The patients age ranged between 25 and 85 years (mean 55 years). Of 215 patients, 203 were in Group I and 12 in Group II. In Group I, 6 patients (3.0%) recurred. LVSI and histological type were significantly associated with recurrence (p=0.009 and 0.017, respectively) in Group I. MELF was seen in 13 of 97 patients with myometrial invasion in group I, none of whom recurred. In group II, MELF was seen in 7 of 12 (58.3%),

one (14.3%) of whom recurred. In the univariate analysis, the MELF pattern of invasion was significantly related to lymph node metastasis in those in pT1 EMC (p=0.0001). **Conclusion** LVSI and histological type are important risk factors of recurrence in stage I EMC. Presence of MELF is a risk factor of lymph node metastasis.

ISP-35-6

Recurrence and prognosis for FIGO 2008 stage I endometrial cancer with partially pelvic lymph nodes sampling in our hospital Nozomi Shiiba[1], Junji Oonishi[1], Mihoko Nishimura[1], Kazuko Fukushima[1], Yasuyuki Kawagoe[1], Kimihiro Nagai[2], Hiroshi Sameshima[1] *University of Miyazaki[1], Oncology Unit[2]*

Objective The diagnostic role of pelvic and para-aortic lymphadenectomy in clinical stage I endometrial cancer is clear for staging FIGO 2008. But the therapeutic role of those lymphadenectomy is unclear in now. It is an unsolved problem whether those lymph-node resections by the primary operation therapy is one of prognostic factor and increase inconvenient complications. Partially pelvic lymph nodes biopsy of both sides in primary operation was performed all preoperative stage I endometrial cancer from January 2008. We investigated recurrence and prognosis for FIGO 2008 stage I endometrial cancer. **Methods** A retrospective study of 60 patients with FIGO 2008 stage I endometrial cancer at a single institution between 2008 and 2013 was performed. All patients were operated simple hysterectomy and bilateral salpingo-oophrectomy with partially pelvic lymph nodes and followed up at least three years. **Results** A total of 52 patients met the study criteria without 3 unknown follow-up and 5 including sarcoma component. The numbers and proportions of FIGO 2008 stage IA and IB were 36 (69%) and 16 (31%). There are 21 patients in stage IA group without the myometrial cancer invasion. A time of the study, 48 patients were alive and 4 patients were dead. Only one case had died of stage IB group with serous carcinoma. **Conclusion** Without uterine serous carcinomas, our results suggest that the operation for endometrial cancer stage I is adopted partial pelvic lymph node sampling as a substitute for pelvic and para-aortic lymphadenectomy.

ISP-35-7

Evaluating the long term prognostic factor in the overall population of patients with clinical and surgical stage IV endometrial carcinoma Yusuke Shimizu, Mika Mizuno, Shinji Kondo, Masahiko Mori, Asuka Uno *Aichi Cancer Center*

Objective This study aimed to evaluate the long term prognostic factor in patients with stage IV endometrial carcinoma according to clinical characteristics and treatment. **Methods** All patients with Stage IV endometrial carcinoma treated between 1982 and 2016 were retrospectively analyzed with the approval of institutional review board obtained. Eighty-five patients treated were analyzed. **Results** The median age was 59 years (range 31 to 79); the most common histologic subtypes were 52 (61.1%) with endometrioid carcinoma, 11 (12.9%) with serous carcinoma, and 10 (11.9%) with carcinosarcoma. Median overall survival time (MST) of all cases were 12 months (range 0 to 189). The presence of metastasis beside peritoneal dissemination was analyzed and differed statistically (with (n=42) vs without (n=43), MST 12, 14 months p=0.0456). Patients undergoing primary surgery following chemotherapy, primary chemotherapy following surgery and chemotherapy alone were 48 (56%), 20 (24%) and 16 (19%) cases retrospectively. Among patients underwent surgery, no postoperative intra-abdominal residual tumor (NRD) or <=1cm, >1cm were 13, 24 and 31 retrospectively. Postoperative intra-abdominal residual tumor significantly differed statistically in MST (NRD, <=1cm, >1cm groups, MST 63, 14, 13 months $p<0.001$). No other characteristics showed statistical difference. Twelve cases (14.1%) showed more than 5 years survival in which 11 were treated with surgery and 7 with no residual tumor after surgery. Four cases (4.7%) dying with in a month after primary therapy (all treated with chemotherapy). **Conclusion** From our result completely debulking abdominal disease regardless of primary treatment appears to be most important determinants of long term survival in patients with Stage IV endometrial carcinoma. Though there are few cases dying in a short time which makes essential to regard the management of treatment.

ISP-35-8

Retrospective study of the 79 recurrent cases in endometrial cancer Daito Noguchi, Hiroshi Tanabe, Jiro Suzuki, Kazu Ueda, Mutoaki Saito, Nozomu Yanaihara, Kyosuke Yamada, Shigeki Niimi, Hirokuni Takano, Seiji Isonishi, Kazuhiko Ochiai, Aikou Okamoto *The Jikei University School of Medicine*

Objective The recurrent sites of endometrial cancer (EMC) are various. We investigated the modality of recurrence including treatment and prognosis of each recurrence site for EMC. **Methods** We retrospectively examined the first recurrence in 79 EMC who underwent complete surgery between 2005 and 2015 in our institutes. The eligibility was pathologically diagnosed stage I/II/III EMC without sarcoma component. We classified into four groups by recurrence sites; hematogenous (H), lymph node (L), peritoneal dissemination (P), and vaginal stump (V), and examined the treatment methods and prognosis. **Results** The median age was 64 years old. The median follow-up period was 40 months. The number of stages I/II/III were 40/11/2, respectively. Histological types included 47 endometrioid adenocarcinoma (EA) Grade1/2 and 32 other histological types or grade. The number of H, L, P, V were 34, 16, 12, 24, respectively (duplicated cases were 8). As for treatments, number of surgery, radiotherapy and chemotherapy for each recurrent site were 5, 6, 19 (H), 3, 2, 9 (L), 4, 1, 7 (P), and 3, 11, 8 (V), respectively. The median prognostic free survival was 15 (H), 13 (L), 9 (P), and 15 (V) months, respectively. We analyzed four prognostic factors including age, stage (I/II vs III), recurrent site, and histological type (EA G1/2 vs others) by multivariate analysis, and found that age was only independent prognostic factor ($p<0.001$). **Conclusion** Age was ascertained to be the only prognostic factor in recurrent EMC, suggesting that we should consider age as priority when making the strategy for recurrent EMC.

ISP-35-9

Safety and detection of paraaortic lymph node metastasis by systematic paraaortic lymphadenectomy in endometrial cancer Teruyuki Yoshimitsu, Koichiro Kawano, Hiroki Nasu, Ken Matsukuma, Atsumu Terada, Shin Nishio, Naotake Tsuda, Kimio Ushijima *Kurume University School of Medicine*

Objective To evaluate the safty and effectiveness of paraaortic lymphadenectomy for patients with endometrial cancer presumably to be intermediate/high risk of recurrence. **Methods** Patients who underwent paraaortic lymphadenectomy with intermediate/high risk of recurrence (PAN) during March 2013 and March 2016 were enrolled in this study. As historical control, patients who underwent pelvic lymphadenectomy only or with paraaortic lymph node sampling between year of 2010 and 2013 were enrolled (PEL). We investigated age, BMI, operation time, blood loss, and perioperative complications (postoperative bleeding, infection, ileus, thromboembolism, others). Furthermore, we compared the incidence of stage IIIC1 and IIIC2 between PAN and PEL. **Results** Among 107 (PAN: 33, PEL: 74) cases who were enrolled in this study, there were no differ-

ence of mean age between PAN and PEL. PAN had longer operation time (PAN：381, PEL：268.5 minutes p＜0.01), and more blood loss (PAN：505, PEL：375g, p=0.100) than PEL. There was no difference of perioperative complication (grade 3 or 4) between PAN and PEL including ileus (PAN：5%, PEL：8%, p =0.063). PAN included more incidence of stage IIIC2 among all stage IIIC cases than PEL.(PAN 6 of 8, PEL 7 of 14). **Conclusion** In spite of longer operation time or more blood loss, adding paraaortic lymphadenectomy as routine procedure for intermediate/high risk endometrial cancer were acceptable and may be effective to detect stage IIIC2 cases.

ISP-35-10

Preoperative Prognostic Nutritional Index (PNI), calculated from serum albumin and lymphocyte counts of patients, might be a prognostic factor in uterine endometrial cancer
Hiroshi Matsushima, Taisuke Mori, Fumitake Ito, Shiori Umemura, Kaori Yoriki, Tetsuya Kokabu, Kyoko Akashi, Hiroshi Tatsumi, Haruo Kuroboshi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Objective Prognostic Nutritional Index (PNI) is a marker to estimate the immune-nutritional status calculated from serum albumin levels and total lymphocyte counts. It can predict not only the preoperative risk, but also the prognosis in various cancers. However, the significance of PNI in uterine endometrial cancer remains unknown. In this study, we aimed to investigate the significance of PNI in endometrial cancer patients. **Methods** Patients with endometrial cancer were retrospectively recruited. PNI was defined as 10×serum albumin (g/dL)+0.005 ×total lymphocyte count (per mL). Cox proportional hazards models were used to assess the correlation with progression free survival and overall survival. Receiver operating characteristic curve was used to set the optimal cut-off points. **Results** One hundred sixty one patients were examined. Median follow up period was 29.4 months. Optimal cut-off points of PNI levels were determined to be 51. Univariate analysis showed that low PNI levels was significantly associated with poor overall survival (hazard ratio=3.35；95% CI=1.22-10.63；P=0.019). Multivariate analysis revealed that PNI could a favorable prognostic factor independent of age, histological subtype, and clinical FIGO stage (hazard ratio=12.35；95% CI=3.40-57.80；P＜0.001). **Conclusion** PNI might be an independent prognostic factor in patients with endometrial cancer. This factor could be valuable for determining the follow-up strategies for endometrial cancer since it can be calculated from routinely surveyed serum data.

ISP-36-1

Differences in clinicopathologic features between endometrioid and clear cell tumors arising from endometrioma
Shingo Miyamoto[1], Koji Matsumoto[1], Takashi Mimura[1], Yuka Asami[1], Kanae Shimada[1], Chiaki Iitsuka[1], Mamiko Onuki[1], Tetsuya Ishikawa[1], Miki Kushima[2], Akihiko Sekizawa[1] *Showa University School of Medicine[1], Division of Diagnostic Pathology, Showa University School of Medicine[2]*

Objective To clarify clinicopathological features of ovarian cancer arising from endometrioma **Methods** A retrospective study was conducted on women diagnosed with epithelial ovarian cancer arising from endometrioma according to the Sampson and Scott's criteria at our hospital between 2005 and 2015. The clinicopathologic characteristics of the study subjects, such as age, pregnancy, delivery, height, weight, body mass index, serum levels of CA125 and CA19-9, the presence of a precancerous lesion and tumor size, were analyzed and compared between patients with endometrial and clear cell tumors. A precancerous lesion was defined as a precancerous lesion characterized by cytological atypia and architecture proliferation more than 1mm in diameter. **Results** We analyzed a total of 38 women with endometriosis-associated ovarian cancer, 20 endometrioid (4 borderlines 16 malignant) and 18 clear (1 borderline and 17 malignant) cell tumors, and most of which were FIGO stage I diseases. A precancerous lesion was more frequently observed in endometrioid tumors compared to clear cell tumors (70% vs. 11%, P=0.00). In addition, endometrioid tumors except grade 3 were significantly smaller than clear cell tumors (the mean diameter, 95mm vs. 118mm, P=0.03), with the difference increasing in women. **Conclusion** In women with ovarian borderline tumor or cancer arising from endometrioma, the clinicopathologic characteristics were different between endometrioid and clear cell tumors. These observations suggested different pathways in carcinogenesis between endometrioid and clear cell tumors.

ISP-36-2

Immunological difference between ovarian and endometrial endometrioid adenocarcinoma
Akiko Okazawa, Hisashi Wada, Shinya Matsuzaki, Eiji Kobayashi, Yutaka Ueda, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

Objective Immune therapy has come to be noteworthy in gynecologic cancer, however, little is known about the similarity and the difference between histological types. In this study, we focused on T-cell immunological status at tumor sites in endometrioid ovarian cancer and endometrioid endometrial cancer. **Methods** We extracted tumor-infiltrating lymphocytes (TILs) and peripheral blood mononuclear cells (PMBCs) from 8 patients of endometrioid ovarian cancer and 15 of endometrioid endometrial cancer. The TILs and PBMCs were analyzed CD8, CD4, CD45RA, PD-1, OX40, 4-1BB, Tim3, ICOS, CD 25 and Foxp3 by flow cytometry. **Results** The CD8/CD4 ratio was increased in tumor compared to PBMCs. In TILs, the expression ratio of CD4+Foxp3+ was statistically higher in ovarian cancer than endometrial cancer (p＜0.05). In ovarian cancer, the expression ratio of PD-1+, Tim3+ and ICOS+ of both CD8+ and CD4+ cells tends to get higher as progressing, however, the ratio tends to get lower in endometrial cancer. The expression ratio of CD4+Foxp3+ tends to get higher as progressing in both ovarian and endometrial cancer. **Conclusion** It is suggested that the status of T-cell mediated antitumor immunity is dissimilar in the same histological type if the primary organ is different.

ISP-36-3

Prognostic factors in patients with platinum-resistant/refractory ovarian cancer
Kaori Yoriki, Taisuke Mori, Hiroshi Matsushima, Tetsuya Kokabu, Kyoko Akashi, Shiori Umemura, Hiroshi Tatsumi, Haruo Kuroboshi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Objective The aim of this study was to investigate prognostic factors in treatment for patients with platinum-resistant/refractory ovarian, fallopian tube, and peritoneal cancer. **Methods** Patients treated for platinum-resistant/refractory ovarian, fallopian tube, and peritoneal cancer at our hospital between April 2010 and March 2016 were retrospectively recruited. The association of clinicopathological factors with prognosis was statistically analyzed using the Cox proportional-hazards and Kaplan-Meier methods. **Results** Thirty patients were examined. The median survival time was 6.9 months (range：1-47 months). In univariate analysis, under 60 years old, worse Eastern Cooperative Oncology Group performance status (≧1), FIGO stage IV, clear and mucinous type, platinum-refractory disease, and short progression-free survival (＜6 months) were identified as unfavorable prognostic factors. There was no significant difference in the distribution of the residual tumor after primary/interval debulking surgery and treatment for relapse. Multivariate analysis showed that FIGO stage was an independent unfavor-

able prognostic factor for survival (HR：4.39, 95%CI：1.2–15.5, P=0.017). **Conclusion** The prognosis for platinum-resistant/refractory ovarian, fallopian tube, and peritoneal cancer was quite poor. Our findings suggest that best supportive care might be considered as a therapeutic option when patients with FIGO stage IV disease experience platinum-resistant/refractory recurrence.

ISP-36-4

Survival analysis of epithelial ovarian cancer on reclassification 2014 FIGO at Tohoku University Yoshiko Oyama, Hitoshi Niikura, Yusuke Shibuya, Shoko Sakurada, Chiaki Hashimoto, Tomoyuki Nagai, Ai Otsuki, Michiko Kaiho, Hideki Tokunaga, Masafumi Toyoshima, Muneaki Shimada, Nobuo Yaegashi *Tohoku University*

Objective The aim of the present study was to analyze the prognostic role of revised version of International Federation of Gynecology and Obstetrics (FIGO) stage 2014 in epithelial ovarian cancer and compare with previous version staging classification. **Methods** We retrospectively enrolled 366 patients with epithelial ovarian cancer treated at our institution from 2001 to 2010. We reclassified the patients based on the revised FIGO staging classification and compared both classification. **Results** Previous stage Ic (n=76) was divided into IC1 (n=39), IC2 (n=12), IC3 (n=25). We could not find significant difference in the OS between three groups. Ten patients in previous stage IIIc was classified for IIIA1 (i) (n=2) and IIIA1 (ii) (n=8). Although there was no significant difference, duration of survival tend to be longer in stage IIIA1. In addition, previous stage IV (n=43) was categorized into IVA (n=10) and IVB (n=33). IVA (pleural effusion with positive cytology) have an equally poor prognosis as IVB. There was no significant prognostic role in our cases. **Conclusion** Revised FIGO stage has more progressed utility for informing prognosis than previous version, especially in stage III. In stage I and IV, we could not get evidence of validity of reclassification. Further accumulation of data is needed to consider adequacy of new staging.

ISP-36-5

Clinical characteristics of primary fallopian tube carcinoma—A retrospective analysis of three institute experience Shoko Sakurada[1], Hideki Tokunaga[1], Yoh Watanabe[2], Hidekazu Yamada[3], Kazuhiro Takehara[4], Hitoshi Niikura[1], Nobuo Yaegashi[1] *Tohoku University[1], Tohoku Medical And Pharmaceutical University[2], Miyagi Cancer Center[3], Shikoku Cancer Center[4]*

Objective Primary fallopian tube carcinoma (PFTC) is a rare malignancy that account for approximately 1% of all gynecologic malignancies. The aim of this study was to evaluate clinical characteristics in Japanese patients with primary fallopian tube carcinoma. **Methods** We retrospectively analyzed patients with primary fallopian tube carcinoma treated at three institute from October 1998 to December 2015. **Results** Included in this study were 37 patients with a median follow-up 59 months and a median age 58 (range：43–85). Patients presented with ascites (16.2%) or vaginal bleeding (13.5%) or pelvic mass (18.9). The most common histological subtype was serous carcinoma (83.7%). Most patients were diagnosed with advanced-stage disease (stages 3 and 4, 67.5%). There is no patient which could diagnosis with PFTC preoperatively. All patients underwent cytoreductive surgery and postoperative chemotherapy. But recurrence occurred in 17 patients (45.9%) after a median of 12 months (range：3–24). The 5-year overall survival rates was 61.7%. The median follow-up period of optimal surgery group (125 months) were longer than non-optimal surgery group (51 months) ($p<0.05$). **Conclusion** Because symptoms are nonspecific, preoperative diagnosis is difficult. Comprehensive cytoreductive surgery followed by adequate cycles of chemotherapy is an important strategy to improve patients prognosis.

ISP-36-6

Clinical significance of MRI findings of mucinous borderline ovarian tumor Akihiko Ueda, Eri Kawai, Ayumi Tori, Tsuyoshi Nishikawa, Kazuyo Kakui, Yukiyoshi Ishikawa *Saiseikai Noe Hospital*

Objective The MRI appearance of mucinous borderline ovarian tumor (mBOT) varies in terms of bilaterality, size, number of septae, and solid or cystic character. The aim of this study was to clarify the clinical significance of MRI features of mBOT. **Methods** The retrospective study included 40 cases of mBOT, managed at our institution between 2006 and 2016. Four cases without contrast-enhanced MRI were excluded. Age, parity, symptoms, tumor makers, MRI features, and histopathology were reviewed. Staging of mBOTs was compared between the different MRI appearances, with reference to tumor markers. **Results** Intestinal and seromucinous types of mBOT were found in 33 (92%) and three (8%) cases, respectively. Staging of tumors was 1A (24 cases), 1B (one case), 1C1 (five cases), 1C2 (four cases), and 1C3 (two cases). All the cases had multilocular cysts, with a solid portion on MRI being observed in 23 cases (64%, SOLID cases). No recurrence was observed. Ascites were detected in the 1C2 and 1C3 cases, in which CA19-9 levels were significantly higher than in those at lower stages (28027 ± 32373 IU/mL vs. 55 ± 160 IU/mL, $p<0.0001$). SOLID cases had a higher prevalence of intraepithelial carcinoma or microinvasion ($p=0.03$) than non-SOLID cases, while non-SOLID cases had a higher prevalence of stage 1C1 ($p=0.03$) than SOLID cases. 80% of non-SOLID 1C1 cases underwent laparoscopic surgeries, resulting in inadequate resection or surgical spill. **Conclusion** A solid portion on MRI may indicate the presence of severe atypia. Careful management is recommended for the cases without a solid portion.

ISP-36-7

Frequency of Malignant and Borderline Neoplasms of Ovaries After Laparoscopic Surgery and Analysis of Preoperative Evaluation Risa Tsunematsu, Ayako Nakajima, Shinichiro Wada, Masae Yamamoto, Kaoru Minowa, Teppei Suzuki, Takuma Matsuda, Yoshiyuki Fukushi, Takafumi Fujino *Teine Keijinkai Hospital*

Objective To analyze the preoperative evaluation of ovarian tumors with laparoscopic surgery and to verify whether it was possible to differentiate benign from malignant. **Methods** Data were collected on the records of 2513 cases with adnexal tumors undergoing laparoscopic surgery. Those with strongly suspected of malignancy, with any history of cancer, and those without basic evaluation were excluded. The preoperative features by age, the size of masses and serum Ca125 and 19-9 level, and suspicious of whether mature teratoma, endometriotic cyst, or others were compared with final histopathological diagnosis at one institution. **Results** Two thousands five hundred thirteen cases underwent laparoscopic salpingo-oopherectmy or ovarian cystectomy. Thirty-five and sixteen were diagnosed as borderline tumors and malignancy at final histopathological report. (1.39%, 0.64%, respectively) The risk of unsuspected borderline or focally invasive ovarian cancer significantly considered by age, size, complex morphology and serum Ca125 and 19-9. **Conclusion** Besides ultrasound imaging and MRI evaluation, age, serum tumor markers, and size of masses may be some factors for better prediction of unexpected malignancies. Neither tumor markers nor new imaging techniques provide precise elements. Consequently, as long as predicting unwanted cyst rupture dur-

ing operation, it is considerable to do laparoscopic surgery on ovarian tumors.

ISP-36-8

A retrospective study of the clinical significance of lymph node status in ovarian, fallopian, and peritoneal cancer
Yoshio Itani, Sayuri Morita, Yoshinori Takeda, Hitomi Sugimoto, Satoko Ishibashi, Atsushi Sugiura, Hitoshi Hirano, Shinji Toyoda, Tsunekazu Kita *Nara Prefecture General Medical Center*

Objective To assess the clinical effects of the greatest dimension (D) of metastatic lymph nodes (LN (+)), the number of LN (+), and the greatest dimension of LN (+) foci (DF) on survival. **Methods** We retrospectively reviewed the cases of 62 consecutive patients who underwent primary debulking surgery or neoadjuvant chemotherapy (NAC) followed by interval debulking surgery plus systemic lymphadenectomy from 2004 to 2015. The patients' median age was 53 years. LN (+) were detected in 4.62% (162/3660) of preparations, and all LN (+) were measured. Multivariate Cox regression analysis of the factors associated with survival among stage III patients was performed. **Results** The LN (+) displayed a significantly larger mean D value (7.9 mm, 95% confidence interval [CI]：7.1–8.8) than the non-metastatic lymph nodes (LN (−)) (4.2mm, 95%CI：4.1–4.3) ($p<0.0001$). The NAC grip (5.0mm, 95%CI：3.7–6.4) demonstrated a significantly smaller mean DF value than the non-NAC group (7.0mm, 95%CI：5.8–8.2) ($p<0.030$). Among the stage III and IV patients, the proportion of LN (−) patients was significantly higher in the NAC group (44%, 4/9) than in the non-NAV group (6%, 1/15 $p=0.022$). Univariate analysis detected significant relative risk values for NAC (3.2) and positivity cytology (5.8) whereas those for the D of of LN (+), DF>,=10 mm, and the number of LN (+) were insignificant. Positive cytology was the only independent predictor of survival identified during the multivariate analysis. **Conclusion** LN (+) exhibit larger D than LN (−). Some nodal metastatic foci shrink after NAC, and hence, become difficult to detect pathologically. The FIGO2014 stage IIIA1 subdivision has little prognostic impact.

ISP-36-9

Pretreatment maximum standardized uptake value of 18F-fluorodeoxyglucose positron emission tomography-computed tomography as a prognostic biomarker in epithelial ovarian cancer
Takuto Matsuura[1], Isao Ootsuka[1], Yuki Shirose[1], Yusuke Enatsu[1], Yoshifumi Ochi[1], Yuriko Seo[1], Yosuke Suzuki[1], Sakiko Emmi[1], Tokumasa Suemitsu[1], Yoshiaki Furusawa[1], Makoto Suzuki[1], Yukiko Shimizu[1] *Kameda Medical Center[1], Tokyo Medical and Dental University[2]*

Objective 18F-fluorodeoxyglucose (18F-FDG) uptake in positron emission tomography-computed tomography (PET/CT) indicates metabolic activities and corresponds to aggressiveness of a malignant tumor. The aim of this study is to evaluate the relationship between maximum standardized uptake value (SUVmax) of a ovarian tumor using 18F-FDG PET/CT and survival outcome in patients with invasive epithelial ovarian cancer (EOC). **Methods** Patients with EOC who underwent pretreatment 18F-FDG PET/CT and surgery from April, 2006 to June, 2016, were investigated. The effects of SUVmax, age, histological subtype, FIGO stage, and size of postsurgical residual tumor on survival outcomes were assessed. **Results** A total of 132 patients were studied. Median age was 60 years (range, 20–81 years). The median value of SUVmax was 9.3. In this study, patients with low SUV (SUVmax $\leq$5.7) or high SUV (SUVmax >5.7) were assessed for progression-free survival (PFS) and overall survival (OS). On univariate analysis, high SUV was a significant risk for resulting in poor prognosis for PFS ($p<0.05$) and OS ($p<0.05$). On multivariate analysis, high SUV was not significant, gross residual tumor was the only significant prognostic factor for both PFS ($p<0.01$) (hazard ratio 2.14, 95% confidence interval 1.56–2.93) and OS ($p=0.015$) (hazard ratio 2.11, 95% confidence interval 1.44–3.09), and age (>60) also was a significant risk for OS ($P<0.05$) (hazard ratio 1.93, 95% confidence interval 1.02–3.68). **Conclusion** SUVmax of EOC is related to survival outcome on univariate analysis, however, is not significant on multivariate analysis.

ISP-36-10

Prognostic impact of ovarian cancer stage IV subclassification in FIGO 2014 staging system
Masafumi Yasunaga, Keisuke Kodama, Hiroshi Yagi, Tatsuhiro Ohgami, Ichiro Onoyama, Yoshiaki Kawano, Eisuke Kaneki, Kaoru Okugawa, Hideaki Yahata, Kenzo Sonoda, Kiyoko Kato *Kyushu University*

Objective FIGO staging system for epithelial ovarian cancer was changed in 2014. Prognostic impact of stage IV subclassification in this new staging system was evaluated. **Methods** Sixty stage IV epithelial ovarian cancer patients treated between 2005 and 2015 at our hospital were retrospectively analyzed. Data regarding the following clinicopathological variables were recorded for analysis：(1) age at the time of initial therapy；(2) FIGO stage；(3) tumor stage；(4) lymph node status；(5) histologic type；(6) neoadjuvant chemotherapy；(7) optimal surgery. Survival analysis included the Kaplan-Meier method, log-rank test and Cox proportional hazards models. **Results** According to the new classification, 14 and 46 patients were classified into FIGO IVA and IVB, respectively. Median overall survival was 28 and 22 months in each stage. In log-rank test, low tumor stage (T1b-3b) and optimal surgery were favorable prognostic factors with statistically significant better overall survival ($p=0.002$ and 0.021, respectively). However, new FIGO system did not induce any prognostic difference between stage IVA and IVB. **Conclusion** In this study, the revised FIGO system did not add any prognostic information for stage IV ovarian cancer patients. We will discuss prognostic impact of FIGO 2014 staging system with bibliographic consideration.

ISP-36-11

Clinicopathological factors and prognosis in the patients with stage IV ovarian cancer
Koki Oku, Yasuhiko Ebina, Senn Wakahashi, Kaho Suzuki, Yoshiya Miyahara, Hideto Yamada *Kobe University*

Objective The aim of this study was to evaluate clinicopathological factors associated with prognosis in women with stage IV ovarian cancer. **Methods** The initial treatment of 99 women with ovarian cancer was performed between 2010 and 2015. Fourteen women with stage IV including IVA (n=2) and IVB (n=12) were enrolled with informed consent in this study. The age of women was median 61 (range, 43–78) years old. Metastasis was found in liver (n=5), parasternal lymph node (n=3), mediastinum (n=2) and inguinal node (n=2). Seven women had serous carcinoma, one clear cell carcinoma, one mucinous carcinoma, one carcinosarcoma, and four other adenocarcinoma. Therapeutic modalities associated with prognosis were evaluated using Kaplan-Meier method and a log-rank test. **Results** In an observation period of median 21 (range 3–60) months, 2 patients were alive with no evidence of disease, 7 alive with disease, and 5 died. There were no differences in the overall survival between 7 women with neo-adjuvant chemotherapy (NAC) and 7 women without NAC ($p=0.52$). However, two disease-free survivors underwent radical surgery after 6 cycles of NAC, and their malignant tumors disappeared pathologically. **Conclusion** Neoadjuvant chemotherapy followed by radical surgery might be appropriate for some women with stage IV ovar-

ian cancer.

ISP-36-12

Paraneoplastic thrombocytosis as a prognostic marker in ovarian cancer Sari Nakao, Yuki Kojima, Hiroko Ito, Ayumi Shikama, Nobutaka Tasaka, Manabu Sakurai, Hiroyuki Ochi, Takeo Minaguchi, Toyomi Satoh *Tsukuba University*

Objective We examined whether thrombocytosis were associated with clinicopathological characteristics and prognosis of ovarian cancer. **Methods** We retrospectively analyzed a total of 300 consecutive women that were treated for epithelial ovarian cancer between 2001 and 2011. Thrombocytosis, defined as > 400,000/mm^3 of platelet count before treatment, was analyzed in relation to clinical stage, histology and prognosis. **Results** Paraneoplastic thrombocytosis was observed in 19.7% (59/300) of all study subjects. The detection rate of thrombocytosis significantly increased with FIGO stage : 10.4% in stage I (n=96), 13.9% in stage II (n=43), 23.3% in stage III (n=116) and 35.6% in stage IV (n=45) (p=0.003, χ^2 test for trend). Thrombocytosis was more common in serous carcinoma (n=112) compared to the other histology (n=188) (26.8% vs. 15.4%, p=0.02), but the significance disappeared after adjustment for clinical stage (p=0.54). Overall, ovarian cancer patients with thrombocytosis were more likely to have a poor prognosis (5-year overall survival rate, 46.4% vs. 73.3%, p=0.0003 ; 5-year progression free survival rate, 25.9% versus 59.6%, p <0.0001). When the analysis was confined to women with stage III or worse disease, paraneoplastic thrombocytosis was still significantly associated with poor prognosis (5-year overall survival rate, 31.2% versus 53.2%, p=0.03). In a multivariate analysis including FIGO stage, histology and age, paraneoplastic thrombocytosis was an independent prognostic factor for overall and progression-free survival (p=0.004 and p=0.0004, respectively). **Conclusion** Our data suggested that paraneoplastic thrombocytosis may be an independent poor prognostic factor in epithelial ovarian cancer.

ISP-36-13

Negative peritoneal washing cytology during interval debulking surgery can predict overall survival after neoaduvant chemotherapy for ovarian cancer Ayaka Iura, Mariko Ikeda, Sachiko Kaminishizono, Kazuaki Imai, Aiko Kawano, Katsuyuki Konnai, Ryo Onose, Hisamori Kato *Kanagawa Cancer Center*

Objective Clinical relevance of the washing peritoneal cytology (WPC) during interval debulking surgery (IDS), which can be easily implemented as a part of the procedure, has not been well determined while optimal debulking in IDS after neoadjuvant chemotherapy (NAC) was reported as a prognostic factor of the patients with ovarian cancer. A retrospective study was performed to assess the efficacy of WPC during IDS. **Methods** A total of 164 patients diagnosed with ovarian cancer in our institutebetween 2011 and 2015 were retrospectively evaluated and 64 of them received NAC. Seventeen patients underwent exploratory laparotomy (EL) followed by NAC, and the others were clinically diagnosed with imaging studies, cytology and tumor markers. WPC was performed before intraperitoneal observation at laparotomy of IDS. **Results** All patients treated with NAC were on clinical stage III or IV. IDS was performed in 77% (49/64) of patients received NAC. WPC was negative in 35% (17/49 ; N-WPC group), and positive in 65%(32/49 ; P-WPC)of them. Fifteen patients were not able to undergo IDS due to their progressive disease status (no-IDS). The median overall survival in N-WPC, P-WPC and no-IDS groups was 53, 30 and 11 months, respectively, and statistically significant difference was seen between any of the groups (p with Mantel-Cox log-rank test <0.01). WPC was found in a multivariate Cox regression model as an independent prognostic factor (p<0.001). **Conclusion** The WPC during IDS should be considered for a prognostic factor of the patients with NAC for ovarian cancer.

ISP-37-1

Screening of Lynch syndrome using risk assessment criteria and deficiencies of mismatch repair proteins in patients with ovarian cancer Takashi Takeda, Kouji Banno, Megumi Yanokura, Kenta Masuda, Yusuke Matoba, Haruko Kunitomi, Masataka Adachi, Yusuke Kobayashi, Akira Hirasawa, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki *Keio University School of Medicine*

Objective Lynch syndrome is a cancer predisposition syndrome caused by germline mutation of DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. Ovarian cancer is known to be one of Lynch-associated cancers ; however, Amsterdam II criteria do not include ovarian cancer. We analyzed deficiencies of MMR proteins in patients with ovarian cancer who met the Lynch syndrome risk assessment criteria of the Society of Gynecologic Oncologists (SGO), with the goal of investigating the frequency of ovarian cancer in Lynch syndrome. **Methods** The subjects were 105 patients with ovarian cancer who visited our hospital in 2015. A new questionnaire for family history was prepared to identify cases meeting the SGO criteria. Microsatellite instability (MSI), immunohistochemistry and methylation of MMR genes were analyzed using surgical specimens of these patients. **Results** Of the 105 cases, 22 (21.0%) met the SGO criteria for a 5-10% chance of having Lynch syndrome. Two of these 22 cases were MSI-high : One case had loss of MLH1 and PMS2 and methylation of MLH1, indicating sporadic ovarian cancer. The second case had loss of MSH2 and MSH6 without methylation, probably having Lynch syndrome with MSH2 mutation. These results indicate that risk assessment using SGO criteria may be able to detect Lynch syndrome in 0.9% (1/105) of patients with ovarian cancer, and in 4.5% (1/22) of patients who meet the criteria. **Conclusion** This diagnosis procedure may be useful for screening of Lynch syndrome in patients with ovarian cancer.

ISP-37-2

Prevalence of a family history of ovarian and breast cancer among patients with ovarian or peritoneal cancer Saya Yamashita, Kae Hashimoto, Michiko Kodama, Seiji Mabuchi, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective Women with a family history of ovarian and/or breast cancer are recommended to be referred to trained healthcare providers for genetic counseling. However, little is known about how many individuals at risk are present and how many of these patients are offered genetic counseling from gynecologic practice. The aim of the current study is to assess the prevalence of individuals at risk of hereditary cancer and the referral rate to genetic counseling. **Methods** We reviewed the medical records of patients who underwent the primary surgery for their ovarian or peritoneal cancer in our hospital from January 2014 to December 2015. We collected information on her previous history, family history and histological data of cancer. **Results** Ninety-one patients underwent primary surgery of ovarian or peritoneal cancer in our hospital during this period. Thirty-one percent (28/91) of patients had a family or previous history either of breast, prostate or pancreas cancer. We could not get information on the onset years of their familial cancer from medical records from most of them. Furthermore, we could not obtain information on hereditary cancer based upon our current medical records except for one patient who received a genetic counseling and testing at the department of genetic counseling. **Conclusion** Current standard clinical practices and medical record system are insufficient for identifying patients in

need of referral to genetic counseling. Thereafter, we have revised the family history questionnaire and have started to gain more information about target family history at the time of hospital admission and offer genetic counseling.

ISP-37-3

About Microsatelite Instability Test for Endometrial cancer in our hospital (the screening for Lynch syndrome) Aki Hara[1], Kensuke Tomio[1], Yuichiro Miyamoto[1], Kazuko Kurihara[1], Koji Horie[1], Harushige Yokota[1], Kei Kawana[2], Yutaka Osuga[2], Tomoyuki Fujii[2] *Saitama Cancer Center[1], Graduate School of Medicine, The University of Tokyo[2]*

Objective Lynch syndrome is an autosomal dominant genetic disease that includes various cancers such as colon cancer or endometrial cancer by germline mutation of DNA mismatch repair (MMR) genes. Microsatellite instability (MSI) occurs when the mismatch repair system is damaged. In our hospital, we have performed MSI test for the person who was diagnosed with endometrial cancer and provided informed consent. To understand clinical and pathological features of MSI-positive endometrial cancer, we performed retrospective research. **Methods** We examined 67 patients who underwent MSI-test from October 2013 until Jun 2016, using 5 microsatellite markers (BAT26, BAT25, D5S346, D2S123, and D17S250) recommended in screening for Lynch syndrome. We compared age, histological type, advanced stage, other organs cancer and family history. **Results** Among 67 patients, 8 patients (12%) showed MSI-positive. The average age of MSI-positive group was 55 years old (43-70) and that of MSI-negative was 61 (33-83), with no significant difference. MSI-positive endometrial cancer tended to be well-differentiated. The proportion of grade 1 endometrioid adenocarcinoma was 75% and 56%, respectively. The advanced stage of 3 or 4 of MSI-positive group was fewer than that of MSI-negative (25% vs 34%). The patients with MSI-positive showed a tendency to have other organs cancer and family history, and one of them was detected early stage colon cancer following two years after hysterectomy by careful health examination. **Conclusion** We clarified the features of MSI positive endometrial cancer of the hospital. It is considered to have a better prognosis as same as the previous reports.

ISP-37-4

N-acetylglucosaminyltransferase IVa promotes invasion of choriocarcinoma Kimihiro Nishino[1], Eiko Yamamoto[2], Kenichi Nakamura[1], Shizuka Sato[1], Kaoru Niimi[1], Fumitaka Kikkawa[1] *Nagoya Univesity[1], Department of Healthcare Administration, Nagoya University[2]*

Objective N-acetylglucosaminyltransferase IVa (GnT-IVa) is a glycosyltransferase which catalyzes the formation of β1, 4 GlcNAc branches on mannose core of N-glycans on several proteins such as human chorionic gonadotropin secreted from gestational trophoblastic neoplasia (GTN). The aim of this study is to elucidate the expression and function of GnT-IVa in choriocarcinoma. **Methods** (1) Imuunohistochemistry using specimens of hydatidiform mole (HM) and GTN (invasive mole and choriocarcinoma) : the GnT-IVa expression and immunostaining of GSL-II recognizing tri-antennary branched N-glycans modified by GnT-IVa. (2) Functional analyses using a choriocarcinoma cell line Jar with transfection of GnT-IVa gene (Jar-GnT4a) or control gene (mock) : (a) cell proliferation, migration, invasion and adhesion assay (in vitro), (b) tumor transformation assay by subcutaneous or intravenous injection of Jar cells into nude mice (in vivo). (3) Lectin immunoprecipitation of whole cell lysate or culture supernatant of Jar cells followed by nano LC-MS/MS to detect target proteins of GnT-IVa modification. **Results** (1) The GnT-IVa expression corresponded to the immunoreactivitiy of GSL-II, and the medians of immunostaining score with GSL-II were significantly higher in GTN than HM. (2) (a) GnT-IVa overexpression increased migration and invasion ability of Jar cells (2.5-fold and 1.4-fold) and adherence ability to ECM, whereas cell proliferation was not changed. (b) The rate of tumor formation subcutaneously and in the lung was significantly higher when injection of Jar-GnT4a than mock. (3) Nano LC-MS/MS revealed some proteins as target proteins of GnT-IVa modification, including LAMP-2. **Conclusion** GnT-IVa may play a crucial role in invasion and metastasis of choriocarcinoma through glycosylation of some proteins such as LAMP-2.

ISP-37-5

Clinical outcome of patients with invasive mole, clinical invasive mole or post-molar persistent hCG treated with 5-day methotrexate regimen Hitomi Imafuku, Yoshiya Miyahara, Kaho Suzuki, Senn Wakahashi, Kotaro Ichida, Yasuhiko Ebina, Hideto Yamada *Kobe University*

Objective The aim of this study was to evaluate the outcome of 5-day methotrexate (MTX) regimen for the patients with invasive mole, clinical invasive mole or post-molar persistent hCG. **Methods** Eight patients (invasive mole : 1, clinical invasive mole : 6 and post-molar persistent hCG : 1) were treated with this regimen between August 2012 and July 2016. The median age at diagnosis was 28 years (range 24-43). Clinical information was obtained by review of the hospital records. Pre-treatment hCG levels, FIGO score, decrease rate of hCG, adverse effects of the treatment were compared between the patients with drug resistance for MTX (DR ; n=2) and patients with complete remission (CR ; n=6) using Mann-Whitney U test. **Results** The median of pre-treatment hCG levels in patients with DR (336,850 mIU/ml) was higher than those in patients with CR (5,155 mIU/ml, p=0.07). The median of decrease rates of hCG during the first to second cycles in patients with DR (38.6%) was lower than those in patients with CR (88.8%, p=0.07). Similarly, the median of decrease rates of hCG during the second to third cycles in patients with DR (25.2%) was lower than those in patients with CR (88.8%, p=0.07). Adverse effects were found in 2 patients with CR ; G2 increase of the liver enzyme and febrile neutropenia. **Conclusion** The patients with pre-treatment high hCG levels and poor decrease rate of hCG might be indicated as the resistance of 5-day MTX regimen.

ISP-37-6

A second curettage for hydatidiform mole : proposal for patient selection Chihiro Odaki, Shingo Miyamoto, Yoshiyuki Okada, Yuka Asami, Yusuke Hirose, Kanae Shimada, Takashi Mimura, Chiaki Iitsuka, Mamiko Onuki, Tetsuya Ishikawa, Koji Matsumoto, Akihiko Sekizawa *Showa University School of Medicine*

Objective The therapeutic role of a second curettage after evacuation of molar pregnancy is still controversial. The aim of the present study was to clarify candidates for the second curettage. **Methods** We retrospectively analyzed a total of 32 women treated for hydatidiform mole (23 complete and 9 partial) between 2012 and 2016. Although ultrasound examination after the first curettage did not detect any residual lesion in the uterine cavity, they received a second curettage at one week after the first curettage. **Results** Residual molar tissues in the second curettage specimens were more frequently found in women with complete mole (21.7%, 5/23) than in those with partial mole (0%, 0/9), but the difference did not reach statistical significance due to limitations imposed by the small sample size (p=0.28). Pre-treatment HCG levels did not correlate with higher risk for residual molar tissues (p=0.64). However, HCG levels before second curettage were significantly higher in women with residual

molar tissues compared with those without residual diseases (median：27995 IU/L [2359–30354] vs. 3800 IU/L [15–3815], p =0.006). Residual molar tissues were found only in women with HCG levels of 1000 IU/L or more at one week after the first curettage. **Conclusion** Our data suggested that a second curettage may be recommended only for women with HCG levels of 1000 IU/L or more at one week after a first curettage.

ISP-37-7

HDlive image of complete hydatidiform mole Kenta Yamamoto, Mohamed A.M. Aboellail, Tamaki Tanaka, Chiaki Tenkumo, Megumi Ishibashi, Masato Mashima, Megumi Ito, Nobuhiro Mori, Uiko Hanaoka, Kenji Kanenishi, Hirokazu Tanaka, Toshiyuki Hata *Kagawa University*

Objectives We present our experiences of using the HDlive techniques to assess complete hydatidiform mole. **Methods** Four cases of complete hydatidiform mole were studied using HDlive image. **Results** The HDlive image (HDlive, HD–flow, HDlive-Flow with the HDlive silhouette mode, HDlive silhouette inversion mode) clearly depicted the number, size, and spatial position of molar vesicles, compared to conventional two–dimensional (2D) sonography. Moreover, spatial relationships among molar vesicles, intrauterine anechoic fluid collection, and the uterine wall enabled the clear localization of the lesion. **Conclusions** HDlive imaging should provide new insights, and have the potential to supplement conventional 2D sonography in the diagnosis of complete hydatidiform mole.

ISP-38-1

Effectiveness and safety of chemotherapy in elderly gynecologic cancer patients. Mihoko Aoki, Yukihide Ota, Mikiko Sato, Yukio Suzuki, Yuichi Imai, Yoshinobu Sugo, Tae Mogami, Naho Ruiz Yokota, Tatsuya Matsunaga, Etsuko Miyagi *Yokohama City University*

Objective This study aimed to evaluate the effectiveness and safety of chemotherapy for the elderly gynecologic cancer patients. **Methods** A retrospective analysis was performed on gynecological cancer patients who were 80 years or older and received any treatment between 2011 and 2015. **Results** The subjects were 42 women with the age from 80 to 90 years (mean 83.7 ± 3.1SD). Chemotherapy was considered for 33 patients but 27 of them (82%) decided not to receive chemotherapy. Nine of these 27 (33%) possessed severe general complications and/or poor performance status that would impede the treatment, whereas 18 patients (67%) did not receive proactive treatment simply because of the advanced age. Consequently, only 6 patients received chemotherapy. Among them, 2 cases stopped chemotherapy because of severe anorexia or disease progression. No other severe adverse event occurred during the treatment. Over all disease control rate of these 6 patients was 66.6%. One of these patients died 4 months after the treatment because of the disease progression. The prognoses of the 27 patients who did not receive chemotherapy were as follows：16 patients (59%) alive, 9 patients (33%) dead by the disease and 2 patients (7%) missed from the follow–up. **Conclusion** Our study revealed that chemotherapy for elderly gynecologic cancer patients was feasible and might be beneficial unless patients conditions is well evaluated. The eligibility criteria for safe chemotherapy in elderly gynecologic cancer patients should be established.

ISP-38-2

Maternal death through Malignancy tumors：Analysis of National registration in Japan Shinji Katsuragi[1], Isamu Ishiwata[2], Junichi Hasegawa[3], Akihiko Sekizawa[4], Masamitsu Nakamura[4], Naohiro Kanayama[5], Masahiko Nakata[6], Takeshi Murakoshi[7], Jun Yoshimatsu[8], Kazuhiro Oosato[9], Hiroaki Tanaka[9], Tomoaki Ikeda[9] *Sakakibara Heart Institute[1], Ishiwata Obstetrics and Gynecology Hospital[2], St. Marianna University School of Medicine[3], Showa University[4], Hamamatsu University[5], Toho University[6], Seirei Hamamatsu General Hospital[7], National Cerebral Cardiovascular Center[8], Mie University[9]*

Objective To analyze the etiologies and clinical courses of malignancy related maternal deaths from registration in Japan. **Methods** All maternal death cases in Japan are reported to a Committee of the Ministry of Health, Labor, and Welfare. Maternal death cases due to malignancy from 2010 to 2015 in this national registration were extracted and evaluated. **Results** Of 266 maternal deaths, 8 were related to malignancy. Ages：30~39 years old, the average：34.3. Origins：four gastric cancers, one ureter cancer, one malignant limphoma, one acute myelocytic leukemia (AML), and one brain tumor. The first symptoms were appearance of blasts in peripheral blood (2cases), digestive symptoms (3), headache (1), lumbago (1), hydronephrosis (1)； and these occurred before and during pregnancy in one and seven cases, respectively. One gastric cancer case died at 24 weeks and in the rest of seven early terminations for maternal therapies were selected by cesarean section at 25–36 (mean 29.9) weeks. These seven neonates survived. Treatments for primary diseases were given after delivery in three cases：marrow transplant in AML, chemotherapy in one of the gastric cancers, craniectomy in brain tumor, and in other cases palliative cares were given. In seven cases patients died post partum 7 to 25 days. Definite diagnosis were made by gastrointestinal fiber (3), pathological anatomy (2), bone marrow puncture (1), biopsy of the brain tissue (1), CT/MRI (1). Except AML and brain tumor cases, multiple metastasis were observed. **Conclusion** Most malignant tumors during pregnancy were found in advanced stages. We have to take in mind that persistent digestive symptoms, headache, lumbago may be the signs of malignancy during pregnancy.

ISP-38-3

A case of venous thromboembolism due to oral contraceptive intake and nights spent in a vehicle—A case from the 2016 Kumamoto Earthquakes— Yoshinori Okamura, Miwa Nakamura, Takeshi Motohara, Takashi Ohba, Hidetaka Katabuchi *Kumamoto University*

Long–flight thrombosis (LFT) is a term used to describe pulmonary thrombosis caused by long–term sedentary behavior. In Japan, evacuees from earthquakes who spend the nights in cars at the time of disasters have been reported to suffer from LFT. Furthermore, low dose oral contraceptive (OC) is a well–known risk factor for thrombosis. Here we report the first case of LFT due to the practice of spending nights in cars and intake of OCs when the earthquakes occurred. A 40 year–old woman, who had undergone laparoscopic surgery for ovarian endometriosis and subsequently prescribed low dose OCs, visited our hospital for routine examination. She experienced the Kumamoto Earthquakes and subsequent aftershocks in April 2016 and had spent 7 nights in a vehicle before her visit. She complained of pain in her left lower extremity and sudden dyspnea on effort. As her serum D–dimer levels were elevated (13.2 μg/mL), she was suspected of deep venous thrombosis and a contrast–enhanced computed tomography–scan revealed the contrast deficit in bilateral pulmonary arteries and in left lower extremity. She was diagnosed with LFT and admitted to the department of cardiology. The mechanisms by which LFT occurred in this case were thought to involve thrombus formation induced by long–term sedentary tendencies due to spending nights in a vehicle in addition to OC use. Although LFT had occurred within 2 nights in the present case, it is essential that all medical staff and evacuees seeking shelter in vehicle should be aware of such information at the time of disasters.

ISP-38-4

Treating gynecologic cancer in oldest old patients, defined as aged 85 years and older Taeko Ueda[1], Rie Urabe[1], Tomoko Kurita[1], Seiji Kagami[1], Toshinori Kawagoe[1], Yusuke Matsuura[2], Toru Hachisuka[1] *University of Occupational and Environmental Health[1], School of Health Sciences[2]*

Objective The aim of this study is to assess disease states of oldest old women with gynecologic cancer and the outcome of their treatment. **Methods** We made a retrospective review of disease states and the outcomes of treating oldest old women with gynecologic cancer, defined as aged 85 and older. **Results** We diagnosed 39 cases of gynecologic cancer in oldest old women whose median age is 89 (85–100). Out of them, twenty-one patients had uterine cervical cancer, 10 had uterine corpus cancer, 5 had vulvar cancer and 3 had ovarian cancer. Eleven patients (28%) had dementia. Only 3 patients had no physical underlying disease. The remaining 36 patients had any physical underlying disease (0–4, median 2). Twelve patients underwent operations, and one of them got adjuvant chemotherapy. Twenty-three patients received radiation therapy, and one of them was given combination concurrent chemotherapy. Four patients got symptomatic treatment only. Ten patients had standard therapy while 25 patients got palliative therapy because of their own general condition. Median follow-up is 9 (0–94) months. Thirteen patients died, 6 patients were alive with disease and 20 patients showed no evidence of disease. The overall survival rates of the 31 patients who were ambulatory at the first examination rose significantly, as compared with eight patients who were not ambulatory ($p<0.05$). Still there is no significant difference in survival rate between patients in early stages (≤ 2) and ones in advanced stages (≥ 3). **Conclusion** Prognosis of oldest old women with gynecologic cancer is related to not only malignancy but also activity of daily living for example ambulation.

ISP-38-5

Trends of routes of hysterectomy performed for benign indications ; A single-center, retrospective study Akimasa Takahashi, Jun Kitazawa, Mari Nakata, Yoshihiko Hayashi *Nagahama City Hospital*

Objective To estimate the recent trends of routes chosen for hysterectomy performed for benign indications in our hospital. **Methods** We retrospectively reviewed patients who underwent hysterectomy for benign indications at our hospital from 2013 to 2016. This study was approved by the Institutional Review Board. We compared the course of perioperative and postoperative outcome for the three different approaches. The date were analyzed using t test or χ^2 and Fisher's exact test. **Results** A total of 155 patients underwent hysterectomy for benign indications during the study period : 111 (71.6%) were total abdominal hysterectomy (TAH), 26 (16.8%) total vaginal hysterectomy (TVH), 19 (12.3%) total laparoscopic hysterectomy (TLH). The operation time was shorter for the TVH group than TAH and TLH groups (respectively, $p<0.001$). The amount of bleeding was smaller for the TVH and TLH groups than TAH group (respectively, $p<0.001$). The C-reactive protein (CRP) 3 days after operation in TVH group was lower than TAH group ($p=0.002$). However, the average size of uterus in TAH group was bigger than TVH and TLH groups (respectively, $p<0.001$, $p=0.003$). Patients undergoing TLH experienced fewer perioperative complications compared with TAH and TVH groups ; however, this difference was not significant. **Conclusion** TVH is better procedures for women requiring hysterectomy. Vaginal hysterectomy is the most minimally invasive approach but the final choice for the route of hysterectomy can depend on many factors such as body mass index, size of uterus and experience of the gynecologist.

ISP-38-6

Trends in incidence and long-term survival of Japanese women with vulvar cancer : a population-based analysis Yusuke Tanaka, Yutaka Ueda, Mamoru Kakuda, Asami Yagi, Akiko Okazawa, Tadashi Iwamiya, Tomomi Takata, Shinya Matsuzaki, Eiji Kobayashi, Kiyoshi Yoshino, Tadashi Kimura *Osaka University Graduate School of Medicine*

Objective The objective of the study is to determine the trends in incidence and long-term survival for vulvar cancer in a Japanese population, using a population-based cancer registry data in Osaka, Japan. **Methods** The age-standardized incidence rate of 815 cases of vulvar cancer diagnosed between the years of 1976 and 2010 was calculated, using the 1985 model population of Japan. We also analyzed 5- and 10-year relative survival for 290 cases of squamous cell vulvar carcinoma, diagnosed between 1976 and 2008. Relative survival is a ratio of the overall survival in cancer patients versus the expected survival in a comparable set from the general population. **Results** We have found that the age-standardized incidence rate for vulvar cancer trended downward during the period of 1976 to 1997 (annual percentage change (APC) -2.7% ; 95% confidence interval [CI] : [-4.2% to -1.2%]), whereas it trended upward from 1998 to 2010 (APC 3.0% ; 95% CI : [0.5% to 5.5%]). There was no statistically significant difference for the 5- and 10-year relative survival between the two periods of 1976–2000 and 2001–2008. **Conclusion** We have found that, despite an increasing trend in vulvar cancer incidence among Japanese population, the relative survival rate for vulvar cancer did not change over the 35 years of this study.

ISP-38-7

Cytotoxic effects of 15-deoxy-delta 12,14-prostaglandin J2 in combination with dasatinib or gefitinb against uterine sarcoma in vitro Takako Kawakita, Masato Nishimura, Eri Takiguchi, Akiko Abe, Minoru Irahara *Tokushima University*

Objective Uterine sarcoma have aggressive character and poor clinical outcome.The most effective treatment for this desease is a complete resection of primary lesion at an early stage. If surgical remission can not achieve, the clinical outcom is poor as both radiation therapy and chemotherapies heve little to no effect. 15-deoxy-delta 12, 14-prostaglandin J2 (15d-PGJ2) has gained attention as a potential cancer treatment because tha it could significantly inhibit cell growth and induce apoptosis in cancer cells through activation of PPAR gamma. Previously we have been reporting that there is a uterine sarcoma cell growth inhibitory effect on 15d-PGJ2, its effect was localized. So this time was examined the possibility of combination therapy with a molecular target drugs. **Methods** We used uterine sarcoma cell lines (MES-SA, MES-SA/Dx5, SKN). Cell viability was assessed using WST-1 assays. Protein expression was assessed using Western blotting. **Results** Cell Cell proliferation was inhibited by treatment with the combination therapy. Furthermore, cell growth suppression effect was not observed in the gefitinib alone. The anti-Src antibody dasatinib and the anti-EGF antibody gefitinib induced a significant down-regulation of AKT and MAPK pathways. **Conclusion** In conclusion, treatment with 15d-PGJ2 combination with dasatinib produced a synergistic effect by negatively regulating both AKT and MAPK pathways. These results suggest that 15d-PGJ2 could be used combination with dasatinb as a potential therapeutic approach of uterine sarcoma. In addition, the combination therapy with gefitinib can be expected synergistic effect. These combination therapies have potential new treatment of uterine sarcoma.

ISP-38-8

The initial experiences of Edoxaban for the treatment of

thromboembolism in patients with gynecological malignancies Mayu Shiomi, Kenjiro Sawada, Aiko Kakigano, Michiko Kodama, Kae Hashimoto, Eiji Kobayashi, Seiji Mabuchi, Yutaka Ueda, Takuji Tomimatsu, Kiyoshi Yoshino, Tadashi Kimura *Osaka University*

Objective Venous thromboembolism (VTE) and the subsequent pulmonary embolism (PE) were a frequent and potentially life-threatening event in gynecological malignancies. While the standard care had been an intravenous (IV) heparin followed by warfarin, the so-called direct oral anticoagulants (DOAC) were introduced recently in clinical practice with a favorable risk-benefit profile. Herein, we present our initial experience to treat patients with Edoxaban. **Methods** Fifteen patients with VTE including 1 patients with PE were treated. After the initial treatment with IV heparin (10000 U/day), 60 mg or 30mg Edoxaban was started once daily. The treatment duration was set to be 6 months unless severe complications occurred. Before discontinuation, vascular ultrasound or enhanced CT was peformed to comfirm vessel blood clots disappeared. **Results** Of 15 patients, 5 were endometrial cancer, 6 ovarian cancer and others. 11 patients were diagonosed preoperatively and the others postoperatively. The mean age of patients was 61 years (41-82) old and BMI of the patients was 22.7. The mean remedy period of Edoxaban was 139 (42-204) days. In all cases, vessel blood clots succesfully diappeared without progession of the diseases. While one case stopped due to genital bleeding, the other 14 cases finished or continued oral administration without any apprent adverse events. **Conclusion** Edoxaban administered once daily after initial treatment with heparin is effective and safe for patients with VTE associated with gynecological malignancies.

ISP-38-9

Preoperative diagnosis of uterine sarcoma using tumor signal intensity by T2 weighted imaging (T2WI) and apparent diffusion coefficient (ADC) of Magnetic Resonance Imaging (MRI) Yasuko Oka[1], Masanori Tamori[1], Yasuhiro Oosaka[2], Jinichi Sakamoto[2], Hiroaki Takagi[2], Toshiyuki Sasagawa[2] *Komatsu Municipal Hospital[1], Kanazawa Medical University[2]*

Objective Uterine sarcoma is a rare and poor prognostic disease, and its pre-operative diagnosis is difficult. We focused on the tumor-to-subcutaneous fat signal intensity ratio (TFSIR) and ADC and previously presented. The purpose of this study is to make the preoperative diagnosis method using MRI more reliable through additional investigation. **Methods** MRI was performed in 10 cases of uterine sarcoma in the last 6 years at our hospital (sarcoma group). In contrast, 29 cases of leiomyoma received MRI in 2016 (myoma group). We calculated TFSIR and ADC for both groups and made comparisons. The threshold value of TFSIR and ADC was also calculated. Finally, we considered a more reliable way of preoperative diagnosis by the combination of these parameters. This protocol has been approved by the local institutional review board of ethics. **Results** The sarcoma group had significantly higher TFSIR than myoma group (0.834 ± 0.204 vs. 0.346 ± 0.335, $p<0.05$). The threshold value to diagnose sarcoma is over 0.512 (sensitivity : 100%, specificity : 88%). The sarcoma group had significantly lower ADC than myoma group (0.754 ± 0.251 vs. 1.18 ± 0.194, $p<0.05$). The threshold value to diagnose sarcoma is under 0.920 (sensitivity : 80%, specificity : 66%). All tumors with over 0.512 TFSIR and under 0.920 ADC are sarcoma. All tumors with under 0.512 TFSIR are leiomyoma. In 5 tumors with over 0.512 TFSIR and over 0.920 ADC, 2 tumors are sarcoma. **Conclusion** Pre-operative diagnosis of uterine sarcoma is possible by a combined use of TFSIR by T2WI and ADC of MRI.

ISP-38-10

Complementary role of contrast-enhanced computed tomography (CECT) and ^{18}F-FDG PET/CT in the assessment of recurrence in patients with gynecologic malignancies Koji Kumagai, Masahiro Sakai, Takayoshi Maeda *Osaka Railway Hospital*

Objective Contrast-enhanced computed tomography (CECT) is the most commonly used modality to detect malignant lesions. However, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) may provide more diagnostic accuracy for detecting recurrent malignancies. In this study, we evaluated the complementary role of CECT and ^{18}F-FDG PET/CT in the assessment of recurrence in patients with gynecologic malignancies. **Methods** We retrospectively reviewed CECT and ^{18}F-FDG PET/CT scans from 11 patients with recurrent gynecologic malignancies, including : stage I - II cervical cancer (n=4) ; stage IV endometrial cancer (n=1) ; stage III ovarian cancer (n=5) ; and stage III peritoneal cancer (n=1). We also reviewed clinical information and how often scans were repeated after recurrence. **Results** The median age at the time of initial therapy was 62 (30 - 78) years. The median follow-up time and recurrence-free interval were 25 (6 - 75) and 9 (2 - 65) months, respectively. CECT identified 17 recurrent lesions in 11 patients. ^{18}F-FDG PET/CT identified 5 additional lesions in 5 patients (1 pelvic nodule and 4 lymph nodes). The mean frequency of CECT and ^{18}F-FDG PET/CT scans after recurrence was 4.4 ± 2.7 and 1.6 ± 0.9 times, respectively. Three patients showed complete response to treatment for each recurrent lesion. Two patients survived with disease, and six patients died of disease. **Conclusion** It is more convenient to repeat CECT, however ^{18}F-FDG PET/CT is more sensitive in identifying recurrent lesions. Thus, the two modalities can play a complementary role in the assessment of recurrence in patients with gynecologic malignancies.

ISP-38-11

Clinicopathological characteristics of ovarian tumor with small mural nodule Yu Ito, Kosuke Hiramatsu, Kiyoshi Yoshino, Yutaka Ueda, Akiko Okazawa, Shinya Matsuzaki, Tomomi Takata, Eiji Kobayashi, Seiji Mabuchi, Kenjiro Sawada, Takuji Tomimatsu, Tadashi Kimura *Osaka University*

Objective Our objective is to evaluate the clinicopathological features of ovarian tumor with small mural nodule. **Methods** We retrospectively reviewed the medical record of patients with surgically treated ovarian tumor having small mural nodule (<2 cm) detected by transvaginal ultrasonography between 2002 and 2016. Patients preoperatively diagnosed with mature teratoma and advanced ovarian cancer were excluded. **Results** Forty seven patients were eligible for evaluation. Final pathological diagnoses were as follows : 25 benign, 13 borderline, and 9 malignant. Of the benign cases, 8 (32%) were endometrial cyst. Of the borderline cases, 5 (38%) were seromucinous and 2 (22%) were mucinous. The histological types and corresponding stages of malignant cases were 4 clear cell carcinoma (all Stage I), 2 endometrioid carcinoma (both Stage I), 1 mucinous carcinoma (Stage I), 1 adenocarcinoma (Stage I), and 1 serous carcinoma (Stage II). Among the clinicopathological factors, "ovarian nodules larger than 10mm", "presence of the contrast enhancement of mural nodules on MRI" and "over the age of 50" categories were found to be statistically significant different factors between the benign and the non-benign (borderline and malignant) group (respectively $P<0.05$). **Conclusion** Our study suggests that ovarian small mural nodules which have following factors "ovarian nodules larger than 10mm", "presence of the contrast enhancement of mural nodules on MRI" and "over the age of 50" are likely to be non-benign lesion.

ISP-38-12

Clinical safety and effectiveness of intensity-modulated radiation therapy for recurrent gynecological cancers Eiji Hirata, Suguru Nosaka, Naoko Terawaki, Iemasa Koh, Yasuko Yamamoto, Yoshiki Kudo *Hiroshima University*

Objective Intensity-modulated radiation therapy (IMRT) has been widely used to treat various malignant tumors. However, few reports have described the use of IMRT for recurrent gynecological cancers. We performed a clinical analysis of IMRT for recurrent gynecological cancers and evaluated the safety and effectiveness of the therapy. **Methods** We retrospectively analyzed 39 cases of gynecological cancer (77 treatments) in which we used IMRT on recurrent lesions from July 2010 to December 2015. The therapeutic effects and adverse events of IMRT were reviewed. Evaluations were carried out using SUVmax on FDG-PET/CT. A decrease of 30% or more was considered a significant decrease, and an increase of 30% or more was considered a significant increase. **Results** We reviewed 21 cases with cervix cancer, 8 with endometrial cancer, 8 with ovarian cancer, and 2 with uterine sarcomas. These cases, categorized by histological types, were squamous cell carcinoma (12 cases), endometrioid carcinoma (9), serous adenocarcinoma (8), mucinous adenocarcinoma (5), leiomyosarcoma (2), clear cell carcinoma (2), and the other (3). Of these 77 IMRT treatments, 64 were evaluable, and SUVmax disappeared and decreased in 76% (49/64) of the treatments, showed no changes in 8% (5/64) of the treatments, and increased in 14% (9/64) of the treatments. Adverse events of grade 2 and above, such as melena, hematuria, neutropenia, thrombocytopenia, and anemia, were found in 26% (9/64) of the cases, and we discontinued IMRT in only one case. **Conclusion** IMRT was effective for recurrent gynecological cancers. Although adverse events were observed, they were mostly within the acceptable range.

ISP-39-1

Functional analysis of Nrf2 in the ovary and the relation of Nrf2 with oxidative stress Nana Akino[1], Osamu Hiraike[1], Hiromi Matsuura[1], Harunori Honjo[1], Michihiro Tanikawa[2], Miyuki Harada[2], Kaori Koga[1], Katsutoshi Oda[1], Tomoyuki Fujii[1], Yutaka Osuga[1] *Graduate School of Medicine, The University of Tokyo[1], Faculty of Medicine, The University of Tokyo[2]*

Objective NF-E2-related factor 2 (Nrf2) is a transcription factor regulating a cellular response that defends cells from oxidative stress and inflammation. Activation of Nrf2 is known to ameliorate the course of relapsing-remitting multiple sclerosis via the downregulation of oxidative stress and inflammation. Considering the fundamental role of oxidative stress in reproductive biology, we conducted a functional analysis of Nrf2 using ovarian tissue and granulosa cells. **Methods** This study is approved by IRB and we performed immunohistochemistry (IHC) of ovaries. Granulosa cells were obtained from ovarian fluids from patients undergoing IVF, and levels of mRNA were quantified by RT-PCR. Western blotting was also conducted to analyze the relationship between oxidative stress and Nrf2. **Results** The presence of Nrf2 was identified by IHC. Oxidative stress was provoked by the addition of H2O2, and it elevated mRNA expression levels of Nrf2, as well as SOD1 and catalase, and these results were confirmed by Western blot. Depletion of endogenous Nrf2 by siRNA resulted in decreased mRNA expression of SOD 1 and catalase. An activator for Nrf2, dimethyl fumarate (DMF) was used and addition of DMF resulted in an elevation of Nrf2 in both mRNA and protein levels. **Conclusion** We have shown that oxidative stress leads to the elevation of Nrf2, and activation of Nrf2 using DMF could lead to protecting the ovary from oxidative stress.

ISP-39-2

Endoplasmic reticulum (ER) stress inhibits progesterone production in human granulosa cells Nozomi Takahashi[1], Miyuki Harada[1], Yasushi Hirota[1], Osamu Yoshino[2], Gentaro Izumi[1], Tetsuya Hirata[1], Kaori Koga[1], Osamu Hiraike[1], Tomoyuki Fujii[1], Yutaka Osuga[1] *Graduate School of Medicine, The University of Tokyo[1], Toyama University[2]*

Objective Obesity in reproductive-aged women is associated with lower progesterone levels. Lipid accumulation in follicles of obese women has been reported to compromise endoplasmic reticulum (ER) function, activating ER stress in granulosa cells. We hypothesized that ER stress activated in granulosa-lutein cells (GLCs) modulates progesterone production and contributes to obesity-associated progesterone deficiency. **Methods** Cultured human GLCs were treated with ER stress inducer tunicamycin (Tm), prior to hCG or cAMP. mRNA expression of steroidogenic enzymes, StAR, 3β-HSD, P450scc, and aromatase were examined by quantitative RT-PCR. 3β-HSD enzyme activity and progesterone production in the supernatant were measured by EIA. StAR protein expression and phosphorylation of PKA and ERK1/2 were examined by Western blotting. To examine the in vivo effects of ER stress activation, pregnant mare serum gonadotropin (PMSG)-hCG-treated immature mice were injected with Tm. Progesterone and estradiol concentration in the serum were measured and ovarian mRNA expression of steroidogenic enzymes was examined. **Results** In human GLCs, pretreatment with Tm decreased hCG-stimulated progesterone secretion and inhibited mRNA expression of StAR and 3β-HSD without affecting the expression of P450scc and aromatase. Tm affected the cAMP-stimulated mRNA expression of steroidogenic enzymes similar to the stimulation by hCG. Tm attenuated hCG-induced StAR protein expression, 3β-HSD activity, and phosphorylation of PKA and ERK1/2. In rodents, Tm inhibited hCG-stimulated progesterone production without affecting estradiol level. Tm inhibited the ovarian expression of steroidogenic enzymes in the same manner as seen in human GLCs. **Conclusion** ER stress in follicles contributes to progesterone deficiency by inhibiting hCG-induced progesterone production in GLCs.

ISP-39-3

Oxidative stress and antioxidant capacity in the primary ovarian insufficiency Toshiyuki Kakinuma[1], Miki Tagawa[1], Kaoru Kakinuma[1], Ken Imai[1], Hiroaki Nonaka[1], Michitaka Oowada[1], Hirotsune Kaijima[2] *International University of Health and Welfare Hospital[1], Minatomirai Yume Clinic[2]*

Objective Premature ovarian insufficiency (POI) is defined as the cessation of the ovarian function before the age of 40 years. POI etiology may be related to iatrogenic or endogenous factors and in many cases remains unclear. POI increases health risks for approximately 1% of women, including infertility and psychosocial issues, in addition to the longterm effects of cardiovascular disease and osteoporosis. Recently, oxidative stress and its defense system have been reported to play important roles in the regulation of reproductive function. The objective of this study was to assess the potential predictive factors of oxidative stress levels (derivatives of reactive oxygen metabolites, d-ROMs) and antioxidant potential (biological antioxidant potential, BAP) for etiology with POI. **Methods** 10 women diagnosed with POI, and 10 women recruited as controls were included in this study. The blood samples were assayed for reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP) by F.R.E.E. (Free Radical Elective Evaluator) ; the oxidative stress index (OSI) was then calculated (OSI=d-ROMs/BAP × 100). **Results** There was no difference between two groups in terms of age, body mass index and smoking status. d-ROMs of

the POI patients were significantly higher than that of controls (475.7 ± 50.5 U.CARR versus 347.8 ± 28.7 U.CARR, P<0.001). As compared to the control group, OSI was higher in POI group (23.4 ± 2.7 versus 16.8 ± 2.0, P<0.001). However, BAPs were not significantly different between the POI group and control group (2040 ± 144.7μmol/l versus 2082 ± 165.3μmol/l, p=0.64). **Conclusion** Our results suggest that d-ROM and OSI may be a useful risk marker for POI.

ISP-39-4

Epigenetic changes of the VEGF promoter region in rat granulosa cells undergoing luteinization after the LH surge
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Objective Vascular endothelial growth factor (VEGF) in granulosa cells (GCs) plays an important role in rapid vascularization after the LH surge, which contributes to corpus luteum formation. VEGF expression is rapidly induced in GCs undergoing luteinization after the LH surge. We investigated whether epigenetic changes including histone modifications and DNA methylation in the promoter region are associated with the rapid increase in VEGF gene expression after the LH surge. **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 were measured by RT-PCR. 2) Histone modifications (transcription active marker : H3K4me3, repressive markers : H3K9me3, H3K27me3), 3) The chromatin condensation 4) DNA methylation status was analyzed in the VEGF promoter region by Chromatin Immunoprecipitation (ChIP) assay, Formaldehyde-Assisted Isolation of Regulatory Elements (FAIRE)-qPCR and sodium bisulfite sequencing, respectively. **Results** 1) VEGF mRNA levels increased after hCG injection and reached the peak at 12h. 2) The levels of H3K9me 3 and H3K27me3 were decreased after hCG injection and significantly lower at 12h than 0h. 3) The chromatin structure became loose after hCG injection compared with 0h. 4) DNA methylation status was hypomethylated, and did not change after hCG injection. **Conclusion** Changes of the histone modification status and chromatin structure in the VEGF promoter region are closely associated with the rapid increase in VEGF mRNA expression in GCs undergoing luteinization after the LH surge.

ISP-39-5

Investigation of the effect of mouse ovary storage duration on fertility. —Basic experiment for clinical application of ovarian transport—
Keiko Kamoshita[1], Takayuki Haino[1], Kouhei Sugimoto[1], Yodo Sugishita[2], Aikou Okamoto[1], Nao Suzuki[2] *The Jikei University School of Medicine[1], St. Marianna University School of Medicine[2]*
Objective This study aimed to clarify the effect of mouse ovary storage duration on fertility. **Methods** Experiments were conducted using C57BL/6J mice. Ovaries of 4-week-old mice were stored at 4℃ for 4, 8 or 24 hours respectively and were subjected to histological examination by HE staining, the TUNEL assay, Ki-67 staining, and counted the number of follicles by electron microscopy. Then orthotopic transplantation of ovaries were performed in 6-week-old C57BL/6J mice, and fertility was assessed by in vitro fertilization and embryo transfer. Fertility was assessed from the number of eggs, fertilization rate, embryo development rate, implantation rate and rate of live pups. Freshly harvested ovaries were used as controls. Experiments were repeated at least 3 times. **Results** There were no significant changes in the number of MII oocytes, fertilization rate, or blastocyst development rate of storage within 24 hours. There were no difference of the implantation rate and the rate of live pups of 4 hours (82.2 (±7.7))%, 23.9 (±6.6)%) compared to the control group (82.7 (±17.3)%, 24.8 (±13.2)%). The implantation rate of 8 and 24 hours were 14.6 (±14.6) % and 4.4 (±4.4) % respectively, which were significantly lower than the control group (groupp<0.05). The rate of live pups of 8 and 24 hours were 4.2 (±4.2)%, and 4.4 (±4.4)% respectively, whitch were significantly lower than in the control (groupp<0.05). **Conclusion** The present results suggest that prolonging the ovarian storage time reduces fertility in mice. Thus, ovaries should be frozen immediately after harvesting or transported as rapidly as possible to minimize damage.

ISP-39-6

Global identification of pregnancy stage-specific progesterone responsive genes in primary human endometrial stromal and decidual cells
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Objective Since progesterone (P4) governs uterine events throughout pregnancy, it may affect uteri in pregnancy-stage dependent manners. However, the pregnancy-stage specific roles of P4 remain elusive. We here identified P4 responsive genes expressed specifically at the different pregnancy stages in primary human endometrial stromal and decidual cells. **Methods** Primary human endometrial stromal and decidual cells were isolated from non-pregnant endometria (cases of hysterectomy due to uterine fibroid), and deciduae in early pregnancy (cases of induced abortion at 6-10 wks), term pregnancy (cases of elective c-section at 37-39 wks) and postpartum period (cases of normal vaginal delivery at 37-41 wks) (n=4 in each group), The cells were pretreated with 17 β-estradiol (E2) for 4 days, and incubated in the culture media with or without P4 for 24 hrs. Total RNA extracted from these cells was analyzed by RNA-seq, and differentially expressed genes with and without P4 treatment were identified. The institutional ethics committee approved all the experimental procedures. **Results** We identified 934, 389, 217 and 143 genes which P4 up/down-regulated specifically in non-pregnant endometrial stromal cells, and decidual cells in early pregnancy, term pregnancy and postpartum period, respectively. Especially, we found 389 genes and 23 pathways (e.g. Prostaglandin Synthesis, Cell surface interaction) were up/down-regulated in decidual cells in early pregnancy. **Conclusion** The current study revealed the presence of pregnancy-stage specific P4 responsiveness in primary human endometrial stromal and decidual cells. These findings suggest that P4 changes endometrial and decidual transcriptional targets according to the pregnancy stages to support full pregnancy.

ISP-39-7

DNA damage induces p21 expression during mouse preimplantation embryo and prevents development of embryo in uterus
Masami Hayashi[1], Kohei Kitada[1], Natsuko Yokoi[1], Hiroko Katayama[1], Akihiro Hamuro[1], Takuya Misugi[1], Akemi Nakano[1], Akane Kizu[2], Daisuke Tachibana[1], Masayasu Koyama[1], Kayo Yoshida[2], Takashi Morita[2] *Osaka City University, Graduate School of Medicine[1], Osaka City University, Graduate School of Medicine, Department of Molecular Genetics[2]*
Objective The preimplantation embryos are more sensitive to ionizing radiation than somatic cells, and they are prone to accumulate DNA damages. The experiment carried out before used relatively high dose such as 3 Gy of irradiation to mouse em-

bryos. Here we now examined the influence of low dose irradiation lower than 1 Gy to mouse embryos and response to irradiation on DNA damages. **Methods** BDF1 mice were crossed, and the 2-cell stage embryos were collected and cultured in vitro for 2 days. The 8-cell stage embryos were irradiated by X-ray (0-1Gy). The rate of normal development of embryos was examined. The RNA was extracted from normally developed embryos and gene expressions of p21, p53, Brca-1 and Caspase-3 were measured by RT-PCR. The normal appearing blastocysts were implanted into pseudopregnant uterus and their development was analyzed. **Results** Most (90%) of X-irradiated preimplantation embryos at doses lower than 1 Gy developed to blastocysts. But after implantation of such normally appearing blastocysts into pseudopregnant mouse uterus they produced almost no fetus. The expression level of p21 gene was increased depending on the dose of irradiation. **Conclusion** With less than 1 Gy of X-irradiation, most of embryos developed into blastocysts, but don't develop in the uterus after implantation. Observed increase of the expression of p21 may result in defects of further development of blastocysts.

ISP-39-8

Effects of versican V1 on human embryo attachment in an in vitro implantation model Yumiko Miyazaki[1], Akihito Horie[1], Yukiyasu Sato[2], Hirohiko Tani[1], Masashi Ueda[1], Asuka Okunomiya[1], Noriomi Matsumura[1], Tamayuki Shinomura[3] *Kyoto University[1], Japanese Red Cross Society Otsu Medical Center[2], Tissue Regeneration, Department of Hard Tissue Engineering, Tokyo Medical and Dental University[3]*

Objective Versican is a major component of extracellular matrix, which regulates cell adhesion by interacting with various molecules such as integrinβ and CD44. Previously, we showed that versican expression in endometrial epithelial cells (EECs) was most prominent in the mid-secretory phase and that versican expression in EECs was up-regulated by ovarian steroid hormones. The aim of the present study was to investigate possible role of versican in human embryo implantation. **Methods** Human endometrial adenocarcinoma cell line (Ishikawa) and spheroid of human choriocarcinoma cell line (BeWo) were used in the in vitro implantation model. Versican V1-overexpressing Ishikawa cells (ISKW-V1) and versican V 3-overexpressing Ishikawa cells (ISKW-V3) were established. First, the numbers of BeWo spheroids attached to the monolayer of ISKW-V1, ISKW-V3, or ISKW-GFP were analyzed. Next, to examine possible importance of chondroitin sulfate (CS) side chains covalently bound to versican V1, conditioned medium derived from ISKW-V1 (V1-CM) was pretreated with chondroitinase ABC (ChABC) and the effect on the attachment of BeWo spheroids to vector-transfected Ishikawa monolayer was evaluated. **Results** The numbers of BeWo spheroids attached to ISKW-V1, but not ISKW-V3, monolayer were significantly higher than those attached to ISKW-GFP monolayer. Addition of V1-CM significantly increased the numbers of BeWo spheroids attached to vector-transfected Ishikawa monolayer. This attachment-promoting effect of V1-CM was abolished when V1-CM was pretreated with ChABC. **Conclusion** Versican may facilitate embryo implantation process by enhancing the attachment of embryo to the endometrium.

ISP-40-1

Eight-shaped hatching occurred near ICM induces spreading of the ICM Yohei Onodera, Natsuki Ono, Hiromitsu Shirasawa, Wataru Sato, Yukiyo Kumazawa, Yukihiro Terada *Akita University*

Objective A hatching blastocyst with a figure-of-eight shape on the inside and the outside of the zona pellucida, 8-shaped hatching, was reported to affect the placement of the inner cell mass (ICM) in human. The purpose of this study was to investigate the factors that affected the ICM placement during 8-shaped hatching. **Methods** We obtained embryos via IVF of B6D2F1 female mice and ICR male mice. We used fluorescence immunostaining to observe an embryo, from insemination to 120 hours post-insemination, under a confocal microscope. We classified the embryos by their hatching behavior into U-shaped hatching, 8-shaped hatching, etc. Furthermore, we classified 8-shaped hatching embryos into two groups, the proximal ICM and distal ICM groups, depending upon the origin of hatching. We measured the ICM size and counted the Oct4-positive cells for each group using ZEN (Carl Zeiss). **Results** Among the 104 blastocysts observed, 12 showed U-shaped hatching and 73 showed 8-shaped hatching behavior. By comparing the origin of hatching, the ICM size was significantly extended in a proximal group (85.4 ± 21.3 μm versus 65.6 ± 15.0 μm, $P=0.0062$). We did not observe significant differences in the Oct4-positive cell count of both groups (21 ± 7 versus 18 ± 6, $P=0.2423$). **Conclusion** When the hatching began near the ICM in an 8-shaped hatching embryo, an extended effect of the ICM diameter was observed. The association between the extended ICM size and rise in fetal death rate was demonstrated via an experiment in mice. The 8-shaped hatching behavior may become the index for choosing embryos for ART.

ISP-40-2

Phenotypic changes of macrophages in the decidua from miscarriage Yasuhiko Ebina[1], Shigeki Shimada[2], Masashi Deguchi[1], Yoko Maesawa[1], Hideto Yamada[1] *Kobe University[1], Mommy's Clinic Chitose[2]*

Objective The aim of this study was to evaluate whether phenotypic changes in decidual macrophages are associated with miscarriages early in pregnancy. **Methods** The decidua was obtained from 21 women whose pregnancies ended in missed miscarriages (MS), and 13 women with induced abortions (IA). Additionally, the endometrium was obtained from 19 non-pregnant women who had a history of recurrent miscarriage (EM). The expressions of HLA-DR and CD206 in $CD68^+CD163^+$ cells (macrophages) and $CD68^+CD163^-$ cells (cells including dendritic cells) were assessed by a flow cytometry, and compared among three groups. The institutional review board approved this study, and all women gave informed consent. **Results** The percentage of $HLA\text{-}DR^+$ cells in $CD68^+CD163^+$ cells in MS (median 96.7%; range 88.5-99.5%) was higher than those in IA (89.0%; 63.6-97.8%, $p<0.01$). The percentage of $CD206^+$ cells in $CD68^+CD163^+$ cells in MS (79.6%; 28.6-94.4%) was higher than that in IA (51.3%; 24.4-93.2%, $p<0.01$). The percentages of $HLA\text{-}DR^+$ cells in $CD68^+CD163^-$ cells in EM (median 89.5%; range 28.7-98.7%) were higher than those in IA (56.5%; 41.5-88.7, $p<0.01$) or those in MS (68.5%; 43.9-83.2%, $p<0.01$). **Conclusion** The activated macrophages that expressed HLA-DR and the matured macrophages that expressed CD206 were increased in the decidua from miscarriage.

ISP-40-3

The Effect of Oil and Water-Soluble Contrast Medium in Hysterosalpingography on Thyroid Function and Pregnancy Shuhei So[1], Wakasa Yamaguchi[1], Takeshi Nakayama[2], Naoaki Tamura[3], Naohiro Kanayama[3], Fumiko Tawara[1] *Tawara IVF clinic[1], Shizuoka Kosei Hospital[2], Hamamatsu University School of Medicine[3]*

Objective To assess thyroid function (thyroid stimulating hormone: TSH and free-T4: FT4 levels) and cumulative pregnancy rate after hysterosalpingography (HSG) with an oil-soluble contrast medium (OSCM) and a water-soluble contrast me-

dium (WSCM). **Methods** Retrospective cohort study. One hundred sixty-four (34.3±4.3 years) and 94 (35.0±4.7 years) infertile women underwent HSG with OSCM or WSCM, respectively, between March 2013 and August 2014 at our clinic. The patients had undergone a thyroid function test at our clinic less than three months before HSG and all showed normal thyroid function. The subjects' thyroid function also was checked at least once following HSG. Pregnancy outcomes were classified as follows: (a) conception by timing and/or the AIH method (artificial insemination with husband's sperm) after HSG; (b) no conception after HSG; (c) decided to stop fertility treatment/move on to ART (assisted reproductive technology) within six months of HSG. The cumulative pregnancy rate after timing and the AIH method were calculated using the formula a/(a+(b-c)). **Results** Women in the OSCM group showed significantly increased TSH after HSG compared to those in the WSCM group; approximately 25% of the women developed subclinical hypothyroidism (SCH). Conversely, patients in the WSCM group did not show a change in thyroid function after HSG. The cumulative pregnancy rate was significantly high in the OSCM group (72.4%) compared to that of the WSCM group (53.7%). **Conclusion** We found that OSCM could increase fertility compared to WSCM; however, OSCM depressed thyroid function.

ISP-40-4

Accuracy and safety verification of ovarian reserve assessment technique using optical coherence tomography for ovarian tissue transplantation Seido Takae[1], Kosuke Tsukada[2], Yorino Sato[1], Naoki Okamoto[1], Tai Kawahara[1], Nao Suzuki[1] *St. Marianna University School of Medicine[1], Keio University[2]*

Objective Except for histological study, there are no suitable techniques for detection of primordial follicles in ovary. Although optical coherence tomography (OCT) is well-established imaging technique without fixation, few reports are available on follicle imaging. In present study, we investigated accuracy and safety of OCT examination toward for effective ovarian tissue transplantation. **Methods** Ovaries were obtained from day 3, 10, 21 and 50 weeks old (aged) mice. And human ovary tissues were obtained from a 15 years old patient with aplastic anemia who received ovarian tissue cryopreservation as fertility preservation. After OCT examination, these were compared with histological images. This study was approved by the IRB, and we received written informed consents from participant. Mice ovaries (day 3 with or without OCT and aged with OCT) were transplanted under kidney capsule of host mice. Two weeks later, they received oocyte pick up to compare the numbers of retrieved oocyte. After the in vitro fertilization (IVF) using these oocytes, the newborns were bred to assess reproductive normality. **Results** The standard OCT images of follicles were established including primordial follicle. No follicles were detected on aged ovary. Additionally, they were matched with histological images. And we obtained 10±1.2 oocytes from transplanted day 3 ovaries with OCT. All of newborns shown normal appearances including reproductive ability. And also, OCT examination did not affect for IVF outcome. **Conclusion** In present study, we demonstrated the accuracy and safety of OCT examination, and bring OCT examination a step closer to clinical application for measuring true ovarian reserve and localizing follicles.

ISP-40-5

The pineal hormone melatonin prevents ovarian aging by reducing declines in quantity and quality of oocytes Hiroshi Tamura, Mai Kawamoto, Yuichiro Shirafuta, Yumiko Mihara, Masahiro Shinagawa, Maki Okada, Fumie Shibuya, Toshiaki Taketani, Hiromi Asada, Norihiro Sugino *Yamaguchi University Graduate School of Medicine*

Objective The present study was undertaken to examine whether long-term melatonin treatment prevents ovarian aging in mice. **Methods** Female ICR mice (10 weeks old) were divided into two groups: half were fed with water as a control (C) and the other half were supplemented with 100μg/ml melatonin water (M) until 43 weeks. Mice were superovulated by PMSG and hCG injection. 1) Oocytes were recovered from the oviduct. 2) In vitro fertilization was performed using spermatozoa from male mice. 3) The number of follicles at different developmental stages was analyzed by histological analysis. 4) Transcriptome changes in the ovaries were analyzed by microarray. 5) The mRNA expression of the aging-related gene sirtuin (SIRT1, 3) and autophagy-related gene (LC3), and the telomere length in the ovaries were analyzed. This study was approved by the ethics committee. **Results** 1) The number of ovulated oocytes was decreased during aging process in C. However, the number of ovulated oocytes was greater in M compared with C. 2) The fertilization rate was higher in M compared with C. 3) The number of primordial follicle was higher in M compared with C. 4) Ribosome-related genes and free radical scavenging network were identified. Pathway analysis identified the pathways related to cellular stress response and DNA repair. 5) The mRNA expressions of SIRT1, 3 and LC3, and telomere length were all higher in M than in C. **Conclusion** Long-term melatonin treatment prevents declines in quantity and quality of oocytes. The present results suggest that melatonin prevents ovarian aging by multiple mechanisms.

ISP-40-6

Case Report; Sarcoidosis of the fallopian tube Takashi Kuno, Zen Watanabe, Keiko Tanaka, Ayako Fujimine, Masumi Ishibashi, Naomi Shiga, Motomasa Ihara, Junichi Sugawara, Masahito Tachibana, Nobuo Yaegashi *Tohoku University Hospital*

Introduction Sarcoidosis is a systemic inflammatory disease which is most commonly manifested in the pulmonary system. However, in rare occasion, extrapulmonary manifestations have also been reported. Here, we report a case of sarcoidosis of the fallopian tube. **Case** A 37-year-old, gravida 2 para 0, Japanese woman who has been diagnosed sarcoidosis in our hospital department of respiratory medicine at 36 years old. She first visited our department due to acute lower abdominal pain. The infection of the right fallopian tube was suspected, and she was given the antibiotic agent. Her symptom was relieved and she discharged hospital for 3 days. However, she experienced the recurrence of right salpingitis shortly, and the pelvic examination revealed that the lasting of abnormal fluid collection in her right tube. Therefore, we took a decision of laparoscopic surgical treatment. The pelvic observation revealed that peri-tubal adhesion with obvious hydrosalpinx. The salpingectomy of the right fallopian tube was performed. The post operative course was uneventful. The pathological diagnosis were granulomatous salpingitis, right fallopian tube. In present case, sarcoidosis of the fallopian tube was highly suspected due to discriminative pathologic feature of an underlying condition. **Conclusion** We reported, here, a rare case of sarcoidosis of the fallopian tube. We also summarized its clinical and histopathological features of rare case of sarcoidosis located in the genital site.

ISP-40-7

POR mutations underlie non-syndromic amenorrhea and infertility Kazuki Saitou[1], Kiyotaka Kawai[3], Kenichi Tatsumi[4], Kumi Oouchi[3], Nobuyuki Kidera[3], Tomonori Ishikawa[1], Naoyuki Miyasaka[1], Maki Fukami[2] *Tokyo Medical Dental University[1], National Research Institute for Child Health and Development[2], Ka-*

meda Medical Center[3], Umegaoka Women's Clinic[4]
Context Cytochrome P450 oxidoreductase (POR) is a cofactor of all microsomal P450 enzymes including CYP17A1. Patients with POR deficiency (PORD) typically manifest skeletal dysplasia, adrenal dysfunction, disorders of sex development, and defective pubertal development. Although POR mutations have been identified in a woman with non-syndromic primary amenorrhea due to partial 17α-hydroxylase deficiency, the association between PORD and this phenotype remains rather speculative. **Cases** Two unrelated infertile women with amenorrhea visited our hospitals. Both patients showed borderline hypertension, but no skeletal features. They manifested normal sexual maturation without genital abnormalities. They underwent ovarian stimulation for the oocyte retrieval. While several follicles were developed, the endometrium remained thin. Blood tests showed relatively low estrogen and slightly elevated progesterone levels. Serum and urinary steroid measurements suggested decreased 17α-hydroxylase activity and normal 21-hydroxylase activity. Thus, these patients were clinically diagnosed with isolated partial 17α-hydroxylase deficiency. **Molecular analysis** Genetic analysis detected no non-synonymous mutations in CYP17A1. However, both patients harbored non-synonymous substitutions in POR (patient 1, p.R457H and p.R550W ; patient 2, p.Q201X and p.Y607C), all of which were estimated to be pathogenic by in silico analyses. **Discussion** This study provides evidence that PORD accounts for small percentage of cases with non-syndromic amenorrhea and infertility. POR mutation analysis should be considered for patients clinically diagnosed with partial 17α-hydroxylase deficiency. Paradoxically thin endometrium in the presence of developed follicles may be characteristic features of women with PORD.

ISP-41-1

Studies concerning the efficacy of immunotherapy with husbands lymphocytes for patients with unexplained recurrent abortion (URA). Analyses in the effectiveness considering the fluctuation of patient age Taro Nonaka, Makiko Takahashi, Kunihiko Yoshida, Koichi Takakuwa, Takayuki Enomoto *Niigata University Medical and Dental Hospital*
Objective Although it has been reported that the prognosis could be improved by the immunotherapy with husbands lymphocytes for URA patients (pts) negative for MLR-BAbs, it is controversial. In this study, the efficacy of the therapy was evaluated in connection with the alteration of patients age for these three decades. **Methods** The immunotherapy with husbands lymphocytes had undergone for patients with primary URA who were negative for MLR-BAbs under informed consent (treated group). The immunotherapy was not performed in patients due to their own volition (control group) and MLR-BE-positive patients (non-adaptive group). Furthermore, the average age and success rate of treated patients in each era (i.e. 1983- 1990 : group A, 1991- 2000 : group B, 2001- 2010 : Group C, 2011- 2015 : group D) compared. **Results** The success rates were 79.2% (137 of 173) and 62.7% (32 of 38) in the treated and non eligible groups, respectively. Those were 30.4% in the control groups, respectively. The success rates in both treated and non-adaptive groups were significantly higher than those in control group ($p<0.00001$ by Chi-square test). On the other hand, the average age in the treated patients is as follows ; group A : 29.0 ± 3.8, group B : 30.7 ± 4.9, group C : 32.1 ± 5.0, and group D : 33.0 ± 3.2. The average age in group C and D were significantly higher than compared to group A ($P<0.0001$), while success rate was not significantly different in each era group. **Conclusion** It is suggested that the immunotherapy is effective for URA pts negative for MLR-BAbs, and the average age of patients who undergo the therapy is increasing gradually.

ISP-41-2

Correlation of K6 psychological stress score to subsequent pregnancy outcome in women with recurrent pregnancy loss Shoko Ikeda[1], Ayumi Kanatani[1], Rieko Shitara[1], Takeshi Nagamatsu[1], Takaaki Nagasaka[1], Seisuke Sayama[1], Toshio Nakayama[1], Takayuki Iriyama[1], Atsushi Komatsu[1], Shuji Hirata[2], Yutaka Osuga[1], Tomoyuki Fujii[1] *Faculty of Medicine, The University of Tokyo[1], University of Yamanashi Hospital[2]*
Objective This study aimed to evaluate the effect of supportive care on anxiety level in women with recurrent pregnancy loss (RPL) and to clarify the relevance of their prepregnancy anxiety to the outcome in the subsequent pregnancy. **Methods** This study was conducted under the approval of the ethics committee in our facility. Anxiety level were assessed by K6 scale in 527 women with RPL (2.5 ± 0.8 miscarriages, mean ± SD) in their first visit to our special clinic from 2010 to 2015. The women were divided into two groups based on the results of the screening tests to detect causative factors ; a group with causative factor identified (group A) and an unexplained group (group B). Supportive counseling for the future pregnancy were given to both groups. Alteration of K6 scoring after the counseling and the relevance of K6 score to the subsequent pregnancy outcome were analyzed. **Results** Improvement of the K6 score following the counseling was confirmed in 72.9% of the women in group A and 75.2% in group B. In group B, miscarriage in the subsequent pregnancy was less (18%) in women showing improved K6 score than that (27%) in women without improvement, although this difference was not statistically significant. This difference was not observed in group A. **Conclusion** Supportive counseling can reduce anxiety level in RPL women. We would like to speculate that the risk of recurrent miscarriage could be increased in unexplained RPL women without improvement of K6 score.

ISP-41-3

Comparison of the validity of next generation sequencing and array comparative genomic hybridization in a chromosome translocation patient Yoshiharu Nakaoka[1], Daiyu Kadokami[1], Kyouko Abe[1], Chinatsu Takaya[1], Yuko Kitano[1], Hiroko Yamauchi[1], Keijiro Ito[1], Yoshiharu Morimoto[2] *IVF Namba Clinic[1], HORAC Grand Front Osaka Clinic[2]*
Objective The use of next generation sequencing (NGS) has been rapidly increasing in preimplantation genetic diagnosis (PGD) including preimplantation genetic screening due to its accuracy. Here we compared NGS with array comparative genomic hybridization (CGH) in a reciprocal translocation woman using identical whole genome amplification (WGA) products. **Methods** The patient with the 46,XX,t (2 ; 4) (q22 ; q23) karyotype had two miscarriages. After obtaining approval from the Japan Society of Obstetrics and Gynecology, we performed PGD using CGH in the trophectoderm biopsy samples of 10 blastocysts. After all the embryos were diagnosed as abnormal, the reserved identical WGA products were re-analyzed using NGS. **Results** The outcome of the chromosome analysis in all the embryos by both methods was abnormal ; the concordance rate was 100%. In the 240 chromosomes from the 10 embryos, 16 (6.7%) were discordant in the two methods. In one of the 10 embryos, re-analysis by CGH after re-biopsy also produced uncertain results. However, NGS provided us a decisive analysis of the embryos. Furthermore, 4 of the 240 chromosomes that had different breakpoints from the patient's karyotype of G-banding in CGH showed the same breakpoint in NGS. **Conclusion** NGS showed more accuracy in analyzing the chromosomes of embryos than CGH when the same WGA products were used. These results suggest that NGS is suitable for PGD in chromosome translocation cases.

ISP-41-4

A proteomic approach to identify pathology-related molecules in patients with seronegative obstetric antiphospholipid syndrome Yoshimitsu Kuwabara, Marie Ito, Mirei Yonezawa, Nozomi Ouchi, Ryuhei Kurashina, Tomoko Ichikawa, Misao Satomi, Rintaro Sawa, Toshiyuki Takeshita *Nippon Medical School*

Objective We performed two-dimensional electrophoresis followed by immunoblotting to identify unknown, pathology-related molecules in patients with seronegative obstetric antiphospholipid syndrome (SN-APS) who clinically satisfy the diagnostic criteria of APS, but not the serological criteria. **Methods** We collected peripheral blood from 12 SN-APS outpatients with known thrombotic predisposition (protein S deficiency, protein C deficiency, factor XII deficiency, or presence of anti-phosphatidylethanolamine antibodies) and from 14 with no known thrombotic predisposition. Four multiparous women without history of miscarriage served as controls. Plasma proteins collected from 6 volunteers were separated and purified to be used as plasma protein antigens. Two-dimensional immunoblotting was performed with pooled control and SN-APS sera as the primary antibody, and reactive spots specific to the latter were identified with a mass spectrograph. A detection system using Western blotting was established, and the presence of autoantibodies in the specimen was examined. **Results** Several molecules including Complement molecule C9 were identified as reactive spots specific to SN-APS serum. We could confirmed a band reactive to C9 by Western blotting only in the condition using protein antigens processed by solubilization with urea and alkylation with iodoacetamide. Western blotting using individual patient sera identified reactions in 2/14 SN-APS patients with no known thrombotic predisposition, and in 1/12 SN-APS patients with a known thrombotic predisposition other than APS. The reaction was not seen in control sera (0/4). **Conclusion** This study suggests that some SN-APS pathologies relate to autoantibodies that react to specific C9 epitopes expressed under fixed conditions.

ISP-41-5

New procedure using ulinastatin and laminaria tent for infertility due to cesarean scar of uterus Akiko Kuwahata *Ochi Yume Clinic Nagoya*

Objective We previously reported a therapeutic procedure for infertility to reduce retrograde exudation into the uterine cavity from a cesarean scar. However, using this procedure, in half of the patients, retrograde exudation could not be controlled, resulting in incomplete embryo transfer and implantation failure. In these unsuccessful cases, we tried a new therapeutic procedure. **Methods** Fifteen cycles in 13 patients were assessed from May 2015. All patients failed to conceive due to s till exudation production conventional procedure, incapable embryo transfer, or implantation failure. For these patients, ulinastatin, an agent for acute pancreatitis, was infused into the uterine cavity and then cervical packing was performed with a laminaria tent. The cesarean scar was also packed with surgecell (new procedure). This procedure was repeatedly performed after the end of menstruation. The volume of exudation and IL-6 levels were determined. Embryo transfer was performed under the controlled cycle with HR therapy after new procedure. **Results** In 11 of the 15 cycles, exudation pooling was not observed in the uterine cavity. In all cycles, IL-6 was decreased. Six (46.2%) of 13 patients achieved pregnancy, including 4 ongoing pregnancies and two miscarriages. **Conclusion** Possible mechanisms of secondary infertility due to a cesarean scar may include retrograde exudation into the uterine cavity from the cesarean scar, resulting in implantation failure, incapable embryo transfer, and chronic inflammation of the uterine cavity. This is supported by the findings of improvement in the pregnancy rate, as well as decreases in the exudation volume and IL-6 levels after the performance of this new procedure.

ISP-41-6

The large yolk sac in the case of missed miscarriage is associated with abnormal chromosomal composition Satoshi Yoneda, Noriko Yoneda, Mika Ito, Tomoko Shima, Akitoshi Nakashima, Osamu Yoshino, Arihiro Shiozaki, Shigeru Saito *Toyama University*

Objective We evaluated the abnormal finding obtained by ultrasonography in the case of missed miscarriage (<12 weeks of gestation) with abnormal fetal chromosomal composition. **Methods** One hundred four patients diagnosed missed miscarriage were enrolled from 2012 to 2015. They had the past history of recurrent miscarriage and the informed consent was obtained to examine the fetal chromosomal abnormality. The findings from study of ultrasonographic images at the point of diagnosis of missed miscarriage between abnormal fetal chromosomal composition and normal chromosomal composition were evaluated. **Results** 1) The rate of fetal abnormal chromosomal composition was 65.4% (68/104). 2) The significant differences (abnormal vs. normal) were fund in maternal age [38 (24-44), vs. 33 (22-44) ; P=0.0074], the rate of miscarriage after visible fetal heart beat [63.2% (43/68), vs. 41.7% (15/36) ; P=0.0350], the rate of small GS (<15mm) [11.8% (8/68), vs. 33.3% (12/36) ; P=0.0079], the diameter of YS [4.0mm (0-11.8), vs. 3.0mm (0-7.3) ; P=0.0001], and the rate of absence of embryo [30.9% (21/68), vs. 58.3% (21/36) ; P=0.0066]. 3) The diameter of YS (>3.2mm) (OR 4.4, 95%CI 1.6-13.1 ; P=0.0036) and maternal age (>35) (OR 5.7, 95%CI 1.8-15.3 ; P=0.0017) were the independent factors to estimate the fetal abnormal chromosome by logistic analysis. 4) The rate of fetal abnormal chromosome at each size of YS (mm) was 60.0% (4<YS<5), 81.8% (5<YS<6), 94.4% (6<YS). **Conclusion** In the case of missed miscarriage, the size of YS was important factor to predict fetal abnormal chromosome and especially it was higher in the case with large YS (>5mm).

ISP-41-7

Protein S deficiency complicated pregnancy in women with recurrent pregnancy loss Mihoko Uchiyama, Masashi Deguchi, Nanae Shinozaki, Yasuhiko Ebina, Kenji Tanimura, Mayumi Morizane, Hideto Yamada *Kobe University*

Objective The aim of this study was to evaluate pregnancy outcome and complications in women with recurrent pregnancy loss (RPL) and low levels of plasma protein S (PS), who received low dose aspirin (LDA) or LDA plus heparin (LDA/H) therapies. **Methods** Consecutive 64 women with PRL and plasma free PS antigen/activity of <60% were enrolled with informed consent in this prospective study. Clinical characteristics, pregnancy outcomes and complications of the 64 women were compared among 3 groups ; antiphospholipid antibody (aPL)-negative women who received LDA alone (group A, n=20), aPL-negative women who received LDA/H (group B, n=34), and aPL-positive women who received LDA/H (group C, n=10). The institutional review board approved the study. **Results** Gestational weeks (GW) at delivery in group C (median 34.5 GW, range 26-41) were earlier than 39 (34-41) GW in group A and 38 (30-41) GW in group B ($p<0.05$). The birth weight in group C (2084g, 750-3384) was less than 2868g (1906-3650) in group A, and 2855g (1716-3890) in group B ($p<0.05$). The incidences of fetal growth restriction (40%) and preterm delivery (60%) in group C were higher than 8.8% and 17.6%, respectively, in group B ($p<0.05$). **Conclusion** Women with RPL, low PS as well as positive aPL had high risks for adverse pregnancy outcomes and complica-

tions, even when they received LDA/H therapy. Among women with RPL, low PS and negative aPL, there was no difference in these risks between LDA alone and LDA/H therapies.

ISP-42-1

Anti-Prothrombin/HLA-DR antibody is one of the autoantibodies in antiphospholipid patients Satoko Morikami[1], Kenji Tanimura[1], Hideto Yamada[1], Masashi Deguchi[1], Yasuhiko Ebina[1], Hisashi Arase[2] *Kobe University Graduate School of Medicine[1], Department of Immunochemistry, Research Institute for Microbial Diseases, Osaka University[2], Department of Immunochemistry, Research Institute for Microbial Diseases, Osaka University[3], Department of Dermatology, Graduate school of Medicine, Osaka University[4], Division of Rheumatology, Endocrinology and Nephrology, Graduate School of Medicine, Hokkaido University[5]*

Objective Antiphospholipid syndrome (APS) is a prothrombotic disorder associated with antiphospholipid antibodies. We have previously found that autoantibodies that cannot be detected by general laboratory test can be detected using β2GPI/HLA-DR complex. Here, we found that prothrombin complexed with HLA-DR is useful to detect autoantibody in APS. **Methods** Prothrombin and HLA-DR were transfected into 293T cells and autoantibody binding to prothrombin associated with HLA-DR was analyzed by flow cytometry. We compared autoantibodies against prothrombin/HLA-DR complex in 121 APS patients and 100 healthy donors. Effects of HLA-DR allele's differences of the autoantibody binding to prothrombin/HLA-DR complex were also evaluated. **Results** When prothrombin was expressed with HLA-DR in 293T cells, prothrombin formed a complex with HLA-DR. When autoantibodies against prothrombin/HLA-DR complex were analyzed, we found 24.8% of APS patients possessed autoantibodies against prothrombin/HLA-DR complex. Antiphospholipid antibodies well bound to prothrombin complexed with HLA-DR4 compared with HLA-DR12. **Conclusion** Prothrombin complexed with HLA-DR is useful to detect autoantibodies in APS. In addition, autoantibodies preferentially bound to prothrombin associated with specific HLA-DR alleles. These findings suggest that autoantibodies in APS bind to prothrombin associated with specific HLA-DR alleles might be involved in pathogenicity of APS.

ISP-42-2

Impact of subclinical hypothyroidism on subsequent pregnancy outcome in women with unexplained recurrent pregnancy loss Sayaka Uchida, Tetsuo Maruyama, Maki Kagami, Fumie Miki, Hanako Hihara, Shoko Tomisato, Satomi Katakura, Yushi Yoshimasa, Hirotaka Masuda, Hiroshi Uchida, Mamoru Tanaka, Daisuke Aoki *Keio University*

Objective Because subclinical hypothyroidism (TSH>4.5 IU/mL) is associated with adverse pregnancy outcomes, including early pregnancy loss, it is recommended that the TSH level should be titrated to 2.5 mIU/l or less in levothyroxine-treated women before pregnancy. The purpose of this study was to determine whether or not borderline-subclinical hypothyroidism (borderline-SCH ; 2.5< TSH<=4.5 IU/mL) impacts the outcomes of subsequent pregnancies in women with unexplained recurrent pregnancy loss (RPL). **Methods** A total of 317 women with a history of unexplained RPL were enrolled. The women were classified into two groups : borderline-SCH, and euthyroidism (0.3<=TSH<=2.5 IU/mL). All women had normal serum levels of free T4 and did not receive levothyroxine before or during the subsequent pregnancy. **Results** There were no significant difference in age, number of previous pregnancy losses, number of live births, and body mass index between the 56 women with borderline-SCH and 261 euthyroid women. The subsequent pregnancy rate did not differ between the two groups (55.4% [31/56 ; borderline-SCH] vs. 51.3% [134/261 ; euthyroid]). The pregnancy loss rate (<22 weeks of gestation) tended to be higher in patients with borderline-SCH than euthyroid patients (29.0% [9/31] vs. 17.2% [23/134]), though not significantly different (P=0.13). **Conclusion** There was no definitive proof that borderline-SCH, as defined by a slightly elevated TSH level alone, is associated with subsequent pregnancy loss in women with unexplained RPL.

ISP-42-3

Low levels of plasma protein S (PS) may be associated with adverse pregnancy outcome Masashi Deguchi, Nanae Shinozaki, Yasuhiko Ebina, Hideto Yamada *Kobe University*

Objective To evaluate an association between pregnancy complications and low levels of free PS activity/antigen or total PS activity/antigen, a prospective study was performed since 2014. **Methods** Peripheral blood samples were obtained with informed consent at 8-14 gestational weeks (GW) from consecutive pregnant women who visited our hospital. Free PS activity/antigen were measured at in-house laboratory using HemosIL reagents. Total PS activity/antigen were measured at Shino-Test Corporation. An association between low levels of PS and pregnancy complications was evaluated by Fisher's exact test. To assess changes of PS levels in normal pregnancy, samples from normal pregnant women were obtained at 18, 28, 34 GW, and the Mann-Whitney U test was used for statistical analysis. The institutional review board approved the study. **Results** A free PS ratio (activity/antigen) of <10%ile was associated with massive bleeding at delivery (OR 2.6), free PS activity of <1%ile was associated with neonatal distress (10.3), and total PS activity/antigen of <5%ile was associated with abnormal CTG pattern (4.5/4.6) ($p<0.05$). Free PS activity/antigen levels decreased to median 43% (5%ile ; 25%) /35% (21%) at 8 GW, then increased until 20 GW ($p<0.05$). Total PS activity/antigen showed no significant change during pregnancy. **Conclusion** Low levels of plasma PS might be associated with massive bleeding at delivery, neonatal distress, and NRFS. It is likely that free PS activity/antigen physiologically decreases to approximately 40% during the first trimester.

ISP-42-4

Autoantibodies against β_2-glycoprotein I/HLA class II complexes may have the potential for improving diagnosis of antiphospholipid syndrome Kenji Tanimura[1], Masashi Deguchi[1], Yasuhiko Ebina[1], Hisashi Arase[2], Hideto Yamada[1] *Kobe University[1], Research Institute for Microbial Disease, Osaka University[2]*

Objective A novel autoantibody against β2-glycoprotein I/HLA class II complexes (aβ2GPI/HLA-II) is involved in the pathogenesis of antiphospholipid syndrome (APS), and recognizes unique epitopes which are not on β2GPI/phospholipid complexes. The aim of this study was to evaluate concentration of aβ2GPI/HLA-II in women with symptoms of APS. **Methods** Women with APS symptoms were enrolled with informed consent in this prospective study. Blood levels of common antiphospholipid antibody (aPL ; aCL IgG/IgM, aCLβ2GPI IgG, and LA) as well as aβ2GPI/HLA-II IgG were measured. Clinical data were collected from medical records. **Results** Twenty of consecutive 95 women with symptoms of recurrent miscarriage (RM) (n=82), fetal deaths (FD) beyond 10 gestational weeks (GW) (n=22), preterm delivery (PD) before 34 GW due to placental insufficiency (n=6), and thrombosis (n=4) tested positive for any of common aPLs. Blood concentration of aβ2GPI/HLA-DR7 in the 95 women was found to be median 11.7 (range, 0-770.8) U. The percentage of women with aβ2GPI/HLA-DR7 of

>=10, >=20, and >=30 U were 56, 28, and 15%, respectively. Eight of 14 women with aβ2GPI/HLA-DR7 of >=30U tested positive for any of common aPLs, and the remaining six (43%) tested negative for common aPLs but had histories of RM. Three of the 6 women who were negative for common aPLs but positive for aβ2GPI/HLA-DR7 had more than 3 RM, and especially one of them had 4 RM and 1 FD at 38 GW. **Conclusion** aβ2 GPI/HLA-DR7 measurements might be useful to detect APS otherwise designated as unexplained RM.

ISP-42-5

Impact of inversion of chromosome 9 on recurrent pregnancy loss Mirei Yonezawa, Marie Ito, Saori Yoshikawa, Hanako Kaseki, Nozomi Ouchi, Ryuhei Kurashina, Tomoko Ichikawa, Katsuya Mine, Yoshimitsu Kuwabara, Misao Satomi, Rintaro Sawa, Toshiyuki Takeshita *Nippon Medical School*

Objective Pericentric inversion of chromosome 9 (inv (9)), considered to be normal variants, can be seen in 1-3% of general population. Its' impact on infertility or recurrent pregnancy loss (RPL) is still controversial. We investigated an imvolvment of inv (9) in the etiology of RPL from the view of the incidence of the association with other risk factors for RPL. **Methods** Patients included in this study were couples who attended the RPL clinic from 2007 to 2015. A total of 763 couples with two or more pregnancy losses were examined. Among them, 379 couples who received the screening for RPL, uterine morphology, thyroid function, anti-phospholipid antibodies, coagulation status, and karyotype, were analized. Informed consent was obtained from all patients before the examination. **Results** Among 1,526 karyotyped individuals (763 couples), inv (9) was identified in 22 patients ; the incidence of inv (9) was 1.44%. Thirteen couples had inv (9) in 379 couples. There was not significant difference between the group of couples with inv (9) and normal karyotype group in the mean age of female, number of previous miscarriages, the incidence of hypothyroidism, coagulation factor XII deficiency, uterine malformation. Among anti-phospholipid antibodies, the positive rate of anti-cardiolipin IgM antibodies was significantly higher in the group of couples with inv (9). **Conclusion** The patients with inv (9) demonstrated no characteristic abnormality. The incidence of positive anti-cardiolipin IgM antibodies was rather more frequent in inv (9) group. These findings suggest that inv (9) may not be a independent risk factor for RPL.

ISP-42-6

Serum human chorionic gonadotropin measured 9 days following day 5 embryo transfer might predict pregnancy outcome in frozen/thawed embryo transfer cycle Shin Oonota[1], Hiroshi Hayashi[2], Mao Hisamatsu[1], Teppei Ichikawa[1], Yuuta Kasahara[2], Miwa Hidaka[2], Kayo Suzuki[1], Atsuko Miwa[2], Makoto Iizuka[1], Satoshi Takakura[1] *Dokkyo Medical University Koshigaya Hospital[1], Keiai Reproductive & Endosurgical Clinic Shiki[2]*

Objective The aim of this study is to investigate the productive value of pregnancy outcome with serum human chorionic gonadotropin (hCG) measured 9 days following day 5 embryo transfer (ET) in frozen/thawed embryo transfer (FET) cycle. **Methods** We retrospectively reviewed medical chart in 138 women received single ET between January 2014 and December 2015. Serum hCG was measured 9 days following day 5 ET in FET cycles. We divided these women into 3 groups consisting in group A : 26 cases with biochemical pregnancy, group B : 50 cases with early spontaneous abortion, and group C : 62 cases with viable pregnancy. This study obtained IRB approval. **Results** Significant differences were detected in serum hCG level among groups (A : 68.6 vs B : 176.0 vs C : 274.0 mIU/ml, P value < 0.01). Serum hCG < 100 mIU/ml measured 9 days following day 5 ET in FET cycle is predictive of biochemical pregnancy with a sensitivity of 88.5% and a specificity of 81.2% (positive predictive value ; PPV=52.3%, negative predictive value ; NPV= 96.8%). Whereas, we could not find appropriate cut-off level between spontaneous abortion and viable pregnancy. **Conclusion** Serum hCG levels measured 9 days following day 5 ET in FET cycle might be a prognostic indicator of pregnancy outcome.

ISP-42-7

High dose intravenous immunoglobulin therapy for pregnancy with aspirin-heparin resistant antiphospholipid syndrome Yoko Maesawa, Masashi Deguchi, Shinya Tairaku, Mayumi Morizane, Kenji Tanimura, Yasuhiko Ebina, Hideto Yamada *Kobe University*

High dose intravenous immunoglobulin therapy (HIVIg) may have therapeutic efficacy for aspirin-heparin resistant antiphospholipid syndrome (AHRAPS) and for thrombocytopenia during pregnancies with APS. From April 2009, we have performed HIVIg on a total of 15 pregnancies with AHRAPS or thrombocytopenia in APS women. Seven pregnancies from five AHRAPS women with a history of pregnancy loss or premature birth before 30 gestational weeks (GW) despite aspirin-heparin therapy underwent HIVIg (20 g/day, 5 days) in addition to aspirin-heparin therapy. Four pregnancies ended in premature births, two in early miscarriages and one intrauterine fetal death at 17 GW. Two developed thrombocytopenia and liver/kidney dysfunction. Eight pregnancies from seven APS women developed thrombocytopenia and then underwent HIVIg. Four pregnancies showed an increase in platelet counts >50000/μL. Two pregnancies showed no changes in platelet counts, and thrombocytopenia deteriorated in the remaining two. HIVIg may have a therapeutic efficacy for AHRAPS, improving pregnancy outcome. HIVIg was found to be effective in 50% of thrombocytopenia during pregnancies of APS women. Further studies are needed to confirm therapeutic efficacy and to determine optimal dose/time of HIVIg in pregnancies of AHRAPS.

ISP-43-1

No association between raised thyrotropin and adverse perinatal outcome in low-risk pregnancies Seishi Furukawa[1], Mitsutoshi Iwashita[1], Kazuko Miyakawa[2], Jyoichi Shibata[3], Yoshihiro Nakano[4], Rei Ikeda[5] *Kyorin University[1], Taisei Hospital[2], Shibata Obstetrics and Gynecology Clinic[3], Nakano Ladies Clinic[4], Tachikawa Sougo Hospital[5]*

Objective We conducted the study to see the effect of subclinical hypothyroidism on perinatal outcomes in low-risk pregnancies. **Methods** We retrospectively reviewed medical charts of 683 low risk pregnant women who had examination of thyroid function using dried blood spots until 20 weeks of gestation. We regarded subclinical hypothyroidism as 3.0 ng/dl or more and less than 10.0 ng/dl. There were no women who treated with thyroxine in the study group. Women were then divided into subgroups based on the level of TSH and the presence of thyroid antibodies. We considered women with low TSH (<3.0ng/dl) without thyroid antibodies as control (n=515). We collected adverse maternal outcomes including spontaneous abortion, premature delivery, gestational diabetes mellitus (GDM), placental abruption, and pregnancy induced hypertension (PIH) ; and neonatal outcomes including still birth after 22 weeks, heavy for date, light for date, and low Apgar score<7 at 5 minutes. The composite outcome of mother and neonate were compared. **Results** The composite outcome of women with any adverse outcomes did not differ between control and the group of subclinical hypothyroidism (n=168, p=0.20). When the presence of thyroid antibodies was considered, the composite outcome of

mother did not differ between control and subclinical hypothyroidism with antibodies (n=27, p=0.65). The composite outcome of infant did not differ between control and subclinical hypothyroidism (p=0.60). Likewise, the composite outcome of infant between did not differ between control and subclinical hypothyroidism with antibodies (p=0.55). **Conclusion** Clinically, screening of subclinical hypothyroidism during pregnancy may be impractical to reduce obstetrical complications in low risk population.

ISP-43-2

The effect of bed rest for threatened preterm delivery on maternal and fetal vitamin D Naoto Yonetani[1], Takashi Kaji[1], Soishirou Nakayama[1], Atsuko Hichijo[1], Yohei Takahashi[1], Kazuhisa Maeda[2], Toshiyuki Yasui[1], Minoru Irahara[1] *Tokushima University[1], Shikoku Medical Center for Children and Adults[2]*

Objective To evaluate the effect of bed rest for threatened preterm delivery on maternal and fetal 25-hydroxy-vitamin D (25 (OH) D). **Methods** Women with singleton pregnancies who received prenatal care at our hospital between 2012 and 2015 were included in this case control study. Twenty pregnant women (cases) who received hospitalization for threatened preterm delivery after the second trimester for at least 21 days and delivered after 35 weeks of gestation and forty normal pregnant women (controls) who were matched maternal age and sample collection season with the cases were enrolled. Women with already-known fetal anomalies, hypertension, pregnancy-induced hypertension, diabetes mellitus, gestational diabetes mellitus, maternal complications on medication, steroid or heparin-medicated were excluded. Maternal serous 25 (OH) D concentrations in the second and third trimester and umbilical serous 25(OH)D concentrations at delivery were compared between the two groups using Student *t* tests. **Results** In the second trimester, maternal serous 25 (OH) D (median ± SD) concentrations were 18.5 ± 6.3 ng/ml in cases and 17.7 ± 6.4 ng/ml in controls. There was no significant difference between groups (p=0.64). On the other hand, in the third trimester, maternal serous 25 (OH) D concentration in cases (13.6 ± 3.2 ng/ml) was significantly lower than that in controls (18.4 ± 7.3 ng/ml) (p<0.01). Umbilical cord serous 25 (OH) D concentrations were 8.5 ± 0.8 ng/ml in cases and 9.7 ± 0.5 ng/ml in controls. There was no significant difference between groups (p=0.22). **Conclusion** Long term bed rest for threatened preterm delivery may decrease maternal serous 25 (OH) D concentration.

ISP-43-3

Transabdominal cerclage (TAC) for patients with ultra-short uterine cervix after operations for uterine cervical cancer : Possibility of its application to pregnancies after radical trachelectomy (RT) Miseon Kim, Shinichi Ishioka, Tsuyoshi Baba, Masahito Mizuuchi, Miyuki Morishita, Sayaka Adachi, Kyoko Isoyama, Saori Kon, Tsuyoshi Saitou *Sapporo Medical University School of Medicine*

Objective Patients with an ultra short uterine cervix due to large conization, repeated conization, or radical trachelectomy (RT), have very high risks for the occurrence of preterm premature rupture of the membrane (pPROM), which leads to preterm birth. Furthermore, transvaginal uterine cervical cerclage for these patients is almost impossible. To improve the obstetrical prognosis of these patients, we have started transabdominal cerclage (TAC) of the uterine cervix. **Methods** We have performed TAC for 10 patients (for 5 after repeated conization, and for 5 having trouble with cervical cerclage after RT). After laparotomy, a TeflonR thread was placed in the avascular space between the uterine vessels and the uterine muscle, and tied firmly. Then we recommended to the patients that they consult with specialists in reproduction and conceive as soon as possible, preferably within 1 year after TAC. **Results** We could perform TAC without any trouble for the ten patients. Seven patients conceived after TAC. Two of them resulted in abortion in the first trimester, one patient is in the second trimester of pregnancy, and 4 of them were able to undergo scheduled cesarean section without any problems. **Conclusion** Although TAC has risks for various complications due to the use of non-absorbable thread, which is a foreign body for the patient, in the abdomen and the need for 2 extra laparotomies, this operation can be a good treatment modality for patients who show cervical incompetence as a result of especially RT or large conization.

ISP-43-4

Colonization of Lactbacillus species and vaginal Nugent score is highly correlated with clearance of group B Streptococcus from birth canal Tasuku Mariya[1], Satoshi Shikanai[1], Hiroshi Shimada[1], Osamu Hayakawa[2], Tsuyoshi Saitou[2] *Hokkaido Social Insurance Obihiro Hospital[1], Sapporo Medical University[2]*

Objective Prevention of neonatal group B Streptococcus (GBS) infection is described in clinical guidelines to administrate intrapartum antibiotics for GBS colonized women. But in our experience, not a few cases could not be administered effective antibiotics in time for recommended 4-hour course. Therefore, we have routinely administrated oral antibiotics for GBS colonized outpatients in addition to standard intrapartum practice. In this study, we retrospectively examined effectiveness of oral antibiotics and other clinical factors for GBS clearance from birth canal. **Methods** We retrospectively examined GBS positive cases from deliveries in our hospital from 2013 to 2015. We reviewed information of vaginal and rectal swabs for GBS culture, colonization of Lactobacillus species and vaginal Nugent scores. Usage of oral antibiotics (penicillin or cephalosporin), GBS clearance status and pregnancy outcomes were analyzed statistically. **Results** Total 124 cases were defined as eligible for the study. For the most part of GBS positive cases (86.2% ; 107/124) were administered oral antibiotics and other 17 cases were not treated. There was no significant difference in GBS clearance rate between treated group and untreated group (69.2% vs 64.7% ; p=0.71). In multivariate analysis using logistic regression model, independent factors of GBS clearance were intravaginal colonization of Lactbacillus species (OR=1.34, 95%CI=1.00-1.79 ; p=0.038) and Nugent score (OR=0.85, 95%CI=0.73-0.99 ; p=0.035). **Conclusion** Administration of prenatal oral antibiotics did not significantly impact for treatment of GBS. Intravaginal bacterial flora might be promising factor of GBS clearance.

ISP-43-5

The effect of high glucose condition on the expression of angiogenic factors through PKCβ—HIF1α pathway in human choriocarcinoma cells Takashi Mitsui, Hisashi Masuyama, Kazuhiro Okamoto, Jota Maki, Takeshi Eguchi, Shoko Tamada, Eriko Etou, Kei Hayata, Yuji Hiramatsu *Okayama University*

Objective Glucose intolerance during pregnancy is well known as a risk factor for pregnancy induced hypertension (PIH). Imbalance of angiogenic factors are deeply involved in pathophysiology of PIH. We examined whether hypoxia induced factor (HIF1α) and protein kinase Cβ (PKCβ) were involved in the regulation of angiogenic factors and PKCβ inhibiter suppressed the expression of these factors under high glucose condition using human choriocarcinoma cells. **Methods** Cells (BeWo and JEG 3) were cultured for each 6 and 24 hours under the conditions of D-glucose 10mM as a control glucose group (CG) and D-glucose 25mM as a high glucose group (HG). Changes in the expression of HIF1α and PKCβ were examined by real time PCR. The ac-

tivity of PKCβ was measured by ELISA. In addition, we examined the changes in the expression of soluble fms-like tyrosine kinase-1 (s-Flt1), placental growth factor (PLGF) and Vascular endothelial growth factor (VEGF) and whether PKCβ inhibiter affected these expressions by real time PCR and ELISA. **Results** The expression and activity of PKCβ significantly increased in the HG compared with CG for 6 and 24 hours culture. The expression of HIF-1α, s-Flt1, PLGF and VEGF also increased significantly in the HG compared with CG. PKCβ inhibiter suppressed an increase in these expressions. **Conclusion** High glucose condition affected the expression of angiogenic factors in choriocarcinoma cells through PKCβ - HIF1α pathway, suggesting the involvement of this pathway in the pathogenesis of PIH. It is possible to prevent the onset of PIH in patients with glucose intolerance by the administration of PKCβ inhibiter.

ISP-43-6

The pathophysiology of gestational diabetes in lean pregnant women evaluated by insulin secretion and insulin resistance Shigeru Inoue, Yutaka Kouzuma, Daizo Hori, Michio Miyahara, Sayo Kubo, Kimio Ushijima *Kurume University*

Objective To elucidate the pathophysiology of gestational diabetes (GDM) in lean pregnant women by evaluating insulin secretion and resistance. **Methods** The subjects were 56 Japanese pregnant women of body mass index (BMI) of <18.5 at the first prenatal visit, cared in our hospital at 2013-2015, who underwent 75-gOGTTs because of casual hyperglycemia of >100mg/dl at 10-14 weeks and/or 50-gGCT of >140 mg/dl at 24-28 weeks. Twenty-two cases were diagnosed GDM (GDM group) and the remaining 34 cases had normal results (control group). The following parameters for evaluating insulin secretion and resistance ; 1) serum immnunoreactive insulin (IRI), 2) I.I.(insulinogenic index), 3) HOMA-β, 4) HOMA-IR, and 5) ISI composite (insulin sensitivity index composite) and the presence or absence of the history of DM in the first degree relatives were compared between the groups using the chi-squire and Mann-Whitney U-tests. The significance was set at $P<0.05$. This study was approved by the institutional review board of our hospital. **Results** There were no differences in the maternal age, parity and the gestational age at OGTT between the groups. In the GDM group, I.I.(0.54 vs. 0.94) and ISI composite (2.50 vs. 3.64) was lower and IRI levels at 60-min.(77.8 μU/ml vs. 47.2 μU/ml), 120-min.(72.3 μU/ml vs. 39.8 μU/ml). The higher incidence of family history of DM (40.9% vs. 3.0%) was found in GDM group. **Conclusion** We suggest that the pathophysiology of GDM in lean pregnant women is indicating decrease of insulin secretion, which is possibly associated with hereditary traits.

ISP-43-7

Pregnancy and Postpartum Outcomes in Women with Complete Atrioventricular Block Ayaka Nakashima, Chizuko Kamiya, Takekazu Miyoshi, Sachiko Narutomi, Yusuke Ueda, Atsushi Nakanishi, Chinami Horiuchi, Mitsuhiro Tsuritani, Ryoichi Hazama, Naoko Iwanaga, Reiko Neki, Jun Yoshimatsu *National Cerebral and Cardiovascular Center*

Objective We previously reported that the obstetric outcomes of women with complete atrioventricular block (CAVB) were mostly benign. However, the further discussion on the outcomes in the postpartum period outcomes has not been done. The current study is aimed to reveal the postpartum outcomes of pregnant woman with CAVB. **Methods** The medical records of 30 deliveries of 20 patients with CAVB were reviewed and analyzed their pregnancy and postpartum outcomes. **Results** The gestational age at delivery was 37.4+-2.3 weeks (mean +- SD). Epidural anesthesia was done in 22 patients out of 28 vaginal deliveries. Cesarean section was performed in two patients with obstetrical indications. Three patients underwent preterm delivery, and three newborn were diagnosed as small for gestational age. Four patients had symptoms (syncope, dizziness, dyspnea) of CAVB during pregnancy or the postpartum period. Four patients had cardiac pause of more than four seconds recorded in 24 hours electrocardiography. Of those who had either symptoms or pause in electrocardiography (four patients), three patients underwent permanent pacemaker implantation (PMI) within six months after delivery, and one patient died suddenly two months after delivery. **Conclusion** The permanent PMI could be required in the patients with CAVB in the earlier timing after delivery. As the symptoms like syncope, dizziness, dyspnea and cardiac pause during pregnancy could be the risk factors of the worsening of CAVB which lead to PMI or sudden death. A careful observation should be done on those women even after the delivery.

ISP-43-8

Relationship between laboratory data of TSH and preventive effect of preterm birth by levothyroxine administration in pregnant women with subclinical hypothyroidism Masahiro Shiba, Koichiro Kido, Takako Higa, Michiharu Seto, Rina Sakurai, Shigenari Namai, Rintaro Kishimoto, Koichi Umezawa, Yasuhiro Matsumoto, Yukifumi Sasamori, Eiji Ryo, Takuya Ayabe *Teikyo University School of Medicine*

ObjectiveTo investigate preventive effect of preterm birth by levothyroxine (LT4) administration in pregnant women with subclinical hypothyroidism (SCH). **Methods**Outcomes of 2,174 pregnant women who delivered singleton infant at 22 weeks of gestation or later from July 2012 through June 2016 were investigated retrospectively. During pregnancy, FT4 was normal and TSH was 2.5 μU/ml or more in 192 cases (Group A), TSH was 3.0 μU/ml or more in 124 cases (Group B), TSH was 5.0 μU/ml or more in 22 cases (Group C). They were randomly assigned to two subgroups depend on whether they received LT4 (LT4 (+)) or not (LT4 (-)). Preterm birth rate (PBR) was estimated by Fisher's exact test. Informed consent was obtained from all participants. **Results** The whole PBR was 15.3% (333 of 2,174 cases). Among LT4 (-) subgroup in each SCH group and non-SCH group, PBR was not significantly different. PBR in LT4 (+) and LT4 (-) subgroups were as follows : In Group A, 11.1% (2 of 18 cases) and 14.4% (25 of 174 cases), respectively ; P=0.52. In Group B, 11.1% (2 of 18 cases) and 11.3% (12 of 106 cases), respectively ; P=0.64. In Group C, 0% (0 of 9 cases) and 23.1% (3 of 13 cases), respectively ; P=0.19. **Conclusion** Although the number of samples is small and there is no significant difference (P=0.19), PBR was reduced by 100% (0% compared with 23.1%) in LT4 (+) subgroup in Group C. LT4 may be effective for SCH with TSH exceeding 5.0 μU/ml to prevent preterm birth.

ISP-43-9

Evaluation of the relationship between the severity of epilepsy and perinatal outcomes Michihiro Yamamura, Hiroaki Aoki, Naoya Kitamura, Haruka Hyuga, Takuma Sato, Akiko Konishi, Tomona Matsuoka, Eri Yoshii, Momoko Inoue, Yuki Ito, Osamu Samura, Aikou Okamoto *The Jikei University School of Medicine*

Objective The risk of pregnant women with epilepsy seems overestimated. Therefore, the aim of the present study was to examine the relationship between the severity of epilepsy and perinatal outcomes. **Methods** The medical records of pregnant women with epilepsy treated at our hospital were reviewed. The severity of epilepsy was scored according to the main seizure type, frequency of seizures before the pregnancy, electroencephalogram findings, and the number of antiepileptic drugs use during pregnancy. Patients were classified into three

groups based on the epilepsy score：mild (0–5 points), moderate (6–8 points), and severe (9–12 points). We compared the perinatal outcomes (gestational week, mode of delivery, birth weight, umbilical cord pH [pH], Apgar score [Ap], and fetal admission to a neonatal intensive care unit [NICU]) among the three groups. **Results** Patients' mean age was 32 years (range 22–41 years), and all patients had a singleton pregnancy. Four patients (13.3%) had a preterm birth, and 1 patient (3.3%) had fetal growth restriction. Four patients (13.3%) underwent emergency cesarean section. Only 1 patient (3.3%) had a pH<7.2, and only 3 patients (10.0%) had an Ap<7. Three newborns (10.0%) were admitted to the NICU. There were 5, 19, and 6 patients in the mild, moderate, and severe groups, respectively. There were no significant differences among the three groups in terms of the perinatal outcomes. **Conclusion** In the present study, the severity of epilepsy was not related to the perinatal outcomes among patients appropriately managed by experienced obstetricians and epileptologists.

ISP-43-10

Efficacy of maternal serological screening for congenital cytomegalovirus infection Shinya Tairaku[1], Kenji Tanimura[1], Ichiro Morioka[2], Kana Ozaki[1], Satoshi Nagamata[1], Mayumi Morizane[1], Masashi Deguchi[1], Yasuhiko Ebina[1], Toshio Minematsu[3], Hideto Yamada[1] *Kobe University[1], Kobe University[2], Aisenkai Niching Hospital[3]*

Objective The aim of this study was to evaluate the efficacy of maternal serological screening for the prediction of congenital CMV infection (CI). **Methods** In this prospective cohort study, pregnant women underwent CMV IgG (IgG) and avidity index (AI) measurements with informed consent. IgG-negative women received educational interventions and IgG re-measurement later. All newborns underwent urine analyses for CMV-DNA. A primary infection during pregnancy was defined as IgG seroconversion, serum AI<35% and/or IgM>1.2, and non-primary infection as AI>45% and negative IgM. The efficacy of maternal screening of IgG, AI and/or IgM for the prediction of CI was evaluated. Logistic regression analyses of pregnancy complications were performed to determine risk factors for fetal infection in mothers with non-primary infection. The institutional review board approved the study. **Results** A total of 2,017 pregnant women were enrolled, and 455 (22.6%) had negative IgG. The 0.9% (4/455) had seroconversion, and 0.2% (1/455) had CI. Seventy-nine (5.1%) of 1,562 women with positive IgG had AI<35% were defined as primary infection, and 2.5% (2/79) had CI. 1,379 women had AI>45% and negative IgM showing non-primary infection. The 0.5% (7/1,379) had CI. The predictive efficacy of serum AI<35% (Sn 22%, Sp 95%, PPV 2.5%, NPV 99.5%) for CI was better than that of IgM>1.2. Threatened miscarriage/preterm labor was found to be a risk factor of fetal infection in mothers with non-primary infection (OR 8.3, 95% CI 1.4–47.5, p<0.05). **Conclusion** This study for the first time demonstrated threatened miscarriage/preterm labor as a risk of fetal infection in mothers with non-primary infection, and that maternal serological screening overlooked CMV infected newborns.

ISP-43-11

Investigation of risk evaluation method for pregnancy with adult congenital heart disease Hironobu Hyodou, Saho Fujino, Yuki Taketani, Naoko Fukuda, Shoko Makabe, Norihiko Nakazato, Etsuko Saito, Yukiko Fuse, Chikako Hikosaka, Midori Funakura, Sorahiro Sunagawa, Koji Kugu *Tokyo Metropolitan Bokutoh Hospital*

Objective The number of pregnancies with adult congenital heart disease (ACHD) has been increasing owing to the advance of medicine and surgery for the management of the disease. Cardiac events such as dysfunction, arrhythmia, heart failure, etc. may sometimes occur during pregnancy even they have never emerged before. As ACHD has diverse conditions, risk evaluation may often be unsuitable. Three methods which have already been proposed were retrospectively applied to our cases. **Methods** The medical records of pregnancy of ACHD women that managed at our hospital from 2005 to 2016 were reviewed. WHO classification, CARPREG score, and ZAHARA score were applied to the cases, and the events during and after pregnancy were verified by each risk evaluation method. **Results** Forty pregnancies of thirty-four cases were identified. All of them were in NYHA 1 at the first of pregnancy. WHO classification was 3 in five cases, seven pregnancy. CARPREG score was all zero. ZAHARA score was 4.75 in one, 0.51–1.50 in three cases. One Ebstein case was WHO 1, CARPREG 0, ZAHARA 0.75 and turned into NYHA 2 in the third trimester. One Marfan case was transferred to us because of aortic dissection and was estimated to be WHO 3, CARPREG 0, ZAHARA 0. **Conclusion** Although most of the cases were uneventful, the three method did not always predict the risks. The case-specific risk should necessarily be considered.

ISP-44-1

Clinical factors associated with pregnancy outcome in systemic lupus erythematosus Shino Kubota, Masashi Deguchi, Yoko Maesawa, Kenji Tanimura, Mayumi Morizane, Noriyuki Morimoto, Hideto Yamada *Kobe University*

Objective Women with systemic lupus erythematosus (SLE) have a high risk for adverse pregnancy outcome and complications. The aim of this study was to determine clinical factors affect pregnancy complications in women with SLE. **Methods** The retrospective cohort study enrolled 63 pregnant women with SLE who were managed in our hospital between 2009 and 2016. An association between pregnancy complications and clinical factors was evaluated using Fisher's exact test. The pregnancy complications involved pregnancy loss, premature delivery, PIH and light for date (LFD). Clinical factors included positive tests for anti-single/double stranded DNA (ss-DNA/ds-DNA), Sm, ANA, and antiphospholipid antibodies (aPL；LA, aCL, aCLβ2 GPI), presence of hypocomplementemia during pregnancy, prednisolone (PSL) of >10 mg/day in first trimester, and a history of lupus nephritis. **Results** Positive tests for ds-DNA (OR 5.2), LA (OR 7.9) and aPL (OR 7.2) were associated with premature delivery of <36 gestational weeks (p<0.05). Positive tests for aCL, aCLβ2GPI, and PSL>10 mg/day tended to be associated with the premature delivery (p=0.05–0.08)；and PSL>10 mg/day with PIH (p=0.05). **Conclusion** It was found that positive tests for ds-DNA and aPL in women with SLE are risk factors for premature delivery. Disease activity and aPL may cause adverse pregnancy outcome.

ISP-44-2

Perinatal prognosis of pregnancy with cytomegalo virus IgM antibody in our hospital Kunihiko Yoshida, Masayuki Yamaguchi, Mina Itsukaichi, Taro Nonaka, Kazufumi Haino, Koichi Takakuwa, Takayuki Enomoto *Niigata University*

Objective The purpose was to consider perinatal prognosis of pregnancy with cytomegalo virus (CMV) IgM antibody. **Methods** The subjects were 30 cases of pregnancy with CMV IgM who delivered in our hospital from January 2006 to December 2015. We investigated the purpose of the examination and the CMV infection of infants. Additionally, we considered retrospectively 9 cases who were CMV IgM positive by pregnant initial inspection and 490 cases of pregnancy who had no complication, as control group. **Results** In 30 cases with CMV IgM, 9 cases

were IgM positive by pregnant initial inspection on former hospital, 15 cases were positive by the examination for fetal growth restriction (FGR) and 6 cases were positive by the examination for fetal structural anomaly. The CMV infection of infants were diagnosed in 3 cases (10.0%). These cases showed mild ventriculomegaly, hydrops or ascites by fetal ultrasound examination. CMV IgM were examined In 99 FGR cases without fetal structural anomaly, and 15 cases (15.2%) of them were IgM positive. However CMV infection of infant was nothing in these cases. In the comparison of 9 IgM positive cases by pregnant initial inspection and 490 control cases, perinatal outcomes was not significantly different. **Conclusion** For the cases of pregnancy with CMV IgM, fetal ultrasound findings are also important to diagnose CMV infection of infant.

ISP-44-3

Study of pregnant women who has medical history of Anorexia nervosa Aiko Sekine, Nahoko Shirato, Miwa Sakamoto, Keiko Miyagami, Keiko Koide, Akihiko Sekizawa *Showa University School of Medicine*

Objective The prevalence of anorexia nervosa (AN) ranged between 0.3–1% in pubertal age. Sometimes we meet pregnant women who have medical history of AN, and who is under treatment. The purpose of this study is to review problems of pregnant women who have history of AN. **Methods** This is a retrospective study of pregnant women with history of AN. Subject were 27 pregnant women (31 deliveries), delivered in our hospital from 1998 through 2016. We reviewed at the points of pregnant, delivery and postpartum course from medical records. **Results** Five patients (16%) became pregnant by ART and 9 (33%) were admitted for AN before pregnant. 14 patients (52%) receive a medical examination of psychiatrist during pregnancy. The median BMI (interquartile range, IQR) of first trimester, delivery and 1 month after delivery were 18.5 (17.5–19.2), 22.3 (20.3–23.3) and 19.3 (18.2–20.2). A patient (3%) developed preeclampsia, 5 (16%) preterm delivered, and 5 (16%) hospitalized with threatened premature delivery. The median birthweight (IQR) was 2791g (2257–2943). We could not detect any significant difference between pregnant women with and without AN history. **Conclusion** Half of pregnant women with history of AN were required the consultation of psychiatrists. We considered they required continuous medical support, because BMI did not reach normal range in any point within observation period. Although it is revealed that the rate of premature delivery was high, we could not detect that a low-birth-weight infant was high in women with a history of AN.

ISP-44-4

Protection from Repeated Intra-Uterine Infection (IUI) Masayoshi Arizawa[1], Tomio Fujita[2] *Tokyo Metropolitan Ohtsuka Hospital[1], Fujita Clinic[2]*

Objective We do not know a lot about repeated Intra-Uterus Infections (IUI). Repeated IUI can be found in cases of repeated abortions and repeated premature delivery when often repeated. This study explores how to treat these repeated IUI cases. **Methods** We examined the placentas or abortion contents from both pregnancies in 23 cases of women who had over two pregnancies, with repeated IUI. We examined the first pregnancy the second, and then third making 52 separate examinations in total. The presence of IUI from the point of view of placental pathology is defined by moderate to severe CAM. In the case of abortions, contents reveal moderate to sever deciduitis or moderate to sever CAM. We also examined the vaginal floor for bad bacteria that might develop IUI in 25 cases (out of 52). **Results** Out of 52 IUI cases under 22 gestational weeks (abortion) there were 19 cases of IUI. The average gestational weeks of these 19 cases was 12 weeks. Out of 52 cases over 22 gestational weeks, there were 6 cases over 37 weeks. The average gestational weeks was 30 out of 33 cases. There were 15 cases under 32 weeks and 28 cases over 32 weeks out of 33 cases. We carried out 25 Vaginal floor examinations and could not find good bacteria, such as lactobacillus, in 20 cases. **Conclusion** There were cases of premature delivery when repeated IUI was present. The detrimental influence of bad bacteria in the body was also clear. For protection from repeated IUI. we should maintain healthy levels of vaginal good bacteria.

ISP-44-5

Two cases of perforated appendicitis with peritonitis during pregnancy : different outcome after appendectomy Michihisa Shiro, Noriyuki Sasaki, Yoshihiro Takiguchi, Mika Mizoguchi, Nami Oota, Sawako Minami, Kazuhiko Inou *Wakayama Medical University*

Background Diagnosis of appendicitis during pregnancy is difficult because of enlarged uterus. As perforated appendicitis during pregnancy lead to poor maternal and neonatal mortality and morbidity, early surgery of appendicitis for pregnant women is important. There is no consensus of appendectomy and cesarean section at the same time in the late term. We experienced two cases of perforated appendicitis with peritonitis during pregnancy. **Case** Case 1 : 33 years old, 1 para woman, 24 weeks and 2 days was admitted to our hospital because of suspected appendicitis. Her result of blood test, WBC (8859/μl) and CRP (2.69mg/dl) were a little high and she had very strong pain in right lower abdomen. She was diagnosed as perforated appendicitis by Computed Tomography (CT) and underwent appendectomy with full peritoneal lavage. After surgery, the symptom of peritonitis was improved. Case 2 : 29 years old, 0 para woman, 35 weeks and 5 days was admitted to our hospital suspected of appendicitis. She was diagnosed as perforated appendicitis by CT and underwent appendectomy. At the surgery, surgeons could not wash the left side cavity of the abdomen because of enlarged uterus. After surgery, she remained to feel strong abdominal pain and showed increasing the results of blood test of inflammatory markers. After 2 days of appendectomy, we performed cesarean section. **Conclusion** We suggest that cesarean section may be concurrently performed with appendectomy at perforated appendicitis during pregnancy in the case that surgeons cannot wash full cavity of the abdomen because of enlarged uterus in the near-term.

ISP-44-6

In vitro fertilization and pregnancy management in a woman with acquired idiopathic chylous ascites Ai Sakamoto[1], Chiaki Kashino[1], Hirofumi Matsuoka[1], Toru Hasegawa[1], Kei Hayata[1], Sayoko Kotani[1], Yasuhiko Kamada[1], Hisashi Masuyama[1], Mikiya Nakatsuka[2], Yuji Hiramatsu[1] *Okayama University[1], Okayama University[2]*

Introduction Chylous ascites accumulates with the extravasation of milky chyle into the peritoneal cavity. A woman with acquired idiopathic chylous ascites achieved pregnancy through assisted reproductive technology (ART). **Case presentation** A 23-year-old woman noted abdominal distention, and ultrasonography revealed fluid collection and polycystic ovaries. A lymphogram revealed leakage of lymph from the right renal hilar region. Conservative management was ineffective. Lymphatic-venous anastomosis of the thoracic duct was performed three times by plastic surgeons at our university hospital, but the chylous ascites was not reduced. She subsequently married and desired pregnancy. Natural pregnancy was not possible because of the ascites. We therefore planned in vitro fertilization using a gonadotropin-releasing hormone (GnRH) agonist long

protocol. Just prior to oocyte retrieval, transvaginal removal of ascites was performed. In total, 22 oocytes were retrieved and 9 blastocysts were obtained. All were cryopreserved to prevent ovarian hyperstimulation syndrome. We performed single frozen embryo transfer (5AA) through hormone replacement therapy with a GnRH agonist. The patient became pregnant, and the ascites decreased as the pregnancy progressed, finally disappearing around the 20th week of gestation. She delivered a healthy baby by normal vaginal delivery at the 41st week of gestation. The ascites began to reaccumulate starting the day after delivery and returned to the original level by 1 month after delivery. **Conclusion** ART effectively achieved pregnancy in a woman with chylous ascites, which spontaneously decreased during pregnancy.

ISP-44-7

A case of pheochromocytoma (retroperitoneal paraganglioma) complicated pregnancy with acute adrenal crisis at 31 weeks Chiyori Sakamoto, Susumu Miyashita, Emi Motegi, Tatsuya Kuno, Shoko Ochiai, Kaori Kiuchi, Kazumi Tada, Ichio Fukasawa *Dokkyo Medical University Hospital*

A 36-year-old woman, primigravida was transferred to our institute at 25 weeks of gestation because of headache, excessive sweating and hypertension. She was complicated with thyroid tumor but had no familial history. The plasma renin activity and serum aldosterone level were within the normal range. Blood pressure was recorded more than 180 Torr in systole occasionally, but fluctuated even in a day. Nifedipine administration was not effective to control the hypertension. Serum norepinephrine level revealed to be elevated considerably (8501 pg/mL) and a retroperitoneal tumor of 55 mm in diameter was demonstrated using magnetic resonance imaging at 30 weeks. Labetalol hydrochloride administration was started at 31 weeks but resulted in inefficient control of hypertension. Hemoptysis and respiratory disturbance developed suddenly, suggesting acute adrenal crisis at 31 weeks and 2 days. An emergent Caesarean section was carried out under general anesthesia and a male infant of 1862 grams in weight was delivered with the APGAR score 3 (1 min) and 6 (5 min). The patient needed several days of intensive care after the delivery. We started prazosin hydrochloride administration at 3 postpartum days and surgical resection of the paraganglioma was scheduled. Early diagnosis and treatment of pheochromocytoma was crucial to improve the outcome of the pregnancy. Exclusion of pheochromocytoma is essential when you observe difficult-to-control hypertension in the mid-trimester of pregnancy despite the low incidence, 0.1% to 1% of hypertension. Pheochromocytoma is related to multiple endocrine neoplasia (MEN) type 2A, which is under the investigation in this case.

ISP-44-8

A case of pregnancy after mechanical valve replacement for aortic stenosis Shotaro Kai, Yuka Sato, Saki Kido, Masahiro Hachisuga, Nobuhiro Hidaka, Yasuyuki Fujita, Kiyoko Kato *Kyushu University*

Pregnancy after mechanical valve replacement for congenital heart disease increases perinatal adverse outcome. Strict anticoagulant therapy is needed to prevent valve thrombosis. However, the consensus about the medication during pregnancy has not been obtained. The patient was 26 years old, who had an aortic valve replacement with a mechanical valve due to aortic stenosis and regurgitation at 4 years old. She had taken warfarin since the operation. Once, she was tried valve re-replacement but the operation was so difficult that coronary arterial bypass graft surgery was performed. Because of desire for a baby, after consultation she stopped medication of warfarin, and got pregnancy spontaneously. She was referred to our hospital for management of her pregnancy at 14 weeks gestation. After informed consent, intravenous drop infusion of heparin was started from 15 weeks gestation. The dose of heparin was regulated based on the activated partial thromboplastin time (APTT) to maintain the APTT value of 1.5-2 fold of normal one. Her condition was evaluated by APTT, d-dimer, chest X-ray, and echocardiography. At 23 weeks, she suffered from heart failure with sacroiliitis and was treated by diuretic agents. At 27 weeks, bacteremia of staphylococcus aureus was happened and treated by intravenous antibiotics. At the moment of 32 weeks gestation, her pregnancy is uneventful and her delivery is planned after 37 weeks. The management of a case with mechanical valve replacement is challenging, but detail observation and communication with other specialists, such as cardiologist and anesthesiologist, may lead the pregnancy successful.

ISP-44-9

Two cases of pregnant women with non-gynecological malignant tumor sowing from deep venous thrombosis in the second trimester Aya Ootsuka, Atsushi Tajima, Rie Seyama, Hanako Kasahara, Akari Koizumi, Shuichiro Endo, Yoko Tsuzuki, Yasuka Miyakuni, Iwaho Kikuchi, Chikako Suzuki, Michio Nojima, Koyo Yoshida *Juntendo University Urayasu Hospital*

The prevalence of malignant tumor during pregnancy is about one out of a thousand pregnancies. We had experienced 2 cases of non-gynecological malignant tumor during pregnancy. Deep venous thrombosis (DVT) had occurred in both cases before we diagnosed malignant tumor. The first case was a nulliparous 28 years old woman who was diagnosed pulmonary adenocarcinoma after childbirth. DVT and pulmonary embolism (PE) had occurred at 25 weeks' gestation. After cesarean delivery in at 39 weeks' gestation, she showed pleural effusion which was caused by pulmonary adenocarcinoma. Because the adenocarcinoma has already metastasized to the brain, the clinical stage was IV. She has been treated with molecular target medicine. The second case was a nulliparous 39 years old woman who was diagnosed squamous cell carcinoma of the retroperitoneal tumor. She DVT had occurred at 26 weeks' gestation. An enhanced CT scan showed huge retroperitoneal tumor and bone metastasis. Cesarean section was performed at 30 weeks' gestation because of poor maternal state due to sepsis. The pathological finding of the sample taken from the tumor was squamous cell carcinoma. DVT occurs in approximately 1.7% of patients during pregnancy. There is a report that an outcome of pregnant womwn with malignant tumor diagnosed from DVT is worse. It should be important to perform the scanning of malignant tumor when pregnant woman has DVT during pregnancy in the second trimester.

ISP-44-10

Case report of a pregnant woman with diffusely-spread small intestinal endometriosis following clinical micro-rupture of endometrioma during pregnancy Erina Kato, Kanoko Shoji, Hideki Takahashi, Takuo Nakayama, Hiromitsu Azuma, Chuyu Hayashi, Go Ichikawa, Yasuji Miyakawa, Shinichi Takada, Masahiko Matsuura, Fumihisa Chishima, Kei Kawana *Nihon University*

This case was a 40 years-old nullpara woman. She had received ovarian cystectomy of bilateral endometrioma, myomectomy and left salpingectomy at 37 years-old. She got pregnancy by IVF-ET after the operation. 4cm of right endometrioma was detected at the first trimester. At 32-gestational weeks, continuous pelvic pain appeared suddenly and had to be controlled in the hospital by medication and then disappeared several weeks

later. She underwent c-section due to obstetrical disorder and the baby was well, 3154 g (Apgar 8 (1'), 9 (5')). At the c-section, we revealed that the size of right endometrioma was decreased to 2cm probably due to micro-rupture during pregnancy (her rASRM score=86, stage 4). We found multiple 5mm nodules on the small intestine spreading up to 20cm of length from the cecum. The lesions appeared cancerous dissemination. We performed intraoperative biopsy of these lesion by frozen section. The nodules were diagnosed pathologically as "Atypical epithelial cells". We performed bilateral ovarian cystectomy as well. Final pathological diagnosis of the nodules was endometriosis, which was diagnosed using immunostaining (vimentin+, CD10 +, PgR+ and ER+.) **Conclusion** Peritoneal endometriosis was shown on the small intestine after micro-rupture. The lesions change to the aspect similar to cancerous dissemination by pregnant state. The phenomenon provide an insight into management of endometriosis during pregnancy.

ISP-44-11

Successful pregnancy in cervical carcinoma stage1b1 patient Makiko Kasahara, Shozo Matsuoka, Kengo Hiranuma, Miho Saitou, Ayako Miwa, Maiko Yamaguchi, Yota Shimanuki, Soshi Kusunoki, Yayoi Sugimori, Daiki Ogishima *Juntendo University Nerima Hospital*

Introduction Recently, there has been more cases diagnosed with cervical carcinoma during pregnancy because morbidity of cervical carcinoma in young age increased and late marriage and late birth progressed. **Case** The patient was a 37-year-old woman with 1 gravida 0 para. She was pointed out Class 3a, HSIL at cervical cytology in pregnancy 8 weeks, and invasive squamous cell carcinoma was suspected from the biopsy of the cervix. Cervical conization was performed in pregnancy 11 weeks, and the result of pathology was squamous cell carcinoma, pT1b1. The cervical cytology continued to indicate NILM since one month after the conization. In addition, we performed abdominal pelvic lymphadenectomy in pregnancy 16 weeks 5 days to determine whether she could continue pregnancy. There were no lymph node metastasis and no local recurrence. Finally, a caesarean section and modified radical hysterectomy was performed in pregnancy 35 weeks 5 days. There was no invasion and metastasis of carcinoma in the pathology. The baby was a girl, 2056g (AFD). Apgar score was 8/9. It has already passed about 5 months since the surgery, there is no recurrence finding. **Discussion** When it is diagnosed cervical carcinoma Stage1b1, recommended termination of pregnancy within 6 weeks from diagnosis, but there is possibility of continuation of pregnancy if there is no metastasis of lymph nodes.

ISP-44-12

A case of lung cancer during pregnancy : its diagnosis and management Ai Higashijima[1], Kiyonori Miura[1], Noriko Nagata[1], Kanako Matsumoto[1], Akiko Nonoshita[2], Hideaki Masuzaki[1] *Nagasaki University[1], Sasebo-City General Medical Center[2]*

Lung cancer, the leading cause of cancer deaths in males for decades, has recently become one of commonest causes for women, too. As women delay the start of their family, the co-existence of cancer and pregnancy is increasingly observed. Herein, we report a pregnant woman with lung cancer. A 30-year-old pregnant woman developed cough and fever at 28th weeks of pregnancy. A medications for common cold were administered, but they were not effective. She was then introduced to another hospital. Lung cancer was suspected from her chest-CT scan. She underwent bronchoscope and biopsy, then diagnosed as lung cancer of epidermoid carcinoma. She was introduced to our hospital for perinatal care and lung surgery. Caesarean section was performed for breech presentation at 34 w5d weeks of pregnancy. After 12 days of caesarean section, upper lobectomy and lymph node dissection (ND2a-2) was performed for lung cancer (pT2aN0M0). Post operative process went well and she discharged our hospital with her baby after 13 days of operation. Generally, lung cancer during pregnancy is detected in advanced stages, chemotherapy provides poor results and overall survival is poor. Because of concerns over the safety of the fetus, physicians' reluctance to use radiologic imaging tests leads to misinterpretation of common respiratory symptoms and the delayed diagnosis of lung cancer. Chest radiographs for pregnant women with protracted cough and hemoptysis should be considered.

ISP-45-1

The importance of genetic counseling for non-invasive prenatal testing : four years experiences in our hospital Yuri Hasegawa, Kiyonori Miura, Shoko Miura, Ai Higashijima, Yuko Murakami, Naoki Fuchi, Akiko Nonoshita, Atsushi Yoshida, Hideaki Masuzaki *Nagasaki University*

Objective The aim of this study is to summarize the results of genetic counseling for non-invasive prenatal testing (NIPT) in our hospital. **Methods** We have performed genetic counseling for NIPT by geneticists and genetic counselors from 2013. We explored the number of all clients who wished to receive genetic counseling for NIPT, clients were examined NIPT and clients were canceled NIPT after genetic counseling. **Results** The number of all clients received genetic counseling for NIPT were 261 pregnant women. After genetic counseling, 216 clients (82.8%) were received NIPT, 45 clients (17.2%) were canceled to receive NIPT. Approximately half of clients who were canceled NIPT received chromosomal study by amniocentesis, 40% of clients did not received any prenatal testing. As results of NIPT, 2 cases were positive (trisomy21 and trisomy18), the other 214 cases were all negative. All clients were received genetic counseling when they debriefed results of NIPT. Two clients of positive for NIPT were performed chromosomal study by amniocentesis. **Conclusion** NIPT is not necessary for all pregnant women. So, it is important to perform genetic counseling for NIPT before receiving NIPT. Additionally, after receiving NIPT, we must perform genetic counseling for all clients regardless of positive or negative of NIPT results.

ISP-45-2

The study of fetus anomalies detected before 22 weeks of gestation Ryoko Ono, Masahiro Nakao, Takuya Kawamura, Yoshiki Maeda, Ryo Suzuki, Ikuno Kawabata, Atsushi Yoshida, Shinji Katsuragi *Sakakibara Heart Institute*

Objective To assess the key findings which led to early detection of fetal anomalies by ultrasonography and to review the outcomes of each case. **Methods** We reviewed the outcomes of thirty-nine pregnant women who were referred to our hospital before 22 weeks of gestation suspected of having foetal physical anomalies. **Results** Fetal heart diseases made up nearly 50 per cent of all anomalies and were found at around 20 weeks of gestation. Other anomalies, including limbs, hydrops, and intracranial abnormalities, were found between 10 and 20 weeks of gestation. The most common cases involved HLHS, which was suspected on the basis of an abnormal four chamber view. Heart diseases with an abnormal cardiac outflow, such as TOF and DORV, could be detected by evaluating the three vessel trachea view. Out of all cases, 18 cases opted for abortion, and 6 cases were normal following specialists examinations. **Conclusion** Adequate check-ups, along with fetal screening protocols recommended by the Japan Society of Obstetrics and Gynaecology, make early detection of fetal anomalies possible, albeit with false negative cases. Early diagnosis of fetal anomalies is impor-

tant in terms of preparation for the best support after birth. On the other hand, it is still controversial due to the issue surrounding the termination of pregnancy.

ISP-45-3

The choice of pregnant women received positive result of prenatal screening for fetal aneuploidy in one institution Hiroko Tanaka, Masayuki Endo, Aiko Okada, Takao Owa, Etsuko Kajimoto, Yukiko Shimazu, Aiko Kakigano, Kazuya Mimura, Takuji Tomimatsu, Tadashi Kimura *Osaka University Graduate School of Medicine*

Objective To investigate whether pregnant women with positive result of prenatal screening for fetal aneuploidy, either nuchal scan or Non-invasive prenatal testing (NIPT), choose to have amniocentesis (AC) to diagnose fetal chromosomal abnormalities or not. **Methods** This was a retrospective cohort study including 1035 pregnant women received prenatal screening for fetal aneuploidy in our hospital. We compared the choice between pregnant women received positive result of nuchal scan from April 2012 to March 2015 (Nuchal scan group) and that of NIPT from April 2013 to March 2015 (NIPT group). **Results** The number of pregnant women received a prenatal screening for fetal aneuploidy in our hospital was increasing, 279, 336 and 420 cases in 2012, 2013 and 2014 respectively. 793 pregnant women received nuchal scan in those three years. 150 cases (150/793, 18.9%) was positive result. Only 80 cases (80/150, 53%) decided to perform AC to confirm fetal aneuploidy. In contrast, 242 pregnant women selected NIPT in those two years. Only two cases (2/242, 0.8%) was positive and all of them (2/2, 100%) chose AC. **Conclusion** Our surveys showed almost half of the pregnant women with positive result of nuchal scan did not choose to have AC to confirm fetal aneuploidy in our institution. This low AC rate in Nuchal scan group suggested not small number of pregnant woman in this group received prenatal screening just for their information, but not for their judgement.

ISP-45-4

The decision making of at-risk couples for the prenatal diagnosis of congenital metabolic disorders Yutaka Iwagoi, Tomoko Honda, Fumiko Ito, Takashi Ohba, Hidetaka Katabuchi *Kumamoto University*

Objective Prenatal diagnosis of inherited metabolic disorders has been provided to at-risk couples not only to avoid the affected baby but to prepare appropriate treatments during neonatal period. Here we report the experience of prenatal diagnosis of inherited metabolic diseases and the decision making of the couples at a single perinatal care center. **Methods** We retrospectively collected 11 couples referred for prenatal diagnosis, and proper managements of inherited metabolic disorders in the last five years of our hospital. The results of prenatal diagnosis, the parental decision, and the pregnancy course were investigated. **Results** Of 11 couples with 13 singleton pregnancies, mid-trimester amniocentesis for prenatal diagnosis was indicated in eight couples with 10 pregnancies. The couples have received genetic counseling and six couples decided to receive the amniocentesis. Five negative women continued their pregnancy and gave birth to healthy babies. One woman was positive for methylmalonic academia and the couple chose induced abortion. Four couples with 4 pregnancies did not receive the prenatal diagnosis. Three of them gave birth to healthy babies, and one chose induced abortion. Among 13 pregnancies, 9 were visited after the commencement of non-invasive prenatal genetic testing (NIPT) for fetal chromosomal aberration in our hospital, 3 of the women over 35 years old chose NIPT and not received amniocentesis for metabolic disorders. **Conclusion** Thirty percent (3/10) of couples who were at risk for congenital metabolic disorders refrained from amniocentesis for prenatal diagnosis. These couples might accept the affected fetus if there were no additional abnormalities. Negative NIPT might help to avoid amniocentesis.

ISP-45-5

A case of 31-year-old woman who repeated the pregnancy with full trisomy 21 at four times Kazuaki Oohashi[1], Kiyonori Miura[1], Yuri Hasegawa[1], Shoko Miura[1], Masako Masuzaki[1], Hideaki Masuzaki[1] *Nagasaki University Hospital[1], School of Health Sciences, Faculty of Medicine, Nagasaki University[2]*

We report a case of 31-year-old woman who repeats pregnancy with full trisomy 21 at four times. Her first pregnancy was at 20 years old and selected artificial abortion, but chromosome banding was not performed. Her second pregnancy was at 24 years old, and her child was diagnosed for full trisomy 21 after birth. Her third pregnancy was at 25 years old, and she selected artificial abortion because the fetus was diagnosed as full trisomy 21 by genetic amniocentesis at 16 weeks of gestation. Her fourth pregnancy resulted in spontaneous abortion at 9 weeks of gestation, and was diagnosed as pregnancy with trisomy 16. She got a divorce and married again. Her fifth pregnancy with next partner was at 30 years old, and she and her husband visited our hospital to get genetic counseling for the first time. Because genetic amniocentesis showed that fetus had full trisomy 21, she selected artificial abortion at 19 weeks of gestation. She and her husband had normal karyotypes. We performed exome-sequencing analysis of her and her parents blood DNA samples, but no candidate gene mutation associated with the development of chromosomal aneuploidy was found. Her sixth pregnancy was at 31 years old, but this pregnancy resulted in intra uterine fetal death (IUFD) at 14 weeks of pregnancy, and the karyotype of placenta was full trisomy 21. This case has a high risk of repeated full trisomy 21 pregnancy. Therefore, the genetic counseling should be necessary to support her pregnancy in future.

ISP-45-6

Factors influencing Japanese woman's decision regarding to choose NIPT Junko Yotsumoto[1], Nahoko Shirato[2], Keiko Miyagami[2], Akihiko Sekizawa[2] *Ochanomizu University[1], Showa University[2]*

Objective To explore women's motivations, expectations regarding NIPT and the outcome of preliminary genetic counselling for NIPT how they experienced the information given and why they did or did not choose NIPT **Methods** Questionnaire concerning women's background, motive and genetic counseling was performed on pregnant 7292 women after receiving genetic counseling who opted for NIPT. **Results** Older, more highly educated and highly income women tended to choose NIPT (mean age was 38.3, over 49% of women graduated university or higher level of degree, annual household income of 7 million yen and more). And the rate of infertility treatment was high among the women who underwent NIPT (42.2%). In addition, 14.4% of the women received a recommendation from their family to undergo NIPT.A higher expectation of NIPT was shown in the group of women who were older and had undergone treatment infertility, and this group was less likely to have change in intention, compared to other group. **Conclusion** Differences in the awareness and evaluation of NIPT ware shown to be dependent upon the individual women's back-ground. We should respect individual intent and history, so as to make an autonomous and informed decision-making.

ISP-45-7

Fetal facial expression in the 3rd trimester Aboellail Mohamed, Nobuhiro Mori, Kenji Kanenishi, Toshiyuki Hata *Kagawa University*

Objective To evaluate the frequencies of fetal facial expressions late in the third trimester of pregnancy when the fetal brain maturation and development are complete in normal healthy fetuses. **Methods** Four-dimensional (4D) ultrasound was used to examine the facial expressions of 111 healthy fetuses between 30 and 40 weeks of gestation. The frequencies of 7 facial expressions (mouthing, yawning, smiling, tongue expulsion, scowling, sucking, and blinking) during 15 minutes recordings were assessed. The fetuses were further divided into two different gestational age groups (43 at 32–35 weeks and 43 fetuses at over 35 weeks). Comparison of facial expressions between these two groups was performed to determine changes in these expressions with advancing gestation. **Results** Mouthing was the most frequent facial expression at 30–40 weeks of gestation ($P<0.05$), followed by blinking. Both facial expressions were significantly more frequent than other expressions ($P<0.05$). The frequency of yawning was decreasing after 30 weeks of gestation ($P=0.031$). Other facial expressions did not change between 30 and 40 weeks. The frequency of yawning at 32–35 weeks was significantly more frequent than that at 36–40 weeks. **Conclusion** Our results suggest that the neurobehavioral regulation is the most important for fetal movement after approximately 30 weeks of gestation, and 4D ultrasound assessment of fetal facial expressions may be a useful modality for evaluating fetal brain maturation and development. Decreasing frequency of fetal yawning after 30 weeks of gestation may explain the emergence of distinct states of arousal.

ISP-45-8

Neurodevelopmental outcome of early-onset fetal growth restriction Yoshiaki Yamagata, Yumiko Doi, Maki Okada, Hiroko Hirata, Tatsushi Nakagawa, Jun Ito, Kei Hirabayashi, Fumitaka Numa *JCHO Tokuyama Central Hospital*

Objective Early-onset fetal growth restriction (FGR) is an important risk factor for neurodevelopmental delay. In this study early-onset FGR cases were investigated in terms of survival and/or neurodevelopmental prognosis. **Methods** Fifteen children with early-onset FGR before 30 weeks of gestational age were prospectively investigated. At 3-years of age, outcome was evaluated by their neurodevelopmental, cognitive and school achievement. In order to identify important prenatal determinants affecting neurodevelopmental outcome, factors such as gestational age, degree of growth delay, rupture of membrane, oligoamnios, and Apgar score etc. were evaluated. Furthermore, cased were divided into good or poor neurological outcome groups. The minimal length of pregnancy in good outcome group was 26 weeks. **Results** To date all children are alive. There is no specific prenatal factor associated with neurological development. Only 5-minute Apgar score was significantly lower in poor outcome group than in good outcome group. **Conclusion** Even in early-onset FGR case after 26 weeks of gestational age, good neurodevelopmental prognosis can be expected unless non-reassuring fetal status is recognized.

ISP-46-1

Maternal nutrient restriction (MNR) in guinea pigs leads to fetal growth restriction (FGR) with sex-related increases in tissue hypoxia Yohei Maki[1], Bryan Richrdson[2] *University of Miyazaki[1], Western University, Canada[2]*

Objective Maternal undernourishment can be causative for FGR with altered placental development. However, whether oxygenation is also decreased as seen with placental insufficiency-related FGR, remains unknown. We have determined the extent to which MNR in guinea pigs as a causative factor for FGR impacts immunoreactivity (IR) for Hypoxyprobe-1 (HP-1), a hypoxia maker. **Methods** Guinea pigs were fed ad libitum (Control) or 70% of the control diet pre-pregnancy switching to 90% at mid-pregnancy (MNR). Near term, HP-1 was injected into pregnant sows then necropsied for fetal body/organ weights, and brain, liver, kidney and placental tissues were assessed for HP-1 IR. Statistical significance was assumed for $p<.05$. **Results** FGR-MNR fetuses (8 males/8 females) were 36% smaller, while their brains and livers were 12% and 40% smaller, respectively. HP-1 IR was increased in the FGR-MNR fetuses by 2-4X in the brain and more so in males than females, by 4X in the liver and proximal convoluted tubules and 15X in the glomeruli but with no sex differences evident, and with no changes in the placenta. **Conclusion** MNR in guinea pigs results in asymmetric FGR with increased local tissue hypoxia in the brain which was more so in males than females, and in the liver and kidneys which was similar for males and females. As such, chronic hypoxia is likely to be an important signaling mechanism for the decreased fetal growth seen with maternal undernourishment. Moreover, there are sex-related differences in the brain which may contribute to the sex-specific expression of adverse neurodevelopment in FGR offspring.

ISP-46-2

The assessment of fetal development of growth restricted fetuses by evaluating fetal facial expressions with 4D HDlive sonography Hideyuki Chida, Akihiko Kikuchi, Gen Haba, Yuri Sasaki, Tomonobu Kanasugi, Chizuko Isurugi, Rie Oyama, Toru Sugiyama *Iwate Medical University*

Objective To assess whether the frequency of fetal facial expressions observed by 4D ultrasound and HDlive can be used as an auxiliary diagnostic measure for prenatal evaluation of fetal brain and central nervous system. **Methods** A prospective study has been carried out since July 28, 2015. Singleton pregnant women at 26 weeks or later of gestation from whom written consent were obtained were enrolled. The study was approved by institutional review board of our university. 15-minute observations of fetal facial expressions by Voluson E10 with RM6c probe were performed. FGR fetuses and AGA counterparts were scanned. After examinations, the recordings were examined to assess the frequency of seven types of previously-reported facial expression : blinking, mouthing, yawning, tongue expulsion, sucking, smiling, scowling. Non-parametric Wilcoxon rank-sum test and Kruskal-Wallis one-way analysis of variance by ranks test were used for inter-group and intra-group comparison, respectively. **Results** Twelve fetuses (FGR : 5, AGA : 7) were enrolled in the study. We noted a tendency for FGR fetuses to have less facial expressions than AGA counterparts. Statistically significant difference was seen in frequency of mouthing between the two groups. In AGA fetuses, the commonest facial expression was mouthing and was significantly more frequent than blinking and sucking. **Conclusion** FGR fetuses may seem to have less facial expressions than normal fetuses in our experience. We continue this study and the promising results could encourage the use of 4D HDlive ultrasound for neurobehavioral evaluation of the neurological condition in FGR fetuses.

ISP-46-3

A new method of predicting a brain hemorrhage risk in Fetal Growth Restriction Takahiro Minato[1], Takuya Ito[1], Naoaki Sato[1], Yoshitaka Kimura[1], Nobuo Yaegashi[2] *Tohoku University Graduate School of Medicine, International Disciplinary Biomedical Engineering[1], Tohoku University[2]*

Objective Fetal growth restriction (FGR) is associated with up to 10- to 30-fold increase in the risk of cerebral palsy (CP) at term. Intraventricular hemorrhage is a main factor of CP. Brain blood pressure is controlled by autonomic nerve system.Immaturity of this system is thought to cause failing in autoregulation of the blood pressure against the change in brain perfusion and results in the rupture of a vessel. We examined the association between maturity of autonomic nerve system and brain hemorrhage by using FGR model mice. **Methods** We used ICR pregnancy mice (term 19.0 embryonic day) under the approval of Institutional Committee. In 15.5 embryonic day, we tied the ligature at the bottom of the uterine artery and created FGR model fetuses by reducing the placental perfusion. We also created a control group. In 17.5 embryonic day, we measured short term variability (STV) as an indicator of autonomic nerve system maturity with a fetal ECG. Then we added intermittent hypoxic load like uterine contraction at delivery. We examined the association between STV and brain hemorrhage rate in the two groups. **Results** In comparison with the control, the hemorrhage rate in FGR fetus was significantly higher (70.6% vs 92.5% p=0.013). Also the hemorrhage areas per point in FGR fetus were larger than that of control (1.46mm^2/point vs 2.50mm^2/point p=0.018). Regarding the STV, it was significantly lower in FGR fetus than in control group (4.05msec vs 11.43msec p=0.015). **Conclusion** Immaturity of autonomic nerve system is a risk factor of hemorrhage and prone to be more severe. We can predict the risk of brain hemorrhage at delivery by using fetal ECG.

ISP-46-4

Changes of umbilical venous blood flow volume during pregnancy in light for date infants Hiroko Takita, Masamitsu Nakamura, Tomohiro Ooba, Tatsuya Arakaki, Junichi Hasegawa, Ryu Matsuoka, Akihiko Sekizawa *Showa University School of Medicine*

Objective To compare the changes of the umbilical vein blood flow volume (UVF) during pregnancy between normal growth infants and light for date infants (LFD), and to clarify the usefulness of UVF for the assessment of fetal and placental circulation. **Methods** One hundred thirty five pregnant women without any maternal complications were subjected after 20 weeks of gestation from 2015 to 2016. UVF was calculated by the following formula. UVF (ml/min) =3.14× (umbilical vein internal diameter (cm) /2)^2×Vm (cm/sec) ×60 (sec). We measured UVF in pregnant women of infants with normal growth and LFD. Additionally we assessed changes of UVF in cases that abnormal ultrasound blood flow such as absent or reverse blood flow of umbilical artery, and reverse of ductus venosus were detected. **Results** We examined infants with 96 normal growth and 40 LFD. In LFD, 6 cases showed abnormal blood flow. UVF in normal growth fetuses increased with advancing gestation {UVF=0.97×(gestational weeks)^2-30.7×gestational weeks+319.7}. The increase of UVF in LFD were significantly smaller than that in normal growth infants. In 6 cases with abnormal blood flow in LFD, UVF volume was much lower than the other cases. **Conclusion** The increase of UVF in LFD during pregnancy were smaller than that in normal growth infants. The changes of UVF in LFD was observed before detecting abnormal umbilical arterial blood flow. This fact indicated that the UVF would be a potential indicator in evaluating fetal circulation.

ISP-46-5

A case of fetal goiter after preconception hysterosalpingography using an oil-soluble iodinated contrast medium Yuri Sasaki, Akihiko Kikuchi, Masatoshi Murai, Tomonobu Kanasugi, Chizuko Isurugi, Rie Oyama, Toru Sugiyama *Iwate Medical University School of Medicine*

Fetal goitrous hypothyroidism is rare in euthyroid mothers. Fetal goiter is reported to be caused by excessive iodine exposure such as oral intake and an oil-soluble iodinated contrast medium. However, there has been only one case report of fetal goiter occurring after hysterosalpingography (HSG) using this medium in English literature. A 28-year-old primigravida woman was referred to our hospital at 29 weeks gestation for polyhydramnios. She had become pregnant immediately after preconception HSG. A large homogeneous goiter was identified in the anterior aspect of the fetal neck. Three-dimensional ultrasound revealed a large goiter with hyperextension of the neck. Maternal low thyroid function was confirmed by serum high TSH, low free T4 and low free T3 level. Prenatal ultrasound and MRI showed that the fetal goiter gradually decreased and became normal in size with no evidence of airway obstruction. A male infant was born at 38 weeks gestation. He had no goiter and a normal thyroid function. Interestingly, it turned out that although maternal urinary iodine concentration/creatinine excretions (UI/Cr) had been extremely high throughout from 31 weeks gestation to one month after delivery, its value progressively decreased in accordance with the decrease in size of the fetal goiter in the perinatal period. This UI/Cr decrease provides strong evidence that preconception HSG actually caused fetal goiter in the current case.

ISP-46-6

A case of mosaic trisomy 2 in amniotic fluid cultures with intrauterine fetal death at 29 weeks of gestation Tomomi Yamazaki[1], Maki Hyoudou[1], Norihumi Tanaka[1], Yasuko Yamamoto[1], Hiroshi Miyoshi[1], Yoshiki Kudo[1], Kenichiro Hata[2] *Hiroshima University[1], National Center for Child Health and Development[2]*

Mosaic trisomy 2 in amniocentesis is a very rare aneuploidy. The outcomes of pregnancies are quite variable, and spontaneous abortions are frequent. Trisomy 2p and trisomy 2q often exhibit growth and developmental retardation and multiple malformations. We experienced a case of mosaic trisomy 2 in amniotic fluid cultures resulting in death in utero at 29 weeks of gestations without obvious anomalies. A 41-year-old woman (gravida 2, para 2) had a dichorionic-diamniotic pregnancy. She underwent amniocentesis at 17 weeks of gestation because of elderly pregnancy and severe fetal growth restriction (FGR) of one of the twins. Cytogenetic analysis of amniotic fluid cells from the fetus with normal growth revealed a normal karyotype, whereas that from the fetus with FGR showed a mosaic karyotype 47,XX, +2 [2] /46, XX [23]. The FGR fetus with chromosomal abnormalities died in utero at 29 weeks of gestation. The other baby, a normal male infant (weight : 2536 g) was delivered by cesarean section and had Apgar scores of 9 at 1 min and 10 at 5 min. The stillborn infant (weight : 228 g) did not exhibit any major malformations, showing a lobed placenta and marginal insertion of the umbilical cord. In this study, we explored the cause of the normal phenotype, FGR, and intrauterine fetal death. We analyzed the distribution and frequency of the fetoplacental mosaic karyotype on the placenta, umbilical cord, and some parts of the fetus using array comparative genomic hybridization (aCGH). Additionally, we analyzed disease-associated genes using exome sequencing.

ISP-46-7

Discordant karyotype in monochorionic diamniotic twins : two cases report Atsuko Hichijo, Takashi Kaji, Naoto Yonetani, Minoru Irahara *Tokushima University*

Monochorionic diamniotic (MD) twins are usually monozygotic twins, that is, their karyotype is match. Nevertheless, some discordant karyotype of MD twins have been reported. As the rea-

sons there are such as twins generated via binovular follicle fertilization (dizygotic) and trisomy rescue. Case 1 was conceived MD twins spontaneously. But ultrasound showed the fetuses were discordant for gender. Delivery in pregnancy 38 weeks, they seemed normal girl and boy. The karyotype of umbilical cord blood was 46,XX [15] /46,XY [15] in the girl and 46,XY [21] /46,XX [9] in the boy. So we investigated their karyotype of buccal mucosa when 1-year-old. That was respectively 46, XX and 46,XY, was determined to be dizygotic MD twins. Case 2 was conceived MD twins by single embryo transfer with a frozen embryo in hormone replacement therapy cycles. In early pregnancy, nuchal translucency was found in one of the twins. The infant had multiple malformation such as both sides cleft lip and palate, double outlet right ventricle, single umbilical artery. However, the other had no obvious abnormalities. Delivery in pregnancy 33 weeks, the first baby without abnormality was healthy, the second died in even 1.5 hours after birth because of respiratory failure. Cytogenetic analysis of umbilical cord blood and the villi showed 46,XY in the first and 47,XY+18 in the second. We experienced discordant karyotype in MD twins. As the causes, dizygotic MD twins in case 1, trisomy rescue in case 2, were considered. We need to take into account the karyotype do not match in some of MD twins.

ISP-46-8

A case of ring chromosome 13 : a rare chromosomal aberration Haruka Gotoh[1], Yasuyuki Fujita[1], Yuka Sato[1], Saki Kido[1], Masahiro Hachisuga[1], Nobuhiro Hidaka[1], Masanobu Ogawa[2], Kiyoko Kato[1] *Kyusyu University[1], National Kyusyu Medical Center[2]*

We present a case of fetal ring chromosome 13. The patient was 23 years old and became pregnant spontaneously. She was referred to our hospital because of severe FGR and suspected oligohydramnios at 25 weeks gestation. On referral, a holoprosencephaly, VSD and hypoplastic right ventricle were additionally noted by ultrasonography. Amniocentesis was performed to rule out chromosomal aberration. Although the analysis by fluorescence in situ hybridization (FISH) showed no numerical abnormality, G-banding revealed a ring chromosome 13, which is 46, XX, r (13) (p13q32). We explained the result of chromosomal analysis to the patient and her family. At 41 weeks of gestation, she delivered a female baby, weighing 2240g, with a good condition. The respiratory status of the neonate was stable and discharged on 30 days after birth. A ring chromosome is rare chromosome aberration. The severity of clinical features depends on the size of the ring chromosome. The prognosis of the case with the ring chromosome 13 is not poor but this aberration is associated with development delay. In conclusion, we, obstetricians, should recognize that the ring chromosome cannot be detected solely by FISH analysis but G-banding, and that the clinical features of this chromosomal aberration is different from trisomy 13.

ISP-46-9

Two cases of large superficial vascular tumor on the fetal head : pitfalls in prenatal diagnosis Takaaki Shinagawa, Tomoaki Fukagawa, Masae Oshima, Daizo Hori, Kimio Ushijima *Kurume University Hospital, Maternal and Perinatal Medical Center*

Introduction Fetal superficial vascular tumors are rare, but prenatal diagnosis is crucial in order to evaluate fetal circulatory and home-coagulation disorders as well as determine appropriate delivery mode. We present two cases with large superficial vascular tumors on the fetal head, initially recognized in the late third trimester. Case 1 : At 36 weeks, fetal ultrasonography showed a cystic mass of 18×28 mm on the left forehead, with scattered dotted hyper echoic parts with acoustic shadows, but no Doppler signals, suggesting a tumor of non-vascular origin including teratoma. A 3,070g male neonate was delivered at 38 weeks by elective Cesarean section (C/S) because of previous C/S. A dark blue soft mass of 30x40x60 mm was found. Magnetic resonance imaging (MRI) showed vascular structures, but not fatty tissues, on T1-weighed image (WI) and dotted low intensity signals on T2WI, indicating thrombi. Venous anomaly was diagnosed. Case 2 : At 34 weeks, fetal ultrasonography showed a cystic mass of 20x35 mm on the right temporal lesion, with venous Doppler signals. High intensity signals were observed on T2WI of MRI, suggesting congenital hemangioma. A 2,750g male neonate was delivered at 37 weeks by emergency C/S. A dark reddish soft mass of 20×30×50 mm was found. Monotonous high intensity signals with flow voids on T2WI of MRI confirmed hemangioma. **Conclusions** Proper diagnosis requires the correct recognition of characteristics of vascular origin by Doppler ultrasonography and/or MRI, however, Doppler ultrasonography has some limitation regarding detection so MRI may be helpful to the prenatal diagnosis.

ISP-47-1

Survey of attitudes and awareness among pregnant women of the public cord blood bank system in Japan Yoko Nishida[1], Shunji Suzuki[2] *University of Human Arts and Sciences[1], Japanese Red Cross Katsushika Maternity Hospital[2]*

Objective The number of patients who require transplantation with hematopoietic stem cells (HSC) derived from cord blood has recently increased.The promotion of appropriate provision of HSC for transplantation Act was legislated during 2014. Based on this background, we administered a questionnaire to pregnant women to determine their awareness of the public cord-blood banking system. **Methods** The general outline of the banking system and the purpose of the questionnaire were explained to pregnant women who attended a maternity class during the second trimester of pregnancy. **Results** Among the 200 women, 113 (56.6%) responded to the questionnaire. Of these, 49 (43%) knew about the system, whereas 60 (53%) did not. Among the 49 who knew, 25 (51%) and 22 (45%) of them learned about it during a parents class or prenatal checkup, and via the TV/radio, respectively. **Conclusion** Face-to-face communication such as parents classes or prenatal checkups was more effective than mass media for informing the public about the cord-blood bank system. Previous studies have suggested that many individuals would like to help others through the public cord blood bank system. Therefore more aggressive activities in terms of enlightening pregnant women are needed from concerned healthcare professionals to build recognition of the public cord-blood banking system in Japan.

ISP-47-2

Cost of illness of the obstetrical diseases in Japan : a time-trend and future projection analysis Eijiro Hayata[1], Kunichika Matsumoto[2], Tomonori Hasegawa[2], Mineto Morita[1] *Toho University Omori Medical Center[1], Toho University School of Medicine[2]*

Objective Many problems associated with pregnancy and childbirth are associated with public health policies and require the attention of society as a whole. We chronologically observed the social costs for obstetrical diseases to obtain an overview of the changes and determine future prospects. **Methods** Using the cost-of-illness (COI) method based on official government statistics, we calculated COI for obstetrical diseases (ICD10 Code : O 01-99) from 1996 to 2014 and estimated future COI projections, i.e., for the period from 2017 to 2029. COI includes both direct and indirect costs (morbidity and mortality costs). **Results** COI

increased by 28.5% between 1996 and 2014 mainly because of increased direct costs during this period. COI of a single birth increased by 54.5% between 1996 and 2014. Our future predictions included an estimation of changes in the constant trends of COI, assuming that current trends of health-related indices would persist (estimated COI in 2029 : 250.6–307.0 billion yen, depending on the model used). COI per birth was estimated to increase until 2029 and (331,000–407,000 yen, depending on the model used). **Conclusion** We estimated that COI would remain unchanged in future, provided current trends of health indices remain constant. While the number of birth would reduce, the economic burden pertaining to each pregnancy and delivery would increase. Accelerated social participation of women and the promotion of measures to prevent the declining birth rate may lead to future increases in COI.

ISP-47-3

Perinatal intervention and care aimed for parenting support at a general obstetric unit Yoko Hasumi, Natsuki Nagashima, Kei Ameda, Ayano Fujihara, Kaoru Morishima, Nao Itaoka, Chiharu Ueshima, Maki Nakata, Minako Koizumi *Mitsui Memorial Hospital*

Objective To assess perinatal risk, intervention and care aimed for parenting support to prevent child maltreatment in an obstetric unit. **Methods** A retrospective study of childbirth cases from August 2015 to August 2016 was performed. **Results** There were 373 childbirth cases during the study period. In 13 cases, the mother had a nationality other than Japan, of which 2 cases were referred to the local public health center and the child guidance center. 9 cases had history of psychiatric complications, of which 2 cases were referred to psychiatric care. 7 cases had economic problems or lack of social and familial support, of which 1 case was referred to the local public health center. There were 3 cases in the last group in which the mother had unstable parenting skills or less interest for the child that could have benefited from referral to the local public health center. **Conclusion** In this study, 7.7% of the cases had at least one possible risk factor that might need parenting support intervention. In the cases in which the risk was evident, proper intervention was introduced. Parents might benefit if the less evident risks that could lead to neglect will be shared among the obstetric staff for further support in the obstetric unit.

ISP-47-4

Return to work after cancer treatment of gynecologic cancer Keiichiro Nakamura, Hisashi Masuyama, Naoyuki Ida, Chiaki Ohmichi, Junko Haraga, Takeshi Nishida, Tomoko Haruma, Tomoyuki Kusumoto, Noriko Seki, Yuji Hiramatsu *Okayama University*

Objective Gynecologic cancer is one of the most common malignant diseases in working-age women. This study investigated whether several characteristics influence return to work after treatment of gynecologic cancer. **Methods** We investigated the correlations between return to work and several characteristics in 213 gynecologic cancer survivors. Questionnaires were distributed to patients with gynecologic cancer who visited our university. The return to work was analyzed for correlations between cervical cancer group (n=113) ; endometrial cancer group (n=33) ; and ovarian group (n=33). The X2 test was used to determine the significance of the correlations. **Results** For all patients, the mean age at the time of diagnosis was 46.0 years. 155 patients (72.8%) were continued to be employed at the same workplace. 32 patients (15.0%) did not return to work and 26 patients (12.2%) changed job. >6-month reinstatement, reduced work time, and reduced personal income were significantly higher job change than same workplace (all ; $p<0.001$). Furthermore, there was a significant difference in >6-month reinstatement, reduced work time, and reduced personal income between ovarian cancer patients and between endometrial cancer patients at the same workplace (all ; $p<0.05$). **Conclusion** Ovarian cancer patients were the one of variable diseases likely to negatively affect return to work. Prevention of not returning to work may be one of the most important factors for positive relationships with the patient, employer, and society. Social support should be established to ensure satisfactory return to work.

ISP-47-5

Estimation of clinical data by artificial intelligence Yasunari Miyagi[1], Yuji Miyagi[2], Keiichi Fujiwara[3], Takashi Oda[4], Takahito Miyake[4] *Okayama Ohfuku Clinic[1], Shizuoka Cancer Center[2], Saitama International Medical Center[3], Miyake Clinic[4]*

Objective A sample size for clinical studies is determined by calculation according to α and β errors. Large sample size is required when the difference of two treatment arms is small. If the sample size can be reduced, the human resources, the financial resources and the time can be saved. We developed a new clinical sample estimation method by modifying the L1 type regularization for compressive sensing of artificial intelligence in computer science. **Methods** Suppose $X={}^t(x_1,\ldots,x_m)$, $Y={}^t(y_1,\ldots,y_n)$ where $m, n\in N$, $m>n$, $\forall x\geq 0$, $\forall y\geq 0$, $\forall S\in N\ (0,1)$ and $A\in S^{n\times m}$. When Y is known, the procedure of $\arg\min(\|Y-AX\|^2)/n+\lambda\Sigma|x_i|$ where $\lambda=0.01$, $\forall y\in X$ was carried out, resulting in acquisition of estimated X. **Results** Surviving analysis is presented. Estimated m patients time data of a group were obtained from n known patients time data under the condition of $m>n$, $2\times\max(\forall y)<\max(\forall x)$. The calculations were carried out for censored and uncensored data, independently. Then the distribution of the estimated surviving fractions was obtained by T times of repeated calculations. Applying the procedures to another group, the distribution of logrank P-values of T^2 sets was obtained. Finally, the probability less than 0.05 of logrank test was obtained. **Conclusion** A probability of a result of larger samples was successfully obtained by compressive sensing from smaller samples. This method would be useful for clinical studies of rare disease or of the delay of the enrollment. It would also be good to validate in a Simon's two stage phase II trial and also be helpful in establishing futility benchmarks.

ISP-47-6

Leptomeningeal metastasis from gynecologic cancers diagnosed by brain MRI Masafumi Toyoshima, Keita Tsuji, Shogo Shigeta, Hideki Tokunaga, Kiyoshi Ito, Hitoshi Niikura, Nobuo Yaegashi *Tohoku University*

Objective Leptomeningeal metastasis (LM) is characterized by diffuse or multifocal seeding of metastatic cancer cells on the leptomeninges. LM is rarely observed among gynecologic cancers, with only a small number of case reports in ovarian or uterine cancers. As gadolinium-enhanced magnetic resonance imaging (Gd-MRI) is highly effective for diagnosing LM, the aim of this study is to describe the clinical behaviors and outcomes of gynecologic cancer patients who were diagnosed with LM by Gd-MRI. **Methods** After securing institutional review board approvals, we retrospectively reviewed patient records from 2005 through 2015 in our gynecologic departments. LM diagnoses were made based on Gd-MRI with or without cerebral spinal fluid cytology. **Results** Eight patients were found to have LM from gynecological malignancies. Four patients had no specific findings in previous CT scan. Diagnosis of LM was made by only Gd-MRI in 6 patients and by MRI and cytology in 2 patients. Primary tumors included three ovarian, one tubal, one peritoneal, two endometrial, and one cervical cancer. Mean duration to LM diagnosis from first visit was 28 ± 20.7 months

(range, 6–57 months). Four patients underwent whole-brain radiation therapy, and no patients received intrathecal chemotherapy for treatment of LM. **Conclusion** Despite its rarity, LM should be suspected in gynecologic cancer patients presenting with unexplained neurologic manifestations. Gd-MRI of the brain and the spine is indicated as the high priority inspection for the diagnosis of this devastating complication. In the gynecologic cancer field, amassment of clinical data concerning LM is needed.

ISP-47-7

New challenges in the clinical development of drugs for rare cancers including gynecologic malignancies Tadaaki Nishikawa *National Cancer Center Hospital*

Objective Rare cancers such as uterine sarcoma are diagnosed in fewer than 6 per 100000 people in Japan each year. However, although each type of rare cancer accounts for less than 1% of all cancers, the frequency increases to 15–20% if all rare cancers are taken into account. Our first challenge was to plan investigator-initiated registration trials (IIRTs) using the Bayesian design and the rare cancer registry data for application to the Pharmaceuticals and Medical Devices Agency (PMDA) for approval of new drugs for rare cancers. Our second challenge was to establish an appealing Japanese producer for the development and worldwide provision of these drugs. **Methods** We launched a study team for the development of drugs for rare cancers as well as translational research (TR) funded by the Japan Agency for Medical Research and Development (AMED). Currently, we are planning IIRTs utilizing clinical trial networks and TR including patient-derived xenograft model technology. **Results** The IIRTs are proceeding. The first trial with nivolumab for clear cell sarcoma and alveolar soft part sarcoma started in 2016/4Q ; the second trial with a new agent for uterine carcinosarcoma will start in 2017/2Q or 3Q. **Conclusion** The clinical development of drugs for rare cancers is very difficult because of the rareness and the small pharmaceutical market. In particular, uterine carcinosarcoma is difficult to incorporate in clinical trials because of its characteristics, although a small number of chemotherapy options do exist. We must strive to establish clinical development platforms for rare cancers through collaborating with the PMDA, the AMED, pharmaceutical companies, and academia.

ISP-47-8

Features of the gestational sac-like structure in tubal ectopic pregnancy : a magnetic resonance imaging study Toshimichi Oonuma[1], Kimihisa Tajima[2], Tarou Ito[1], Aya Shirafuji[1], Hiroshi Kawamura[1], Akiko Shinagawa[1], Jin Takahashi[1], Yoko Chino[1], Koji Nishijima[1], Makoto Orisaka[1], Tetsuji Kurokawa[1], Yoshio Yoshida[1] *University of Fukui Hospital[1], Fukui Red Cross Hospital[2]*

Objective To evaluate the gestational sac (GS)-like structure in tubal ectopic pregnancy using magnetic resonance imaging (MRI). **Methods** Patients who underwent surgery for ectopic pregnancy and underwent MRI preoperatively from April 2004 to March 2016 were reviewed. **Results** The GS-like structure on MRI scan was detected in 48 cases, and chorionic villi was a pathological finding detected postoperatively in all these cases. On T2-weighted imaging scans, the typical GS-like structure of an iso-low/high intensity with three discrete layers of rings was detected in 17 cases. Intestinal tract (IT)-like findings showing a mixture structure of high and low intensity layers (IT-like rings) were detected in 25 cases. Other findings were observed in 6 cases. The average size of the rings was significantly different between the 3 rings and IT-like ring groups (20.5 mm and 27.4 mm, respectively ; $P<0.05$). The GS-like structure in which the wall was unevenly thickening was significantly different between the 3 rings and IT-like ring groups (35% and 92%, respectively ; $P<0.05$). Enhanced MRI was performed in 15 cases with 3 rings and in 24 cases with IT-like rings. On enhanced MRI scans, a papillary nodule in the GS-like structure was significantly different between the 3 rings and IT-like ring groups (33% and 67%, respectively ; $P<0.05$). **Conclusion** GS findings using MRI mostly include 3 rings and IT-like rings. Compared to 3 rings, the IT-like rings were larger, had an unevenly thickened wall, and enhanced papillary nodule.

ISP-47-9

Influences of obstetrics & gynecology simulation training on resident doctors Ikuji Shimazaki[1], Mina Morimura[1], Ryo Uemura[2], Reiko Tasaka[2], Sakika Yanai[2], Akihiro Hamuro[2], Takuya Misugi[2], Koyumi Enomoto[2], Daisuke Tachibana[2], Tomoyo Yasui[2], Toshiyuki Sumi[2], Masayasu Koyama[2] *Osaka City University[1], Osaka City University[2]*

Objective To protect womens health throughout their lives, it is important to train the doctors who engage in the womens medical issues. But at the early stages of medical internship the trainees have little chance to perform gynecological examination. It prevents young doctors from experiencing this practice. In our hospital since 2007 the attendance to the gynecological examination simulation training for the first-year resident (1st Y R) has been mandatory. Since 2010 the second-year residents get the chance to teach and learn about proper gynecological examination procedures in training their juniors as instructors (INST.) In this study, we will report on the overview of the simulation training and consider its impact on the residents. **Methods** Analysis was based on the results of the questionnaires and the interviews of the residents (1^{st} Y R n=15, 2^{nd} Y R n=6) considered qualitatively and quantitatively. **Results** All 1^{st} Y R and INST, answered that the gynecology simulation training were useful to their future practices. 60% of 1^{st} Y R and 50% of INST felt this simulation training had a considerable positive impact on choosing their own medical specialty. **Conclusion** Residents had little or no opportunities to do proper Gynecological examination because of its sensitive nature. The gynecology simulation training is expected to make the residents, both 1^{st} Y R and INST., want to regularly apply gynecological examination if it is necessary during their daily clinical practices. This study shows the possibility of positive effect of simulation training on the choice of obstetrics and gynecology as medical specialty.

ISP-48-1

A 9-years Experience of Induced second trimester abortion in a single tertiary refferal center Masayuki Endo, Kazuya Mimura, Takuji Tomimatsu, Shinya Matsuzaki, Keiichi Kumazawa, Yuri Matsumoto, Yasuto Kinose, Tadashi Iwamiya, Tadashi Kimura *Osaka University*

Objective To review cases of induced second trimester abortion in a single tertiary referral center **Methods** A retrospective analysis was conducted from a single, tertiary referral center of patient ended up with second trimester termination of pregnancy (TOP) from 2007 to 2015. **Results** 218 TOP cases were discussed. All cases were terminated due to either social, economical or both indications. The number of TOP cases has tended to increase through the years. 133 (61%) were 30s year old. 109 (50%) were terminated from 20 through 21 weeks of gestation. 179 (82%) were fetal abnormality cases. Almost half of fetal abnormality cases (92 out of 179) were categorized as multifactorial genetic diseases. The number of aneuploidy cases has tended to increase through the years. **Conclusion** Most of TOP cases were associated with fetal abnormalities. With them, the number of aneuploidy cases has tended to increase through the

years.

ISP-48-2

Is physical activity associated with pelvic shape during peri-adolescent period? Keiichiro Narumoto, Ken Joko, Motoi Sugimura *Hamamatsu University, School of Medicine*

Objective The proportion of pregnant females with anthropoid type of pelvis has increased. Pelvis rapidly grows during peri-adolescent period but determining factors for pelvic shape are unknown. The purpose of this study is to examine any correlation between physical activity (PE) and pelvic characteristics among children. **Methods** We have followed a population of 4th and 7th grade female students in 3 elementary and 3 middle schools from two rural areas in Japan since 2015, whose parents agreed on the participation to the study. We assessed physical activity with a questionnaire validated for Japanese children and classified intensity as "vigorous", "moderate" and "light." We evaluated pelvic characteristics by measuring (1) intertrochanteric distance (ITd), (2) distance between anterior superior iliac spines (ISd) and (3) external conjugate (EC) with external pelvimetry method. We regarded a sum of "vigorous" and "moderate" physical activity as "physical activity" and conducted multivariate analysis. **Results** This is a cross-sectional report from three-year prospective cohort study. Ninety-nine (55%) 7th grade and 46 (45%) 4th grade students participated. Seventy-two (72%) 7th grade students had had menarch, while none of the 4th grade students had. In 4th grade, there was no association between pelvic shape and physical activity. In 7th grade, menarch was positively associated with both ITd ($p<0.01$) and ISd ($p=0.03$), but not with EC ($p=0.15$). Physical activity was positively associated only with ITd ($p<0.01$). **Conclusion** Physical activity with vigorous and moderate intensity may be associated with transverse growth of the pelvis among the adolescent.

ISP-48-3

The etiology of primary amenorrhea of recent Japanese women : a single-center experience Mayuko Miyamoto, Kae Hashimoto, Erika Nakatsuka, Eriko Yokoi, Michiko Kodama, Kenjiro Sawada, Tadashi Kimura *Osaka University*

Objective Little is known as for the etiology of primary amenorrhea in recent Japanese women. The aim of this study is to evaluate the causes and characteristics of primary amenorrhea. **Methods** We reviewed the medical records of patients who visited to our hospital during 2010 to 2016. **Results** Forty nine women were diagnosed as primary amenorrhea during this period. The distribution of the courses were as follows ; hypo-normogonadotropic hypogonadism (central amenorrhea) (26.5%), post childhood cancer treatment (CCS) (22.4%), Mullerian agenesis (16.3%), Turner syndrome (12.2%), other gonadal dysgenesis (8.2%), androgen insensitivity syndrome (8.2%), imperforate hymen (6.1%), polycystic ovary syndrome (2.0%) and unknown (probably constitutional delay) (2.0%). The average age, height, weight and BMI (kg/m^2) at the first visit, excluding CCS and Turner syndrome were 17.2 years old, 159.6cm, 51.7kg and 20.2, respectively. Central amenorrhea includes anorexia nervosa (3/12), constitutional delay (3/12) and hypopituitarism after operation (1/12). Three cases were considered as constitutional delay, while it is uncommon in girls. Among these, one case has history of anorexia nervosa. The average BMI of unknown reason central amenorrhea was 17.9 and lower than other etiologies. **Conclusion** Patients with CCS is the most common, may reflecting the specificity of university hospital ; however the classification of central amenorrhea would not differ from previous reports. The lower body weight among central amenorrhea population suggests that low body weight in adolescence has negative effects on puberty.

ISP-48-4

Young Female athletes' insufficient recognition of their menstruation-associated problems Shiori Umemura, Koichi Iwasa, Taisuke Mori, Fumitake Ito, Hiroshi Tatsumi, Jo Kitawaki *Kyoto Prefectural University of Medicine*

Objective Dysmenorrhea and pre-menstrual syndrome (PMS) often affect young female athletes' performance negatively. Amenorrhea brings harmful effects on not only their present practice but also their later life. **Methods** This was a questionnaire-based study obtained from 448 young (age 10-20's, average 17.66 y) female athletes in and around our prefecture about menstruation-related problems. **Results** It turned out that 52 (11.6%) had amenorrhea, 152 (33.9%) were out of regular menstrual cycle, though a number of them answered that their cycle was "within normal range". Long-distance runners (n=112), who were required physically taxing training and strict weight restriction, showed lower BMI/body fat (19.5 vs. 21.66/22.7% vs. 25.15%), later menarche (13.19 y vs. 12.54 y), higher rate of amenorrhea (33.0% vs. 4.5%), and higher frequency of stress fracture (27.7% vs. 14.3%). Dysmenorrhea was seen in 265 (59.2%) athletes and among them 162 (61.1%) had moderate to severe symptoms. PMS symptoms were seen in 119 (26.6%) athletes. However more than half of athletes with symptoms avoided using pain killers, and only 17 (3.8%) have used oral contraceptives for pain control and/or cycle control. **Conclusion** A number of young female athletes, more than we expected, lacked accurate knowledge about menstruation and misunderstood how to deal with related problems, indicating urgent need for education to athletes and their trainers.

ISP-48-5

Retrospective analysis of 26 cases of congenital vaginal agenesis in the last 5 years Yasuhiko Kamada[1], Mari Ando[1], Chiaki Kashino[1], Hirofumi Matsuoka[1], Toru Hasegawa[1], Ai Sakamoto[1], Sayoko Kotani[1], Mikiya Nakatsuka[2], Yuji Hiramatsu[1] *Okayama University[1], Okayama University Graduate School of Health Sciences[2]*

Objective To assess and improve management of congenital vaginal agenesis (CVA) in women. **Methods** Clinical records of 26 cases of CVA managed at our hospital from 2011 to 2015 were analyzed. The study was approved by the IRB. **Results** Twenty-two cases (84.6%) were of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. At the first visit, women with a functional uterus were significantly younger than women without a functional uterus (15.8 ± 2.1 years vs. 21.0 ± 4.6 years [mean ± SD] ; P=0.00197). Sixteen women (61.5%) began nonsurgical vaginal dilation (Frank method), and 11 women (42.3%) underwent surgery. There was no significant difference in age at vaginoplasty between women with and without a functional uterus. Four women achieved a sufficiently long vagina for sexual intercourse only with daily nonsurgical dilation. For women with MRKH syndrome, we usually perform a laparoscopically-assisted, modified McIndoe procedure by using artificial dermis (an atelocollagen sponge) instead of skin grafts. In particular, we attempt to create a wider vesicorectal vaginal canal, and have continually improved the technique of vaginoplasty. Postoperative active vaginal self-dilation is important to maintain a functional neovagina. The length of the neovagina in 5 cases more than 12 months postoperatively was 9.3 ± 2.0 cm (range, 7-12 cm). **Conclusion** The timing of vaginal reconstruction for CVA should be individualized.

ISP-48-6

Case report : "Gourd-shaped sign" in ultrasonography might

be useful to diagnose imperforate hymen in adolescents with abdominal pain Hajime Ota, Takuma Matsuda, Masae Yamamoto, Kaoru Minowa, Risa Tsunematsu, Kanako Takimoto, Teppei Suzuki, Takeru Higa, Yasuhiro Yamamoto, Yoshiyuki Fukushi, Shinichiro Wada, Takafumi Fujino *Teine Keijinkai Hospital*

Background Adolescents with an imperforate hymen may present with low abdominal or anal pain and urinary retention as symptoms of molimina. These symptoms might mimic an acute abdomen and therefore, ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) scan are recommended for diagnosis. However, preferred diagnostic methods or characteristic ultrasonographic signs of imperforate hymen have not been reported in Japan. We report a case where the "gourd-shaped sign" seen in a transabdominal ultrasound helped to diagnose imperforate hymen. **Case Description** A 12-years-old girl who had not had menarche yet, was transported to the emergency department complaining of intermittent low abdominal and anal pain for 3 days. A transabdominal ultrasound found a large cystic pelvic mass, which was thought to be an ovarian tumor with possible pedicle torsion. A repeat pelvic transabdominal ultrasound (GE Healthcare, Voluson E8) was performed rather than a computed tomography (CT) to avoid radiation exposure. The ultrasound revealed a gourd-shaped, low echoic lesion extending from the intrauterine cavity to the vagina (gourd-shaped sign) in the sagittal view. The patient was diagnosed with molimina with imperforate hymen. Both ovaries and kidneys were intact. We punctured the hymen obtaining 550 ml of hematocolpometra and almost immediately, the abdominal pain resolved. Ten days later, we performed hymenotomy. **Conclusion** In adolescents with acute abdominal pain, transabdominal ultrasonography showing a "gourd-shaped sign" might be helpful to diagnose molimina with imperforate hymen and avoid unnecessary radiation exposure with a CT.

ISP-48-7

A case of vaginoplasty by Granjon's method for the treatment of recurrent restenosis following resection of transverse vaginal septum Yuko Hagiwara[1], Tomomi Nakamura[1], Shin Saitou[1], Taku Tsuburai[1], Yoshinobu Sugo[1], Sachiko Ohori[1], Keisuke Saitou[1], Hideya Sakakibara[2], Etsuko Miyagi[1] *Yokohama City University Hospital[1], Yokohama City University Medical Center[2]*

Introduction Transverse vaginal septum is a rare condition. It develops during embryogenesis when there is an incomplete fusion between the Muller duct and the urogenital sinus. Here, we report a case of Granjon's operation used for recurrent restenosis in transverse vaginal septum. **Case** When the patient was ten years old, she was diagnosed with transverse vaginal septum and hematocolpometra, and underwent vaginal septostomy. Following surgery, she had restenosis and received vaginal septectomy twice. After the third surgery, restenosis never recurred and a normal menstrual flow was restored. When she turned 15 years old, however, she saw a local doctor, complaining primarily of an increased amount of foul-smelling vaginal discharge. She was then referred to our department for evaluation of possible hematocolpometra. She was diagnosed with restenosis of a transverse vaginal septum and underwent Granjon's operation. After surgery, protease injection and FGF spray were administered to promote the epithelialization of the wounded area. Two months after the surgery, the patient has not had restenosis. **Discussion** There have been only a limited number of reports on the long-term prognosis of patients surgically treated for vaginal septum. Therefore, management protocols for these patients have not yet been established. Even if septum incision and drainage are performed, there is still risk of vaginal stenosis and adhesion which makes the second operation more difficult. **Conclusion** To prevent restenosis, it is critical to perform complete resection of the septum, vaginoplasty that minimizes mucosal damage, and postsurgical vaginal expansion.