Invited Lecture 1

Genome editing：from modeling disease to novel therapeutics

Chad Cowan

Department of Stem Cell & Regenerative Biology, Harvard University, USA

Our research is focused on understanding the molecular underpinnings of metabolic diseases such as type 2 diabetes mellitus（T2DM）and coronary artery disease（CAD）. Metabolic diseases such as T2DM and CAD are responsible for an increasingly large burden of morbidity and mortality worldwide, afflicting hundreds of millions of people. The development of new and effective treatments for these diseases requires the identification and validation in humans of novel disease mechanisms. Recent advances in human genetics have begun to explicate the heritable susceptibility to metabolic diseases. We seek to convert novel genetic findings into the knowledge needed to develop therapies for patients. Our approach to linking human genotypes to human phenotypes has three key steps. The first is to perform human genome editing to introduce disease-associated gene mutations and DNA variants into human pluripotent stem cells（hPSCs）. The second is to differentiate and engineer hPSCs into tissue types relevant to disease in order to develop ex vivo models of disease. The third is to perform functional assays in the genetically modified（and control）differentiated tissues to obtain pathophysiological insights. Once we have identified disease relevant phenotypes we plan to use our human cell-based models of disease to perform genetic and drugs screens to develop novel therapeutics.

Chad A. Cowan, Ph.D.

Principal Faculty
Harvard Stem Cell Institute

Associate Professor

Center for Regenerative Medicine, Massachusetts General Hospital

Department of Stem Cell and Regenerative Biology, Harvard University

Chad Cowan received his BA and BS, with honors, from the University of Kansas. He received his PhD, from the University of Texas Southwestern at Dallas, garnering the Nominata award for most outstanding thesis. He subsequently completed a Damon Runyon postdoctoral fellowship with Professor Douglas Melton at Harvard University. He was named a Stowers Medical Investigator in 2006 and in 2008, he became an Assistant Professor at Harvard University. He is currently an Associate Professor at Harvard University in the Department of Stem Cell and Regenerative Biology and Massachusetts General Hospital, with appointments in the Center for Regenerative Medicine, Cardiovascular Research Center and Center for Human Genetics Research. He is an Associate Member of the Broad Institute and a Principal Faculty member of the Harvard Stem Cell Institute where he directs the Diabetes Disease Program and the iPS Cell Core Facility. Professor Cowan has led or been a member of several large efforts to utilize stem cells to better understand disease, including the NHLBI's Next Gen iPS Cell Project and the Progenitor Cell Biology Consortium. In 2013, Professor Cowan received a Transformative Research Award from the NIH to create isogenic human pluripotent stem cell–based models of human disease mutations. More recently, Professor Cowan has focused on using genome–editing tools as therapeutics and as a co–founder of CRISPR Therapeutics hopes to see these discoveries translated into treatments or cures.

Invited Lecture 2

Chronic Pelvic Pain：What to do when everything else fails?

Juan Diego Villegas–Echeverri

ALGIA Advanced Laparoscopy and Pelvic Pain Center, Pereira, Colombia

Chronic pelvic pain is pain lasting longer than 6 months and is estimated to occur in 15% of women. The history and physical examination are crucial in evaluating a woman with chronic pelvic pain and must address all of the possible systems potentially involved in chronic pelvic pain, not just the reproductive system. Chronic pelvic pain is a complex condition that requires evaluation of the reproductive, gastrointestinal, urologic, musculoskeletal, psychological, and neurological systems. Usually, diagnosis and management entail identifying a network of disorders rather than a single cause of pain with a definitive cure. The multidisciplinary nature of chronic pelvic pain may complicate diagnosis and treatment. Treatments may be directed toward specific causes or may be targeted to general pain management. The most effective therapy may involve using both approaches and must include medical, behavioral, and surgical treatments. It is unfortunate that many women are left with the belief that if a laparoscopy fails to provide a diagnosis of a pain generator, then it means there are no diagnoses other than that the "pain is in her head," often disparagingly termed "supratentorial" by clinicians. This presentation aims to give a practical approach to deal with patients with persistent pelvic pain and to cope with difficult patients.

Juan Diego Villegas–Echeverri, MD, FACOG

Juan Diego Villegas–Echeverri was born in Pereira (Colombia), the heart of the coffee growing region in the country. After concluding high school with honors, he moved to Bogota, graduating as an MD at Colegio Mayor de Nuestra Señora del Rosario. Following the compulsive social service, he returned to Bogotá where he completed the Obstetrics and Gynecology Residency and graduated with Honors and as best resident of his promotion from the Hospital Universitario Lorencita Villegas de Santos–Universidad del Rosario. In 1998 he returned to his hometown and has been living in Pereira since then, with his wife and his two kids.

Early in his practice, Dr. Villegas–Echeverri realized that chronic pelvic pain patients did not have adequate medical care, not only locally but in the entire country. So, in 2004, he completed a fellowship at C. Paul Perry's Pelvic Pain Center in Birmingham, Alabama. Coming back from Alabama, he started up ALGIA, the Advanced Laparoscopy and Pelvic Pain Center, where he is currently the Scientific Director and has been taking care of patients from all over Colombia and some places in Latin America. ALGIA has developed not only a focused care center, but a fellowship in minimally invasive gynecologic surgery and pelvic pain to address the concern that most graduating residents in Obstetrics and Gynecology were not fully trained in modern MIS techniques and chronic pelvic pain.

Between 2001 and 2014, was appointed Chairman of the Department of Obstetrics and Gynecology at Clínica Comfamiliar.

He served as President of FECOLSOG, the Colombian Federation of Obstetrics and Gynecology, among 2012 and 2014. As President of FECOLSOG, he was designated 2012–2018 Executive Board member for FIGO, the International Federation of Obstetrics and Gynecology.

In 2016, Dr Villegas–Echeverri will act as President of the IPPS, the International Pelvic Pain Society, after performing as secretary, treasurer, and VP.

He is a recurrent speaker in multiple national and international conferences and has published in different medical journals and textbooks.

Invited Lecture 3

The Great Obstetrical Syndromes：a common pathway?

Gian Carlo Di Renzo

Centre for Perinatal and Reproductive Medicine, University of Perugia, Perugia, Italy

The opening editorial of the former Journal "Prenatal and Neonatal Medicine"（which eventually became the "Journal of Maternal Fetal and Neonatal Medicine"）, entitled 'Prenatal Medicine：The Child is the Father of the Man', articulated the agenda of the journal in 1996 and remains topical and visionary even today. The two themes of the editorial were the emphasis on the developmental origins of adult disease（also known as the "Barker hypothesis"）and the concept of the 'great obstetrical syndromes'. The first theme has gained worldwide acceptance thanks to imaginative epidemiologic studies conducted around the world. The concept has served to establish the International Society for Developmental Origins of Health and Disease, which holds congress and workshops on a regular basis where scientists and clinicians aim at understanding the mechanisms responsible for programming, and also, to translate what has been learned into clinical practice.

The second theme aimed at re-examining the nature of disease in obstetrics, and proposed that the clinical conditions responsible for maternal and perinatal morbidity and mortality is syndromic in nature. The term 'the great obstetrical syndromes' was coined to refer to conditions with the following characteristics：(1) multiple etiologies；(2) a long preclinical period；(3) adaptive in nature；(4) fetal involvement and (5) the result of complex interactions between the maternal and fetal genome and the environment. The complexity and importance of the interaction between the fetal and maternal genomes is now being explored. The definition of environmental exposure *in utero* is also a challenge. The current taxonomy of disease in obstetrics is based on the *clinical presentation* of the mother and/or fetus, and not on the mechanism of the disease responsible for clinical manifestation The diagnosis simply describes the clinical manifestations without consideration of the specific etiology

Accumulating observations now indicate that preterm labor, preterm premature rupture of membranes, preeclampsia, small for gestational age（SGA）, large for gestational age（LGA）, stillbirth, recurrent miscarriage and many other conditions that we deal with in clinical practice are not discrete entities, but are syndromes with more than one cause.

The purpose of the term 'the great obstetrical syndromes' was to try to explain the disappointing results when we tried to predict and prevent obstetrical diseases. It called attention to the idea that etiologic heterogeneity was followed by a common pathway. Implantation and immune tolerance, placental bed formation, balance between angiogenic and antiangiogenic factors, spiral arteries remodelling, oxidative stress are the paths which accomunate most of these late epiphenomena of pregnancy disease.

Medicine is now committed to identifying biomarkers to predict disease. This is also the case for maternal-fetal medicine and obstetrics. It is hoped that prediction will lead to prevention, however, this has not been the case in obstetrics thus far. A positive fetal fibronectin/PAMG-1 or a short cervix can identify patients at risk for spontaneous preterm delivery. We are yet to prove that prediction can be used

for prevention–perhaps such proof is around the corner.

The content of prenatal care is quickly changing from one in which the focus was on the prevention of maternal disease to one in which the goal is to improve also fetal health and prevent preterm birth, fetal death, SGA, LGA, congenital anomalies (aneuploidy) and other fetal complications. This will be the major challenge for what is better to call periconceptional medicine in the 21st century. Our discipline is unique in that it faces conditions that are not present in adult medicine–for example, monochorionic twinning associated with the twin–to–twin transfusion syndrome is a diagnostic and therapeutic challenge.

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GIAN CARLO DI RENZO
MD, PhD, FRCOG（hon）FACOG（hon）

HONORARY SECRETARY OF FIGO
University of Perugia, Perugia, Italy.

Prof Gian Carlo Di Renzo is currently Professor and Chair at the University of Perugia, and Director of the Reproductive and Perinatal Medicine Center, and Director of the Midwifery School, University of Perugia, in addition to being the Director of the Permanent International and European School of Perinatal and Reproductive Medicine（PREIS）in Florence.

After graduation cum laude at Medical School of the University of Padova, he was a research fellow at the Universities of Verona, Messina and Modena. After training at CHUV in Lausanne (Switzerland), at UCH in London（UK）, at the University of Texas in Dallas（USA）, and at the Catholic University in Nijmegen（NL）(1977–1982), he became a senior researcher at the University of Perugia. Since 1992 he is Professor of Obstetrics and Gynecology ; Prenatal Medicine and Director of the Perinatal and Reproductive Center at the University of Perugia. Since 2004 he is Professor and Chairman of the Department of Obstetrics and Gynecology at the University of Perugia.

He is founding member of the World Association of Perinatal Medicine (1991–), of the International Society of Ultrasound in Obstetrics and Gynecology（1991–）, and of the International Academy of Perinatal Medicine（2005–）.

He has organised more than 250 national and international congresses and courses.

From 1996 he is Editor–in–chief of the "Journal of Maternal Fetal and Neonatal Medicine", for Informa Health Care, UK, and since 1999 he is corresponding editor of the American Journal of Obstetrics and Gynecology.

Presidential Lecture

Towards establishment of kinder and less invasive surgical techniques

Keiichi Isaka

Tokyo Medical University

Laparoscopy is a technique that has long been utilized in the field of gynecology, mainly for examinations ; however, since the introduction of *in vitro* fertilization in 1978, it has been widely used by many gynecologists for oocyte retrieval. The use of laparoscopy almost disappeared when a method of oocyte retrieval was established using transvaginal ultrasound guidance. Although laparoscopy was on its way to becoming outdated, with the introduction of the TV monitor by the French surgeon Philippe Mouret in 1987, the technique once again gained a large amount of attention and began to be used widely in surgeries. With the introduction of the TV monitor, surgeries changed drastically from those in which the surgeon would look directly through the endoscope, to surgeries in which everyone could observe the operating field together. The fact that the surgeon no longer needed to operate the endoscope and could now use both hands for the actual surgery itself was a landmark change.

Laparoscopic surgery is less invasive than traditional open surgery and hence causes less pain ; therefore, it is thought to be a kinder surgical technique for patients. However, it is in fact not an easier technique for the surgeon to perform. Similar to open surgeries, it takes a considerable amount of training and effort for a surgeon to become able to perform safe and accurate laparoscopic surgeries. This is what is hindering laparoscopic surgery from completely replacing open surgery.

During the early days after the introduction of laparoscopic surgery, we encountered a patient who developed serious complications. This led us to begin our pursuit for safer and more outstanding laparoscopic surgery techniques, and after a long period of trial and error, we finally developed the abdominal wall lift technique for gasless surgery. We subsequently refined the technique over many years, from a single-hole technique to the present 1.5-holes subcutaneous steel wire lifting technique. The minimal-incision technique was also developed as a byproduct. Then, 20 years after introduction of the lifting technique, there was a sensational encounter with robotic surgery. From an economical point of view, these two techniques are at different extremes ; however, they are similar regarding the ease of learning their operating procedures. Regarding surgeons who learn laparoscopic surgery techniques, there are thought to be two types (of course, both types are assumed to perform safe and complete procedures). The first type are surgeons who acquire difficult skills through intensive training and who make the utmost effort to continue acquiring further high-level skills. The second type are those who aim to acquire simple skills that can easily be performed by anyone. I myself am of the latter type, and have aimed at simple procedures and surgeries that can be easily performed by surgeons. Since beginning laparoscopic surgery, I have aimed at developing surgeries that are kind to both the patients as well as the surgeons. During this process, the unexpected encounter of gasless surgery with the lifting technique and robotic surgery was the most fortunate event in my surgical career, and I believe that it is now my duty to standardize this technique and to pass it on to surgeons of the next generation.

A CURRICULUM VITAE

Keiichi ISAKA, MD, PhD

Birth Date and Place
6th of July 1951
Iwaki, Fukushima, Japan

Citizenship
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Education and Work Experiences
1976： graduated from Tokyo Medical University
1984： studied for one year at the University of Geneva for research of placental proteins
1985： studied for one year at the University of London for research of placental proteins
1991： Lecturer at the Department of Obstetrics and Gynecology of Tokyo Medical University
1994： Associate Professor at the Department of Obstetrics and Gynecology of Tokyo Medical University
2003： Professor and Chairman at the Department of Obstetrics and Gynecology of Tokyo Medical University

Medical Specialist
Specialist of Japan Society of Obstetrics and Gynecology
Specialist in technical authorization of Japan Society of Gynecologic Obstetric Endoscopy
Specialist for Gynecologic Oncology of Japan Society of Gynecologic Oncology
General Clinical Oncologist of Japanese Board of Cancer Therapy

1） Reconsideration of round spermatid injection into human oocytes (ROSI)

Atsushi Tanaka

St. Mother Hospital, Japan

Objective

Round spermatid injection（ROSI）has been considered ineffective for non-obstructive azoospermia due to its extremely low success rates, that is, no maturation arrest at the stage of second meiosis existed. In order to improve the success rates, we developed new techniques for selection of round spermatids and oocyte activation and evaluated their clinical usefulness. The study followed the Ethical Guidelines set by the Ministry of Health, Labour and Welfare of Japan after receiving the approval of our ethical committee.

Material & Methods

A total of 76 non-obstructive azoospermic men whose first Micro-TESE conducted by andrologists showed no testicular spermatozoa or late staged spermatids but had round spermatids found at our hospital received ROSI in 204 treatment cycles from September 2011 to March 2014.

Round spermatids, cytologically selected after thawing, were injected into ooplasm which was activated 10 minutes before the injection by electrical stimulation with an alternating current pulse of 2V/cm for 8s+direct current pulse of a single 1.2kV/cm for 99μs.

Results

The pregnancy rate per transferred cycle, miscarriage rate and birth rate in fresh embryo transfer cycles and freezing-thawed transfer cycles were［16.5%（20/121）, 65.0%（13/20）, 5.8%（7/121）］,［23.8%（10/42）, 50.0%（5/10）, 11.9%（5/42）］respectively. No abnormal karyotype and genomic imprinting abnormalities were identified in any of the newborn babies. All of 4 female and 10 male babies are healthy and no serious physical or cognitive disorders have been reported so far.

Conclusion

This study reconsiders ROSI and acknowledges its high potential to help many non-obstructive azoospermic men.

Atsushi Tanaka, M.D. Ph.D.
Saint Mother Hospital, Director

Education

1970–1976	Juntendo University School of medicine, Tokyo Degree：M.D.
1978–1982	Juntendo University Graduate School of Medicine Degree：Ph. D. in Medicine

Professional experience

1983–1989	Koshigaya city hospital, Chief Doctor of Obstetrics and Gynecology
1990–Present	Saint Mother Hospital, Director
2015–Present	Juntendo University Hospital, Visiting Professor of Obstetrics and Gynecology

Credentials and professional associations

1981	Board Certified in Cytodiagnosis by Japanese Society of Clinical Cytology
1987	Board Certified Obstetrician and Gynecologist by Japan Society of Obstetrics and Gynecology
1998–2000	Expert members of Scientific Committee of Ministry of Health, Labor and Welfare
2003	Board Certified in Clinical Genetics by Japan Society of Human Genetics
2005	Board Certified Reproductive medicine Doctor by Japan Society for Reproductive Medicine
2006–Present	Vice President of Japan Society of Fertilization and Implantation
2008	Chairman of the 26th Annual Meeting of Japan Society of Fertilization and Implantation
2009–2011	President of Japanese Institution for Standardizing Assisted Reproductive Technology
2011–Present	Global Fertility Academy Steering Committee Member
2015	Board Certified Obstetrician and Gynecologist medical instructor by Japan Society of Obstetrics and Gynecology

2）MicroRNAs in Female Reproduction

Sihyun Cho

Gangnam Severance Hospital, Yonsei University College of Medicine, Korea

MicroRNAs (miRNAs) are a class of endogenous, small, noncoding single-stranded RNA molecules approximately 22 nucleotides in length and estimated to regulate the translation of mRNAs in 30% of all genes in animals by inhibiting translation. Increased expression of a specific miRNA causes the repression of translation from the targeted mRNA, whereas down-regulation of the miRNA exerts the opposite effect. These modifications in mRNA translation determine distinct protein profile expression, affecting numerous molecular pathways and causing many different cellular and tissue changes. Emerging evidence indicates that miRNAs are expressed within the organs of the female reproductive tract where they function to regulate cellular pathways necessary for proper function of these organs. It is also evident that aberrant miRNA expression is associated with multiple human reproductive tract diseases including preeclampsia, endometrioid endometrial adenocarcinoma, uterine leiomyomata, ovarian carcinoma, endometriosis, and recurrent pregnancy loss. Specifically, several miRNAs are found to be involved in the pathogenesis of endometriosis, and they may hold promise for discovery of non-invasive diagnostic tool and development of new therapeutic approach for endometriosis.

Biography of SiHyun Cho., M.D., Ph.D.

SiHyun Cho is Associate Professor of the Department of Obstetrics & Gynecology, Yonsei University College of Medicine, Seoul, Korea. He graduated Yonsei University College of Medicine in 1997 and completed his Ob/Gyn residency training at Gangnam Severace Hospital, Yonsei University College of Medicine in 2004 and worked as a clinical and research fellow at the Division of Reproductive Endocrinology and Infertility, the Department of Obstetrics and Gynecology, Yonsei University College of Medicine until 2007. He was appointed as an Assistant Professor of the Department of Obstetrics & Gynecology, Yonsei University College of Medicine in 2009 and became an Associate Professor in 2014. His main research fields are pathophysiology and discovery of diagnostic biomarkers for endometriosis. Recently, he served as a visiting professor in the Department of Obstetrics, Gynecology, and Reproductive sciences, Yale University School of Medicine and focused his researches on the association of miRNAs and endometriosis, and potential role of endometrial stem cells in the field of regenerative medicine. He received numerous awards including the Best Research Paper Award (Reproductive Endocrinology & Infertility) and the Best Oral Presentation Award at the annual congress of the Koreans Society of Obstetrics and Gynecology in 2009 and 2015. He published more than 40 peer reviewed journals, has authored several book chapters and presented more than 40 times in both Korean and International academic meetings.

1）Physiology and pathophysiology of myometrial inflammatory reaction in parturition

Hiroaki Itoh

Hamamatsu University School of Medicine, Japan

Three major parts composed pregnant myometrium, i.e. cervix, isthmus, and corpus. After the onset of active labour with vigorous contraction of the uterine corpus, rapid ripening and dilatation of the uterine cervix as well as tremendous elongation of uterine isthmus forms the soft birth canal, followed by the delivery of the conceptus, when physiological intensive local leukocyte infiltration and rapid degradation of extracellular matrix proteins are usually observed in uterine cervix and isthmus but not in the uterine corpus. Imbalance of these exquisite changes of gravid uterus by physiological inflammatory reaction sometimes leads to sever postpartum hemorrhage（PPH）. For example, excess elongation of uterine isthmus, classically called as “pathologic retraction ring”, is eventually liked with laceration or rupture of uterine isthmus, causing massive PPH. The diagnosis and treatment of the former situation, laceration of uterine isthmus, will be discussed. We recently showed the intensive local leukocyte infiltration and rapid degradation of extracellular matrix proteins were also observed in the uterine corpus of refractory astonish bleeding characterized by soft and enlarged uterus with massive PPH. We named this abnormal leukocyte infiltration into uterine corpus as Acute Postpartum Myometritis（PAM）. The pathophysiology and future treatment of PAM will be discussed.

CV

1986. Graduated from Kyoto Univ Faculty of Medicine.
1986. Clinical Resident, Dep of Gyn & Obs, Kyoto University Hospital
1988. Clinical Staff, Dep of Ob & Gy, Hyogo Prefectural Amagasaki Hospital
1994. Assistant Professor, Kyoto Univ Hospital, Dep of Gyn& Ob
1996. Visiting Assistant Professor, Department of Ob & Gyn, University of Wisconsin-Madison, c/o Professor Ronald R Magness（two years）
2005. Associate Professor, Kyoto Univ Graduate School of Medicine, Dep of Gyne & Ob
2007. Clinical staff, National Hospital Organization Osaka National Hospital, Dep of Ob & Gyn
2008. Associate Professor, Hamamatsu Univ Hospital, Maternal-Fetal and Neonatal Care Center
2011. Clinical Professor, Hamamatsu Univ Hospital, and Director of Maternal-Fetal and Neonatal Care Center

Clinical subspecialty；Perinatal Medicine
Research interest；Developmental Origins of Health and Diseases（DOHaD）

2）Recent strategies and impact of a critical pathway for management of postpartum hemorrhage

Yong Won Park

Yonsei University Health System, Korea

Postpartum hemorrhage（PPH）is a major cause of maternal morbidity and mortality worldwide, and it is associated with approximately 1% of deliveries in developed countries. When intractable obstetric hemorrhage occurs, there is a higher risk of maternal mortality.

Causes of PPH are uterine atony, trauma, retained placenta, and coagulopathy, commonly referred to as the "four Ts".

Management options for PPH patients include uterotonics, bimanual uterine compression, uterine arterial ligation, B-lynch uterine compression sutures, uterine balloon tamponade, pelvic arterial embolization, and hysterectomy. However, arterial ligation and compression suture have a low success rate among inexperienced surgeons, pelvic arterial embolization requires high medical costs and sophisticated facilities, and hysterectomy has high morbidity and mortality and can be cause of fertility loss. In 1992, Bakri introduced intrauterine balloon tamponade for the treatment of obstetric hemorrhage. Uterine balloon tamponade is effective, simple to deploy, allows rapid placement, and can provide immediate results with minimal complications for PPH. Intrauterine balloon tamponade should be considered as the second-line treatment in massive hemorrhages that are unresponsive to uterotonics.

PPH, so called "a bloody business", requires immediate care involving multiple departments that obstetricians, emergency medicine specialists, anesthesiologists and nurses who have abundant experience with PPH. The specific critical pathway system for PPH, named the **S**everance **P**rotocol to save postpartum bl**E**eding through **E**xpeditious care **D**elivery (SPEED) was set up in Severance Hospital in 2009. The construction of comprehensive protocols and sharing of these protocols with the involved departments has enabled us to standardize treatment of patients with PPH and to maximize the multidisciplinary team approach.

CURRICULUM VITAE

NAME：Yong-Won Park, M.D., Ph.D.

PROFESSIONAL EDUCATION AND EXPERIENCES

Feb. 1976.	Yonsei University College of Medicine, Seoul, Korea Certified as Physician（No.16322）
Feb. 1980	Master of Medical Science（M.S.）, The Graduate School, Yonsei University, Seoul, Korea
Feb. 1981	Certified as Obstetrics & Gynecology（No.1513）
Aug. 1984	The Graduate School, Yonsei University, Seoul, Korea -Degree of Doctor of Medical Science（Ph. D.）

PROFESSIONAL EXPERIENCES AND ACADEMIC APPOINTMENTS

Mar. 1983-Feb. 1986	Instructor of Obstetrics and Gynecology Yonsei University College of Medicine, Seoul, Korea
Nov. 1986-Feb. 1988	Fellowship, Division of Perinatal Medicine Wesley Medical Center, University of Kansas
Mar. 1986-Feb. 1992	Assistant Professor of Obstetrics and Gynecology Yonsei University College of Medicine, Seoul, Korea
Mar. 1992-Feb. 1998	Associate Professor of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea
Mar. 1998-Present	Professor of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea
Mar. 2004-Feb. 2008	Professor and Chairman, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea

ADMINASTRATIVE RESPONSIBILITIES

Mar. 2001-Feb. 2003	Assistant director, Office of Planning and Coordination, Yonsei Medical Center, Seoul, Korea
Mar. 2003-Feb. 2004	Superintendent, Yong-In Severance Hospital, Kyungi-do, Korea
Aug. 2010-Jul. 2012	General Director, Severance Hospital
Sep. 2012-Aug. 2014	Director, Yongin Dongbaek Severance Hospital Construction Operations Division

ORGANIZATIONS

1993-1999	Board of Committee, Korean Society of Obstetrics and Gynecology
1999-2001	Board of Financial Committee, Korean Society of Obstetrics and Gynecology
1996-Oct. 1998	Secretary General, Korean Society of Perinatology
2000-2002	Head of Organizing Committee, Korean Society of Perinatology
2003-2005	Chairman of Financial Committee, Korean Society of Perinatology
1997-1999	Treasurer, Korean Society of Ultrasound
1997-2003	Board of Committee, Korean Society of Ultrasound
1998-2000	Editorial-in-Chief, Korean Society of Fetal Medicine
2001-2002	Chairman of Scientific Committee, Korean Society of Fetal Medicine
2003-2005	Vice-president, Korean Society of Fetal Medicine
2000-Present	Mediation Committee for Medical Litigation, Seoul District Court Research Committee
2002-2004	Head of Scientific Committee, Korean Society of Ultrasound in Obstetrics and Gynecology
2004-2005	Vice-president, Korean Society of Ultrasound in Obstetrics and Gynecology
2003-2005	Vice-chairman of Scientific Program Committee, Asian Oceanic Congress of Obstetrics and Gynecology
2003-	Vice-Chairman of Organizing Committee, 11th Congress of the World Federation for Ultrasound in Medicine and Biology
Nov. 2005-Oct. 2007	President, Korean Society of Ultrasound in Obstetrics and Gynecology
2006-2008	President, Korean Society of Fetal Medicine
Jun. 2006-Jun. 2008	Head of Scientific Committee, Korean Society of Obstetrics and Gynecology
Oct. 2009-Sep. 2011	Chairman of the Executive Board, Korean Society of Obstetrics and Gynecology
Oct. 2011-Present	Honorary Chairman of the Executive Board, Korean Society of Obstetrics and Gynecology

**Field of interest：Obstetrics and Gynecology
（Maternal-Fetal Medicine, High-risk pregnancies）

1）Optimizing Management for Patients with Advanced Ovarian Cancer

Yukio Sonoda

Memorial Sloan Kettering Cancer Center, USA

There has been much debate as to the optimal management for patients with advanced ovarian cancer. Traditional approaches have included primary cytoreductive surgery followed by chemotherapy. Recent studies employing the use of neoadjuvant chemotherapy have demonstrated comparable results to primary cytoreductive surgery. Some have questioned the overall survival outcomes reported with the neoadjuvant approach citing inferior survival outcomes than that which have been historically reported with primary surgical cytoreduction.

Proponents of primary cytoreduction have championed the use of aggressive surgical techniques to achieve complete gross resection of tumor. Complete resection of all visible disease has been associated with the best oncologic outcomes, and has become the new goal for cytoreductive surgery. However, despite the use of these aggressive approaches, a portion of patients may be left with suboptimal residual disease and may have benefitted from a neoadjuvant approach.

This presentation will focus on novel approaches to optimize management of patients with advanced ovarian cancer.

Dr. Yukio Sonoda is an Associate Attending Surgeon on the Gynecology Service, Department of Surgery at Memorial Sloan Kettering Cancer Center. He is also an Associate Professor in the Department of Obstetrics and Gynecology at Weill Cornell Medical College.

He completed his undergraduate studies at Johns Hopkins University in Baltimore, Maryland and obtained his medical degree from George Washington University in Washington, D.C. He did his residency in obstetrics and gynecology at the State University of New York at Buffalo and his fellowship in gynecologic oncology at Memorial Sloan Kettering Cancer Center. Dr. Sonoda spent one year at Centre Oscar Lambert and at Hôpital Edouard Herriot training with some of the pioneers in laparoscopic and radical vaginal surgery.

Dr. Sonoda is a board-certified gynecologic oncologist who specializes in the surgical treatment of known or suspected tumors of the female genital tract. He is Co-Director of the Pelvic Reconstruction Group and Director of Medical Students and Residents on the Gynecology Service. He has authored or co-authored over one hundred peer reviewed articles and written multiple book chapters.

2）Targeting Treatment Failure in Endometrial Cancer with Enhanced Staging：Sentinel Lymph Node Mapping and Infra-renal Aortic Lymphadenectomy

Robert W. Holloway

Florida Hospital Cancer Institute, University of Central Florida College of Medicine, Orlando, Florida, USA

Traditional pelvic and aortic lymphadenectomy for staging endometrial cancer provides prognostic information that also guides use of adjuvant therapies. Nevertheless, two separate phase III clinical trials in Europe failed to show a survival advantage for patients who underwent staging lymphadenectomies[1) 2)]. Furthermore, analysis of patterns of recurrence in surgically staged patients reveals that about one third of recurrences were retroperitonal or systemic with retroperitoneal, suggesting the possibility of "staging failures"[3)].

Sentinel lymph node（SLN）mapping has been increasingly reported in endometrial cancer and is now listed as an acceptable practice in the NCCN guidelines[4)]. SLN mapping is proposed as a staging method that may reduce morbidity, primarily lymphedema and nerve injury. Through enhanced pathology techniques of ultra-staging and immune-histochemical stains, more low-volume micrometastases（MM）and isolated tumor cell（ITC）metastases have been detected[5)]. Isolated infra-renal lymph node metastasis occurs in 1% to 3% of cases, and infra-renal lymphadenectomy has been accomplished in the majority of cases, despite obesity[6)].

Our data on SLN mapping and infra-renal lymphadenectomy in selected high risk cases indicates an upstaging of 16% clinical stage I cases due to low-volume metastasis（MM, ITC），and a doubling of the overall lymph node metastasis rate compared to standard lymphadenectomy. When pelvic nodes are positive, and aortic nodes are negative below the inferior mesenteric artery, there is still a 17% chance that infra-renal nodes have metastatic disease. Enhanced surgical staging and pathology may lead to appropriate use of adjuvant therapies that could improve survival in patients with endometrial cancer.

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BIOGRAPHY

Robert W. Holloway, MD, FACOG, FACS

Dr. Holloway is the Director of Gynecologic Oncology at Florida Hospital Cancer Institute in Orlando, Florida. He is a founding member of Florida Hospital's Global Robotic Institute, and Clinical Professor of Ob/Gyn at the University of Central Florida College of Medicine and the Florida State University School of Medicine. Dr. Holloway joined Florida Hospital in 1994 and lectures regularly at national and international conferences, serves as the principle investigator for several clinical trials in oncology, and conducts advanced training courses for robotic surgeons. The Florida Hospital Cancer Institute is the largest provider of cancer services in Florida. Florida Hospital was nationally ranked # 13 in Gynecology by the U.S. News & World Reports in 2015–16.

Dr. Holloway graduated from the University of Illinois, Urbana–Champaign with a bachelor's degree in Biology and the Vanderbilt University School of Medicine with M.D. degree. He completed Residency at the University of Alabama–Birmingham in Obstetrics and Gynecology, and Fellowship in Gynecologic Oncology at Georgetown University in Washington, DC. He is a Fellow in the American College of Obstetrics and Gynecology and the American College of Surgeons, and board certified in Gynecologic Oncology. His CV includes over 175 abstracts, scientific publications, and book chapters.

1）Native Tissue Transvaginal Repair of Apical Prolapse Using Uterosacral Ligaments

Bob L. Shull

Baylor Scott and White Texas A&M College of Medicine, USA

Apical prolapse in association with uterine prolapse or following hysterectomy often requires surgical management. I plan to discuss the transvaginal approach using uterosacral ligaments as the preferred technique for primary as well as recurrent prolapse. The discussion will include a demonstration of the surgical findings, the identification of surgical landmarks and a review of the potential intraoperative injuries, the postoperative care, and the success and failures as a function of time following surgery.

SHORT CV：

BOB SHULL, M.D.
Professor of Obstetrics and Gynecology
Baylor Scott & White Healthcare

Past President of the Society of Gynecologic Surgeons, The American Urogynecological Society, and of the International Urogynecological Society.

Life Time achievement award from both AUGS and IUGA

Author of more than 50 articles relating to the evaluation and surgical management of pelvic organ prolapse.

2）Is There a Place for Mesh in Prolapse Surgery? A International Update

Heinz Kölbl

Medical University of Vienna, Austria

Since 2002 more than 60 different meshes have been introduced in Urogynecology to reduce the rates of recurrence in prolapse surgery. Recurrence rates after native tissue repair range between 54–70% as the reason for this development. However, multiple alerts by the U.S. Food and Drug Administration have been released due to safety events and complications from mesh use.

Hence, the situation about the use of meshes worldwide especially in Europe remains unclear. Moreover, it is unclear how often and for which indications mesh is used and whether short term outcomes differ between mesh and non–mesh interventions and there remains a lack of knowledge about the long term sequele.

Looking at 15 countries worldwide 684,250 interventions for prolpase and 410,392 surgical for stress incontinence have been performed in 2012. The most frequent surgical interventions for prolapse surgery have been in the anterior compartment in 54%（15.7% mesh）, 43%（17% mesh）in the posterior compartment and 20% due to apcial defects（70% vaginal approach）.

Looking at the different countries between 2010 and 2012 we are confronted with both decreasing（e.g. USA 17%, Canada 20%）and increasing rates of mesh related prolapse surgery（e.g. Israel 14%, Sweden 54%）.

There is a shift from transvaginal mesh（−3.7%）surgery towards（laparoscopic）abdominal sacrocolpexy（+25%）.

The five fold variation in the rate of prolapse interventions within OECD countries and the significant heterogeneity（＞10 times）in the selection of prolapse procedures indicates a lack of uniformity. These findings might be due to the absence of clearly defined guidelines lacking sufficient evidence to give definite recommendation.

Heinz Kölbl M.D.,
Professor of Obstetrics and Gynecology
Chairman of the Division of Gynaecology and Gynecological Oncology
Dept. of Obstetrics and Gynaecology
Medical University of Vienna, Austria

Heinz Kölbl was born in Vienna, Austria in 1957. After his medical education from 1975–1981, he graduated in 1981. Between 1981–1983 he passed various medical education programs in Internal Medicine, General Surgery, Nephrology, Oncology, Neurology and Neonatology. His medical education in Obstetrics and Gynecology started in 1983 at the former 2nd Department of Obstetrics and Gynecology, University (Wertheim Clinic) of Vienna. His special fields of scientific interest were all forms of Gynecologic Surgery, Urogynaecology and Gynaecologic Oncology.

Since 1990 he was working as Associate Professor, and became Vice-head of the 2nd Department of Obstetrics and Gynaecology University of Vienna in 1992. Between 1994 and 1998 he was President of the Urogynecology Association of the German Society of Obstetrics and Gynecology. He is Professor of Obstetrics and Gynecology since 1996. Since October 2012 he is Chairman Division of Gynaecology and Gynecological Oncology, Department of Obstetrics and Gynaecology, Medical University of Vienna, Austria.

Heinz Kölbl was acting as guest and visiting professor in Los Angeles (University of California Irvine-Prof. Ostergard), Univeristy of Arizona (TusconCancerCenter-Prof. Hatch), and University of Perugia (Prof. Porena).

Prof. Kölbl received the degree of a honorary doctor by the University of Athens in March 2010. In May 2010 Prof. Kölbl received the TeLinde Lecture Award from the Society of Pelvic Surgeons.

Prof. Kölbl was involved in various clinical studies (e.g. Miraberon in OAB patients, and various oncological trials) as principal investigator.

International Workshop for Junior Fellows：
Keynote Lecture

Classification of Urgency of Caesarean Section

Sir Sabaratnam Arulkumaran

FIGO Immediate past president / Emeritus Professor of Obstetrics & Gynaecology, St George's University of London, UK

The fourth confidential inquiry into still births and deaths in infancy in the UK（1997）revealed that 50% and possibly another 25% of intra-partum deaths after 32 weeks were due to a) inability to interpret the CTG, b）failure to incorporate the clinical picture, c）delay in intervention and d）poor communication. In order to avoid the delay in intervention the RCOG（2010）introduced a sliding scale of decision to delivery interval and is given below. Abruption, cord prolapse, scar rupture, scalp blood pH ＜7.20 and prolonged deceleration ＜80 bpm for more than ＞six minutes falls into category 1. The maternal indications for category 1 CS, are hemo-dynamic disturbance following an antepartum hemorrhage related to pregnancy（e.g. placental abruption）.

Figure 1. A classification relating the degree of urgency to the presence or absence of maternal or fetal compromise

Urgency	Definition	Category
Maternal or fetal compromise	Immediate threat to life of woman or fetus	1
	No immediate threat to life of woman or fetus	2
	Requires early delivery	3
No maternal or fetal compromise	At a time to suit the woman and maternity services	4

This good practice paper jointly produced by the Royal College of anaesthetists on the subject of 'Classification of urgency of Caesarean section—A continuum of risk' was released in April 2010 but the concept was understood and followed in all good units long before this date. Some of the key points to note from the document are that 'all staff should be aware that, within each category, the degree of risk in each individual case can vary'. It also states 'this variance in degree of risk requires an individual, case-by-case approach, in deciding the specific decision-to-delivery interval（DDI）'. In case of fetal bradycardia one has to note that the outcome will depend on onset of bradycardia to delivery interval than decision to delivery interval.

It is well known that the delay in delivery is due to the delay to take the patient to the OT, possibly because of no organized lines of communication, which is better when a consultant is present. There have been studies from busy hospitals that better organization and training can enable immediate CS deliv-

ery to be accomplished within 15 minutes. The CTG patterns in labor can be sub-divided into as those representing acute, sub-acute, gradually developing or long standing hypoxic patterns. These patterns with the incorporation of the clinical features would define the degree of urgency which if followed would result in optimal outcome for the mother and the new-born. In Obstetric units' discussion of case examples by the multidisciplinary team of anesthetists, obstetricians, pediatricians and midwives would help to improve the efficiency, safety and quality of care. Case examples would be presented.

1）Indication and technique of cesarean section

Trevor Quiner

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ACOG

Cesarean delivery is the most frequently performed major surgery in the world. The ability to perform a safe abdominal delivery changed the field of obstetrics and has decreased maternal and perinatal mortality. There are a variety of indications for a cesarean delivery, but the most common diagnoses for primary cesarean section include arrest of labor, non-reassuring fetal heart tracing, malpresentation, fetal macrosomia, and maternal-fetal indications. There has been a steady rise in the number of cesarean deliveries throughout the world without a concordant decrease in perinatal morbidity and mortality. Conversely cesarean delivery carries a demonstrable risk for increased maternal morbidity and mortality. This morbidity includes more physical complications including an increased rate of excessive bleeding, infection, pain—and complications that are less apparent—effects such as decreased breastfeeding rates and maternal satisfaction. It is clear that cesarean delivery should be limited to instances where the benefits outweigh these real risks.

This review will briefly address two of the many potential methods for decreasing the burden of morbidity from cesarean delivery. First, decrease the number of cesarean deliveries by gaining a better understanding of the physiology and timing of normal parturition and adopting management practices that decrease the premature diagnosis of arrest of labor. Second, use evidence based practices that have the potential to decrease complications and comparative morbidity when performing indicated cesarean sections.

2）Indication and technique of cesarean section

Ji-Geun Yoo

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KSOG

The cesarean section rate in Korea was 36.9% in 2012, and it is much higher compared with OECD mean cesarean section rate. It has remained at around 36～37% since the cesarean section rate has risen to the highest of 43.0% in 1999. Older maternal age, increasing multifetal gestation due to popularization of IVF, increasing medico-legal problems, growing proportion of maternal obesity, and maternal request for cesarean delivery are causes of high cesarean section rate.

Common indications of cesarean section in Korea are previous cesarean section history, breech presentation, fetopelvic disproportion, and nonreassuring fetal heart rate pattern during labor.

In the 1980～90, many obstetricians used traditional incision in Korea. Now many obstetricians use Pfannenstiel or Joel-Cohen incision, and it seems it depends on the operator's choice or is individualized to patients. The lower cervical transverse uterine incision is mostly used, but vertical uterine incision is also used for rare cases.

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3）Indication and technique of cesarean section

Hsiu-Ting Tsai, Ming-Chao Huang, Yeou-Lih Wang, Jian-Pei Huang, Chie-Pein Chen

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TAOG

Taiwan's birth rate is one of the lowest in the world. In the past 10 years, the fertility rate was around 1 and the maternal mortality rate was around 7 per 100,000 live births. From 2004 to 2014, the rate of cesarean delivery rose from 33.1% to 36.2% in Taiwan. Our National Health Insurance defines twenty medical indications for C-section as fetal distress, dysfunctional labor, antepartum hemorrhage, malpresentation, cord prolapse, induction failure, active genital herpes, previous cesarean, prior uterine surgery, condyloma acuminatum infections, treatable fetal congenital abnormalities, extremely premature fetus, pelvic deformity, fetal macrosomia, obstructive delivery and so on.

In MacKay Memorial Hospital（MMH）one of the medical centers in northern Taiwan, there were about 4,100 live births annually. In the past 10 years, the average rate of C-section was 30.34%, the rate of cesarean hysterectomy was about 0.0004% and there was no maternal death. The common indications for c-section in 2014 were described as follows：35.95% for previous C/S, 24.37% for malpresentation, 12.38% for fetal distress, 11.11% for elective C/S and 8.7% for prolonged labor.

In MMH, a low-segment cesarean section is the most commonly used type of cesarean delivery. We performed C-section mostly as recommended evidence-based procedures which were described as bellow：single dose 1st cephalosporin as prophylactic antibiotics, Pfannenstiel skin incision, bunt, cephalad-caudad direction for expansion of uterine incision, bladder flap development, oxytocin infusion for prevention postpartum hemorrhage, cord traction for placental removal, uterine exteriorization or not, two-layer uterine closure, peritoneal closure and subcutaneous suture closure.

4）Cesarean section in Japan：Epidemiology, trends, and surgical procedures

Akihiko Ueda, Makoto Akiyama, Takashi Nakasuji, Shota Nii
JSOG

Recently, the rate of cesarean section（C/S）is increasing in developed countries. In Japan, it has increased from 8.5% in 1987 to 19.7% in 2014. Many theories have been proposed to explain this trend, including a decrease in vaginal births after cesarean delivery (VBAC) or breech presentation, an increased prevalence of high-risk pregnancies owing to factors such as an increase in maternal age, advancements in artificial reproductive technology, and liability concerns. In Japan, there were 2,363 facilities handling deliveries in 2014. The mean number of obstetrics and gynecologist doctors per facility was 2.5. The mean number of deliveries per facility was approximately 400 per year. In Japan, it has been quite common for small-scale facilities such as local hospitals and general practitioner offices to handle deliveries. In recent years, there has been a shift toward the centralization of deliveries taking place at large-scale perinatal medical centers. Nevertheless, there are still a large number of child birth taking place at small facilities which lack both pediatricians and anesthesiologists.

Under such circumstances, emergency cesarean section is sometimes difficult, particularly for very urgent cases, such as grade 1（urgent threat to the life or the health of a woman or fetus）. A decision-to-delivery interval of less than 30 minutes is desirable；however, only 30% of facilities and 47% of perinatal centers were able to achieve this time interval.

An absolute indication of C/S is limited to placenta previa, umbilical cord prolapse, etc. Twin pregnancy, malpresentation, pregnancy after C/S, nonreassuring fetal status, and arrest of dilatation are relative indications of C/S.

It is important to reduce the rate of primary cesarean sections, and to manage relative indications of C/S that are listed in the Guidelines for Obstetrical Practice in Japan. These guidelines were first published in 2008 by the Japan Society of Obstetrics and Gynecology, and are renewed every 3 years. Providing medicine in accordance with these guidelines will contribute to the improvement in the quality of and safety of perinatal care in Japan. To avoid unnecessary C/S, it is important to expand the indications for vaginal birth and to improve obstetric management.

Pregnancy after C/S is increasing owing to the increase in C/S rate. C/S can lead to thinning of the myometrium and adhesion of the pelvic peritoneum, and thinning of the myometrium can cause uterine rupture in subsequent pregnancies. Thus, careful selection of the surgical procedure, such as the type of myometrium incision, methods of suture, and use of antiadhesive material are important. VBAC is considered to have a higher risk of uterine rupture than C/S in pregnancies after C/S. The American Congress of Obstetricians and Gynecologists proposed expanding the indication of VBAC to avoid unnecessary C/S. Accurate repairment of the myometrium and antiadhesive procedures for C/S require further discussion. Regarding surgical procedures, we mainly focused on methods of myometrium incision and suturing, as well as the use of antiadhesive material.

International Workshop for Junior Fellows：
2. How to diagnose the uterine sarcoma

1）The diagnosis of Uterine Sarcoma

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ACOG

Uterine sarcomas account for only 6% of malignancies arising from the corpus but a disproportionate number of deaths. Many patients with uterine sarcoma present with metastatic disease at diagnosis and have a poor prognosis versus patients with endometrial adenocarcinoma. In contrast to endometrial adenocarcinoma, the early diagnosis of uterine sarcomas is hindered by the absence of symptoms, such as vaginal bleeding, and the low sensitivity of detection by endometrial biopsy. The diagnosis of uterine leiomyosarcoma is often made by pathologists after a hysterectomy has already been performed. Differentiating between benign and malignant uterine masses presents a diagnostic dilemma for clinicians who must decide whether uterine preservation is safe in young women that desire fertility preservation. Several preoperative screening modalities and patient characteristics have been proposed to predict patients at higher risk for a diagnosis of uterine sarcoma. These include age, preoperative hematology, serum lactate dehydrogenase levels, magnetic resonance imaging, and endometrial cytology. This review will discuss current insights in preoperative diagnosis of uterine sarcomas as well as the limitations of available data.

International Workshop for Junior Fellows：
2. How to diagnose the uterine sarcoma

2）Prognostic value of total lesion glycolysis on preoperative PET-CT in patients with uterine carcinosarcoma

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KSOG

Purpose：Metabolic tumour volume (MTV) and total lesion glycolysis (TLG) is measure of metabolic activity of tumours determined by fluorine-18 fluorodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography-computed tomography (PET-CT) images. The purpose of this study was to investigate the relationship between functional tumour parameter of preoperative PET-CT and clinical outcomes in patients with uterine carcinosarcoma.

Methods：We retrospectively reviewed patients with pathologically proven uterine carcinosarcoma who underwent preoperative ^{18}F-FDG PET-CT scans to evaluate the prognostic significance of PET-CT parameters and other clinicopathological variables. For each patient, we determined highest (SUV_{max} and SUV_{avg}), cumulative TLG, sum of all MTV, and compared their predictive value on recurrence, and the effects of pretreatment functional tumour activity on patient survival.

Results：Clinical data, treatment modalities, and results were reviewed for 30 eligible patients. The median duration of PFS was 13 months (range, 3 to 80 months), and twelve (40%) patients experienced recurrence. High value for the TLG (P=0.014, hazard ratio (HR) 132.764, 95% CI 2.697-6536.478), uterine serosal invasion (P=0.020, HR 18.451, 95% CI 1.574-216.308), and age (P=0.026, HR 1.095, 95% CI 1.011-1.186) were independent risk factors for recurrence in multivariate analysis. The Kaplan-Meier survival graphs showed that progression-free survival significantly differed in groups categorized based on TLG (P=0.004, log-rank test).

Conclusion：Preoperative TLG level on PET-CT had statistically significant association with recurrence in patients with uterine carcinosarcoma. Metabolic functional parameter can be useful quantitative criteria for disease prognostication in patients with uterine carcinosarcoma before treatment.

Keywords：FDG PET-CT・TLG・Recurrence・Prognostic・Uterine carcinosarcoma.

3）How to diagnose sarcoma?
The literature review and experience in Taiwan

Chin-Jui Wu, Wen-Chun Chang, Bor-Ching Sheu

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TAOG

The use of serum tumor markers and image for the early detection of uterine sarcoma has been limited because of their low sensitivity and low positive predictive value. Recently, researchers focused on statistically combined multiple factors to improve sensitivity and specificity. Retrospective chart review and literature review have been analyzed in women with uterine sarcoma. Preoperative ultrasound, computed tomography, or magnet resonance image（MRI）and serum marker have been studied alone and in combination in this setting. Complementarity and logistic regression analyses have been performed to assess those markers with the highest likelihood of improving sensitivity and specificity for early detection.

Analyses have shown that MRI or serum were not routinely checked in Taiwan. Ultrasound markers such as heterogeneous component, central necrosis, or resistance index are more likely to indicate sarcoma. Preoperative CA125 may elevated, but there is no standard for the cut-off value. Rarely, endometrial biopsy proves uterine sarcoma.

Currently, most cases are diagnosed by intraoperative frozen section or postoperative pathology. Statistic calculation of uterine sarcoma index with multiple markers is currently considered. We hope this could provide a cost-effective means of early detection and could significantly decrease the probability of surgical intervention for false-positive test results.

International Workshop for Junior Fellows：
2. How to diagnose the uterine sarcoma

4）Preoperative diagnosis of uterine sarcoma in Japan

Yusuke Shibuya, Gentaro Izumi, Takashi Ushiwaka, Ryoko Omura
JSOG

Uterine sarcoma is a rare tumor that accounts for 3%–9% of all uterine malignant neoplasms. Uterine sarcoma is divided into two major types, leiomyosarcoma and endometrial stromal sarcoma. In Japan, the median age at diagnosis of leiomyosarcoma and endometrial stromal sarcoma have been reported as 51 years old（range：29–84）and 53 years old（range：26–91）, respectively.

To decide on a course of treatment, it is important to differentiate between uterine sarcoma and uterine leiomyoma, which is a benign and common disease that occurs in 20%–25% of women over 35 years old. Uterine sarcoma and leiomyoma present the same symptoms, such as bulk–related symptoms, heavy or prolonged menstrual bleeding, and irregular genital bleeding. Both tumors also have the same structure, such as a solid and spherical mass developing from the uterine myometrium. Thus, a differential diagnosis between these two diseases may be complicated in some cases.

The standard treatment for uterine sarcoma is a hysterectomy. For long–term survival of uterine sarcoma patients, the tumor must be resected completely during the early stages by hysterectomy. Thus, misdiagnosis of uterine leiomyoma as uterine sarcoma must be avoided for patients who wish to have children.

Performing a surgical procedure for a uterine mass while overlooking the presence of uterine sarcoma also decreases a patient's long–term survival. The U.S. Food and Drug Administration is warning against the use of laparoscopic power morcellators in myomectomies or hysterectomies for the treatment of uterine leiomyomas, because the prevalence of unsuspected uterine sarcoma in patients undergoing a hysterectomy or myomectomy for presumed benign leiomyoma is one in 352 upon review of published and unpublished scientific literature.

There has been an increase in maternal age in recent decades, and the rate of children born from women over 35 years or older reached 27.6% in Japan in 2014. Thus, more women are diagnosed with benign leiomyoma at a childbearing age and hence require treatment with a myomectomy rather than a hysterectomy. This is the reason why more medical resources should be used for the diagnosis of uterine sarcoma in Japan.

In the investigation by the Japan Society of Gynecologic and Obstetric Endoscopy（JSGOE）, 99.5% of patients who underwent a hysterectomy or myomectomy had their tumors evaluated by magnetic resonance imaging（MRI）to confirm the positions and properties of the uterine masses. This may be owing to the low cost and easy access to MRI in Japan. Cytology of the endometrium and serum LDH（lactate dehydrogenase）are also evaluated depending on the situation. Furthermore, the prevalence of unsuspected uterine malignancies（not only uterine sarcoma）in patients undergoing a hysterectomy or myomectomy for presumed benign leiomyoma was 1 in 1,145 in a questionnaire survey targeting facili-

ties with technical authorization from the JSGOE. This prevalence is clearly lower than that of other studies.

Although the method of diagnosis of uterine sarcoma by MRI is established, in some cases it is still difficult to differentiate between uterine sarcoma and leiomyoma and choose hysterectomy or myomectomy, particularly in those involving women of childbearing age. In Japan, many studies were published regarding the diagnosis of uterine sarcoma using other methods combined with MRI, such as positron emission tomography (PET), etc. Methods to set the conditions as well as interpretation of the MRI were also studied in many institutions.

PET combined with computed tomography (PET/CT) is becoming a common imaging tool for malignancies. Many studies showed that fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET/CT is a useful tool for the diagnosis of uterine sarcoma. Some types of uterine leiomyoma take up ^{18}F-FDG ; however, better cut-off values of maximum standardized uptake values are discussed. Other groups demonstrated the usefulness of a new tracer for PET.

In this presentation, we will introduce the standard procedure for as well as new approaches for the diagnosis of uterine sarcoma in Japan.

International Workshop for Junior Fellows：
3. Duty and graveyard shift in OB/GYN

1）Duty and graveyard shift in OB/GYN

George Will Stone

National Capitol Consortium, Walter Reed National Military Medical Center

ACOG

Within the past twenty years increasing attention has been turned to the working habits of doctors in training. Until recently, it was not unusual to have resident physicians routinely working ninety to one hundred hours per week. Truly the term ‘resident’ comes from the expectation that the hospital served as the primary home to these young doctors. Fatigue had always been part of the work of medicine.

After the highly-publicized death of Libby Zion in 1984 due to a prescribing error in the context of thirty-six hour shifts, policy makers began paying attention. Legal and political pressure stemming from this incident has led to the creation of national work hour restrictions for resident physicians. Simply put, residents may only work eighty hours per week, with no single shift lasting longer than twenty-four hours.

The downstream effects of these changes remain controversial, and topics of vigorous debate. The limitation on consecutive hours worked has led to most residency programs developing shift work schedules, with separate day and night coverage teams. The remainder of this discussion will focus on the various implications of shift work policies, the current research about this approach to patient care, and how these training practices reflect postgraduate medical practice in Obstetrics and Gynecology.

2）Duty and Graveyard shift in OB/GYN

Eun Ji Nam

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KSOG

Resident duties are determined by a notification of the Ministry of Health and Welfare In Korea. Residency training is a four year course and duties are described by year. Minor procedures, inpatient cares, and assisting delivery are mostly covered by low-grade residents. Major procedures including delivery and outpatient cares are mostly covered by high-grade residents. More than 200 inpatients and 300 outpatients are seen and more than 120 cases of operation notes should be written during resident training. Academic activities are encouraged. More than 50 times of journal club participations per year are mandatory. More than one first-authored article should be written to have an examination for board certification.

Residency training in OB/GYN is considered hard work compared with those in other departments. The number of applicants failed to meet the quorum for 7 years. Decreased birth rate, low medical cost of OB/GYN procedures compared with prime cost, and the higher risk for law suit are the main reasons. Graveyard shift and duty of emergency room have been highly dependent on residents, however, things have been changed recently. From 1st year resident in 2014, resident duty hours must be limited to 80 hours, inclusive of all in-house call activities and all moonlighting by following policy from the Ministry of Health and Welfare. Resident must be scheduled for a minimum of one day free of duty every week and a maximum of 24 hours of continuous duty in hospital.

International Workshop for Junior Fellows：
3. Duty and graveyard shift in OB/GYN

3）Survey of Obstetrics and Gynecology Resident Working Hours in Taiwan

Po-Kai Yang, Hong-Nerng Ho, Yu-Shih Yang

National Taiwan University Hospital, Taiwan

TAOG

With advances in managed care and organized health care systems, overnight shifts have become the norm in large health-care centers. Granted, the obstetrical profession has a long history of being constantly on stand-by due to the nature of the childbirth, but the effect of extended working hours on resident performance has been the focus of guidelines ever since the Accreditation Council for Graduate Medical Education（ACGME）released their Standards for Resident Duty Hours in 2003.

In Taiwan, the Ministry of Health and Welfare released the first guidelines for residents working hours in 2013 in an official document titled "Guidelines for Resident Labor Rights." In it, they limited the working hours of residents to a maximum of 88 hours per week. A normal workday should be 12 hours or less with an extension for duty shifts not exceeding 36 hours at the maximum. A 10 hour rest period is required between working shifts. However, the highest goal will be a working week of less than 88 hours and a maximum shift length not extending past 24 hours. Resident working hours will officially be an item on the upcoming hospital evaluation in 2015, and hospitals will be graded on where the resident working hours lie on the spectrum. In this report, we evaluate the working hours of the obstetrics and gynecology residents in the major teaching hospitals of Taiwan.

4）Duties and graveyard shifts of obstetricians and gynecologists in Japan

Masaru Hayashi, Saori Aoki, Satoshi Nakagawa, Yoko Furutake
JSOG

Obstetricians and gynecologists in Japan, particularly obstetricians that are able to undertake overnight work are decreasing. The reasons are as follows：a decreasing number of new obstetrics and gynecology (ob-gyn) doctors, an increasing number of female doctors who are unable to work at night, and withdrawal from overnight work of older obstetricians. Furthermore, in Japan, there are fewer ob-gyn doctors in rural areas than in urban areas.

In 2015, the number of live births in Japan was about 1 million. Of these, 19.7% were born by caesarean section. According to an investigation by the Japan Association of Obstetricians and Gynecologists (JAOG), there are 1,074 hospitals that perform deliveries in Japan, and there are about 200 facilities that are handled by only one or two doctors. The average number of deliveries per hospital is about 500 per year.

Characteristics of the night duty system in Japan include the following points.

1) Apart from genital perinatal medical centers, obstetricians in many facilities perform night duty or on-call duty alone.

2) Obstetricians may be contacted by the hospital regarding a patient they are in charge of, even if they are off duty.

3) During an operation, obstetricians are often solely in charge of the anesthesia.

4) Because of the insufficient number of doctors, obstetricians often need to perform emergency duties.

5) Even after a full day-time and night-time shift, most ob-gyn doctors are required to work full-time on the next day.

6) Ob-gyn doctors working at university hospitals usually undertake night-time work not only in their own university but also in adjacent hospitals.

The conditions of the duty system of Japanese obstetricians are harsh in many areas. As a result of various actions by the JSOG and JAOG, the labor circumstances have improved slightly in the past 10 years. For example, the number of deliveries per doctor decreased from 98 in 2008 to 80 in 2015. The mean number of overnight duties decreased from 6.3 times a month in 2007 to 5.8 times in 2015. Estimated working hours decreased from 317 hours a month in 2008 to 296 in 2015. However, this improvement is insufficient, and still exceeds the limit of the Japanese Labor Standards Law (190 hours/month), and may lead to psychological disorders, cardiac disorders, or even death owing to overwork. In some hospitals, owing to the insufficient number of doctors, obstetricians are required to administer spinal anesthesia by themselves, and they even undertake emergency care at night. We hope that the labor environment of obstetricians will improve continuously and rapidly.

1）CERVICAL CANCER MANAGEMENT IN CAMBODIA AND ITS CHALLENGES

Seang Tharith

University of Health Sciences, Cambodia

Low-income countries are more affected than high-income countries. Indeed, 80% of the cervical cancer cases occurring in developing countries usually lead to death because it is diagnosed too late for treatment to be effective.

In Cambodia Hospital-based cancer registries（2001-2003）, showed that cervical cancer is the most common type of cancer among women and is a major public health concern.

Recent studies show that cervical cancer has a higher overall mortality among women than maternal mortality. It is estimated that in Cambodia 1,500 women are newly diagnosed cervical cancer cases and at least 900 women die of cervical cancer each year. Evidence shows that cervical cancer is preventable if detected at early stage and WHO recommends cheap and effective screening and treating methods for developing countries. Such a program is urgently needed in Cambodia to decrease mortality.

Over the last decade, only a number of mainly private providers have started to provide gynecological check-ups to help control cervical cancer.

The Ministry of Health is increasingly giving priority to cervical cancer from 2005, MoH staffs went to a training in Bangkok on VIA and cryotherapy/LEEP.

Since 2012, a screen and treat（VIA+Cryotherapy）project has been conducted as well as priorities of the Department of Preventive Medicine.

That is why 3 projects（VIA+Cryotherapy）funded by World Bank have been done and one new project（VIA+LEEP）with the collaboration of SCGO and JSOG has been conducted recently in PPSEZ from October 2015 to 2018.

In waiting for Standard operational procedure from these implementing, The MoH/Preventive Medicine will to be taken those strategies in the near future for national wide.

Curriculum vitae

Name： Seang Tharith
–Assistance to Dean of Faculty of Medicine of the University of Health Sciences.
–General Secretary of Cambodian Society of Gynecology and Obstetric
Education：
–1980–1981：Medical Doctor graduated from Faculty of Medicine, Phnom Penh, Cambodia
–1985：Internship of OBGYN residency in Viet Nam.
–1994：IEC and Population Program for Family Planning in Indonesia.
–1999：Hospital Administrative management program in France.
–2000：Professor of OBGYN Department of the University of Health Sciences, Cambodia
Occupation：
–1980–1991：Head of the Gynecology and Obstetric, the Department of Hospital 7 January.
–1991–2001：Head of Gynecology and the Obstetric, the Department of National Mother and Child Health Centre.
–From 2002–2012：–Vice Dean of the Faculty of Medicine of University of Health Sciences
–From 2012：Director of OBGYN Residency.
Director of OBGYN Department at University of Health Sciences
–General Secretary of SCGO
Work Experiences：
–Vice President of Cambodian Medical Association
–Vice President of Cambodian Society of Gynecology and Obstetric
–Country Coordinator Committee Member of Global Fund for Fighting HIV/AIDS, Tuberculosis and Malaria.
–Member of Medical Education of ASEAN.
–DSMB Member in trial therapy research on HIV with Tuberculosis
–Thesis Supervisors and mentor of the University of Health Sciences

2）HEALTH INDICATORS OF MONGOLIA

Bayasgalan Gerel

First Maternity Hospital, Ulaanbaatar, Mongolia

Research goal

To determine main health indicators of health sector in our country.

Study result

Population of Mongolia reached 2 million 930.3 thousand by the end of 2013, which means an increase of 62.5 thousand people or 2.2% compared to the previous year. Considering the age structure, 27.4 percent of children are under age 15. The life expectancy of the population in 2013 to 69.11 in previous increased by 0.4.

For the last ten years total of 615.9 thousand infants were born although there was a twofold reduction in birth rate from 35.3 per 1,000 population in 1990 to the minimum rate of 17.8 in 2005, it has been 27.5 per 1,000 population in 2013.

By the Millennium Development Goals Mongolian health has three goals, there are to reduce child mortality, improve maternal health and to combat HIV/AIDS, tuberculosis.

Maternal mortality rate was 176.0 per 100,000 live births in 1996 and were high in 1990s and as a result of implementing two strategies to reduce maternal mortality rates, which conducted in 2001–2010, maternal mortality rates significantly decreased to 42.6 in 2013. In 2013, 13.7% of pregnant women had any co-morbidity diseases of urogenital system –39.6%, of circulatory system –16.8%, of digestive system –12.8%, of respiratory system –8.0%.

The percentage of pregnancy complications such as pre-eclampsia and, eclampsia was 44.6% and 0.2% respectively. First and secondary failure to progress in labor was in 41.8% which is the most common complication during birth. Postpartum hemorrhage accounted for 81.3% of all post-delivery complication.

In 2013, active monitoring rates of infants and children under-five years were 99.6% and 96.1% respectively.

Conclusion

1. Mongolia has become a country with moderate level of maternal mortality and has fully accomplished the objective to reduce under-five mortality rate for 4 times.

2. The three leading causes of infant mortality were disorders derived from the perinatal period, diseases of respiratory system, and congenital abnormalities or genetic disorders

3. Compared to the previous year, deaths caused by diseases of respiratory system and diseases derived from the perinatal period have decreased.

BAYASGALAN GEREL

Education

2007
Health Sciences University of Mongolia. Academic Training Center（PhD）degree in Medicine

2002–2003
Health Sciences University of Mongolia, Ulaanbaatar city
Master's Degree in Medicine

2001–2003
Academy of Management
Manager of Management Science

2000–2002
Health Sciences University of Mongolia. Academic Training Center.
Obstetrician and Gynecologist

2001
University of the Philippines Manila. Department of Obstetrics and Gynecology（1 month）
Training of Trainers in the Management of Complications of Pregnancy and Childbirth

1–14 June, 2000
Health Sciences University of Mongolia. Department of Obstetrics and Gynecology
Project Planning Process Training in Reproductive Medicine

1989–1997
Health Sciences University of Mongolia, Ulaanbaatar city
Medical Doctor. Bachelor Degree in Medicine

1997 up to present
Maternity Hospital number 1
Obstetrician and Gynecologist

1979–1989
High Russian school number 3. Ulaanbaatar city
Secondary education

Work experience

First Maternity Hospital, Ulaanbaatar, Mongolia
Ob&Gy, Head of Training and Foreign relation department *Jun 2010–current*

First Maternity Hospital, Ulaanbaatar, Mongolia
Deputy director *Jan 2006–Jun 2010*

First Maternity Hospital, Ulaanbaatar, Mongolia
OB&GY, Maternity departments Jun 1997–Jun 2010

Professional memberships

From 2003
Member of Mongolian Federation of Obstetrics and Gynecologist

3）Maternal Health Service（MHS）in Myanmar：Challenges of Low Resource Countries

Mya Thida

Obstetrical & Gynaecological Society of Myanmar Medical Association, Myanmar

The Republic of the Union of Myanmar has a population 51.49 million. 70% resided in rural area and 13.9 million are of reproductive age. High Maternal Mortality Ratio, Infant Mortality Rate and Under Five Mortality Rate are the critical challenges. MHS provided at 1,684 Rural Health centers and 8,420 Sub-centers by 21,435 midwives and 30,000 auxiliary midwives for 64,134 villages shows inadequate health workforce. It is also important to improve distribution and retention of existing midwives and to facilitate shifting of non-midwifery task to other health care providers and to transform training to improve "hands-on" skills and promote evidence-based practice, and increase managerial capacity at different levels of the health system to ensure quality of care. Out of seven signal functions of basic emergency Obstetric care, midwives can provide only 4 functions and need to improve technical competency of remaining 3 signal functions to save mother and baby. Low utilization of MHS due to maternal health knowledge gap is also one of major challenges. Abortion related maternal death；the third most common cause of maternal death is related to high unmet need of contraception of 17.7% and low contraceptive prevalence rate of 41%. Increased availability and uptake of contraception and right-based informed choice is a key for prevention of unplanned pregnancy. Another challenge is the availability and quality of information about maternal and perinatal mortality. Current maternal death review on available data cannot reflect the picture of whole country and also need to include responses to prevent the avoidable death.

Biography of Professor Mya Thida

Professor Mya Thida is the current president of Obstetrical and Gynaecological Society of Myanmar Medical Association (MMA), serving previously as a medical educator as well as a service provider and researcher for maternal and child health in medical universities and various states and regions in Myanmar for 33 years. She is also an Executive Committee member and Treasurer of MMA. She graduated in 1980 and started specializing in Obstetrics & Gynaecology after attaining Master degree in OB–GYN in 1987. She became a member of Royal Collage of Obstetricians & Gynaecologists (UK) and of Faculty of Family Planning and Sexual Health (UK) in 1996. She got Doctorate degree in Ob–Gyn in 2002 and became a fellow of Royal College (UK) and of Faculty of Sexual and Reproductive Health (UK) in 2007 and 2008 respectively. She also finished Diploma Medical Education in 2004 and worked as the head of Department of Obstetrics & Gynaecology in University of Medicine 1, University of Medicine 2 and University of Medicine Magway. She has mentored over 20 researchers and authored 47 papers. She is also a member of editorial board of Myanmar Medical Journal of Current Medical Practice.

1）MANAGEMENT OF DIFFICULT ISSUES IN MULTIPLE PREGNANCIES

Tony Tan Yew Teck[1,2,3,4]

Raffles Hospital, Singapore[1],

Singapore General Hospital and National University Hospital, Singapore[2],

Obstetrical and Gynaecological Society of Singapore, Singapore[3],

Maternal Fetal Medicine Committee, Asia–Oceanic Federation of Obstetrics and Gynaecology, Singapore[4]

INTRODUCTION

The main causes of mortality and morbidity in multiple pregnancies are prematurity, fetal anomalies, intrauterine growth restriction, specific consequences of monochorionic twins, and higher order multiple pregnancies.

PREMATURITY

Prematurity in multiple pregnancies is due to premature labour, premature rupture of membranes and iatrogenic premature delivery especially for preeclampsia which occurs earlier and more severely in multiple pregnancies. Prediction of premature labour can be achieved through a combination of ultrasound cervical length measurements and biochemical tests. There is no evidence to show that cervical cerclage in multiple pregnancies reduce premature delivery. Appropriate timing of corticosteroid administration reduces the risks of morbidity due to prematurity, and appropriate monitoring after corticosteroid injection reduces the need for inappropriate iatrogenic premature delivery. Weekly intramuscular progesterone injections or daily vaginal micronized progesterone pessaries have been shown to reduce premature labour in singletons, but do not work in multiple pregnancies. Delayed interval delivery may be an option to prolong the pregnancy for the remaining fetus（es）when the first twin is delivered vaginally before 30 weeks. Selective fetocide of the previable and severely growth restricted fetus in a multiple pregnancy with severe and early onset preeclampsia may reverse the process of preeclampsia, allowing prolongation of the pregnancy for the other appropriately grown fetus（es）with little risk to maternal well being.

FETAL ANOMALIES

Fetal anomalies are more common among multiple pregnancies. Combined with the increased technical difficulty of assessment in twins, fetal anomalies may be more commonly missed in multiple preg-

nancies. A screening scan at a good tertiary center is recommended for multiple pregnancies. Selective fetocide of the anomalous fetus may be considered for selected lethal and non-lethal conditions.

INTRAUTERINE GROWTH RESTRICTION

Intrauterine growth restriction (IUGR) is more common in multiple pregnancies, necessitating a need for closer surveillance. Difficulty in monitoring and the need to consider both the IUGR and appropriately grown fetuses often makes the decision to deliver a challenging one to make. It is especially difficult to manage IUGR in monochorionic twins. The Gratacos' classification of selective IUGR in monochorionic twins may be useful in guiding the management of these special groups.

SPECIFIC COMPLICATIONS OF MONOCHORIONIC PREGNANCIES

Monochorionic pregnancies are at higher risk of miscarriages, prematurity and IUGR than di- or multi-chorionic pregnancies. The presence of vascular anastomoses in monochorionic placentas specifically puts the pregnancy at risks of twin-twin transfusion syndrome (TTTS), twin anaemia polycythaemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence and the high risk of death or neurologic damage to the co-twin in the event of the death of one twin. Close surveillance for TTTS, TAPS and IUGR by ultrasound and Doppler techniques allows early detection of such complications in some cases, and hence earlier intervention which includes amnioreduction, selective laser ablation of placental vascular anastomoses, even closer surveillance with ultrasound and cardiotocography (CTG), or early delivery.

HIGHER ORDER MULTIPLE PREGNANCIES

Higher order multiple pregnancies are at high risk of miscarriage, prematurity and intrauterine growth restriction. Improvements in assisted reproductive techniques and its governance reduce the occurrence of higher order multiple pregnancies. When the multiple pregnancy is that of quadruplets or higher order, multifetal pregnancy reduction (MFPR) is an option to reduce the risk of miscarriage and extreme premature labour and the complications of severe prematurity.

Short Curriculum Vitae
Dr Tony Tan Yew Teck

Short CV

Dr Tony Tan is a Consultant Obstetrician & Gynaecologist and Maternal Fetal Medicine Specialist at Raffles Hospital since Nov 2006. He is also a Visiting Consultant to the Departments of Obstetrics and Gynaecology in both Singapore General Hospital and National University Hospital, was the President of the Obstetrical and Gynaecological Society of Singapore（OGSS）from April 2013 to April 2015, and is now the Immediate Past President of OGSS, and the chairman of the Maternal Fetal Medicine Committee of Asia–Oceanic Federation of Obstetrics and Gynaecology.

Dr Tan was trained in fetal medicine and fetal therapy at the renowned Queen Charlotte's Hospital, London under Professor Nicholas M Fisk. He subsequently trained with Dr Kurt Hecher, Hamburg, Germany in laser treatment for TTTS and acardiac twins. In KK hospital till November 2006, he was responsible for the monochorionic twin pregnancy clinic and First Trimester Screening clinic.

His areas of interests include monochorionic twins and its manifestations of twin twin transfusion syndrome and acardiac twins, fetal screening, fetal therapy, threatened and recurrent miscarriages, and strategies to reduce unexplained stillbirth.

In his clinical work, he does general obstetrics and gynaecology（ie. deliveries and gynaecological operations）, and also specialises in the management of high risk pregnancies. Dr Tan is skilled in all aspects of clinical management of multiple pregnancies including prenatal diagnosis, surveillance, treatment of complications and reducing risk of premature delivery. He is also a specialist in fetal screening（eg. first trimester screening, fetal anomaly scan, growth scan and Doppler studies）, invasive diagnostic procedures（eg. amniocentesis, chorionic villus sampling, fetal blood sampling）and fetal therapy.

Summary of qualifications

16 June 1993	Degrees of Bachelor of Medicine and Bachelor of Surgery（MBBS）, National University of Singapore, Singapore
24 June 1996	Designated Factory Doctor（compressed air works）
30 April 2000	Member, Royal Australian and New Zealand College of Obstetricians and Gynaecologists
19 May 2000	Member, Royal College of Obstetricians and Gynaecologists
31 July 2000	Degree of Master of Medicine（Obstetrics and Gynaecology, National University of Singapore）
2003	Specialist Accreditation Board
2013	Fellow, Chapter of Obstetricians and Gynaecologists, Academy of Medicine Singapore
2014	Fellow, Royal Collge of Obstetricians and Gynaecologists

2）THE NEW TSUNAMI：OBESITY IN PREGNANCY

Ravi Chandran

Asia-Oceania Federation of Obstetrics & Gynecology, Malaysia

Obesity and its sequelae may prove to be the greatest threat to human lifestyle and health this century. Previously thought to be a problem of developed nations, this obesity "tsunami" is set to sweep into nations that are transitioning to first world economies and the Asia-Oceania region is no exception. No practising Obstetrician can avoid facing the long list of medical and surgical complications associated with obesity in pregnancy and many of these have been addressed eloquently elsewhere. This paper will limit itself to some of the current controversies such as the increased risk of congenital anomalies in fetuses of obese women and the difficulties associated in their detection, the association with childhood obesity and lifelong nutritional maladaptation and finally, the potential link with autism spectrum disorders in the offspring of obese women.

CURRICULUM VITAE

NAME
CHANDRAN, Ravi

REGISTRATION
Malaysian Medical Council
General Medical Council UK

QUALIFICATIONS
Member of the Royal College of O&G UK（MRCOG）1988
Masters in O&G（MOG）1989
Fellow of the Royal College of Physicians Ire（FRCPI）1998
Fellow of the Academy of Medicine Malaysia（FAMM）1999
Fellow of the Royal College of O&G UK（FRCOG）2001

SUB-SPECIALITY
Maternal-Fetal Medicine

CURRENT POSITION
Consultant OB/GYN Gleneagles Hospital Kuala Lumpur

PREVIOUS POSITIONS
1990-1991：Research Fellow King's College London
1991-1992：Research Fellow University of Oxford
1992-1993：Lecturer National University of M'sia
1993-1996：Associate Professor National University of M'sia

Dr Ravi Chandran is a Consultant Obstetrician and Gynaecologist at the prestigious Gleneagles Medical Centre in Kuala Lumpur Malaysia. He obtained his Membership of the RCOG UK in 1988 followed by sub-speciality training in Maternal Fetal Medicine at King's College Hospital London and the John Radcliffe Hospital at Oxford University. He pursued an academic career at the National University of Malaysia and during his tenure as Associate Professor, was involved in research activities culminating in publications in leading journals including the BJOG, AJOG and Lancet. In 1998 he was made a Fellow of the Royal College of Physicians of Ireland and in 2001 was elevated to the Fellowship of the RCOG UK.

Over the last 15 years, he has been actively involved in the AOFOG and joined the Executive Board as Treasurer in 2009. As Vice-President in 2013-2015, he played a leading role in the review of the AOFOG Constitution. He is currently the President Elect and will assume the Presidency of AOFOG in 2017.

Asian session collaborating with AOFOG：
Minimally Invasive Gynecologic Surgery（MIGS）

1）Laparoscopic Tissue Rentrieval Techniques－ Issues, Advances & Solutions

Prakash Trivedi

Trivedi's Total Health Care Pvt. Ltd. & Akkar, Rajawadi Hospital, Mumbai, Jaslok Hospital, Mumbai, India

Uterine morcellation of presumed leiomyomas inadvertently results in an increase in morcellated uterine leiomyosarcoma（ULMS）. Morcellation alters the natural course of ULMS, leading to an increased incidence and earlier recurrences. Recurrences following tumor morcellation are significantly more likely to occur in the peritoneum. Since there is no reliable method for predicting whether a woman with fibroids may have a uterine sarcoma, the US FDA（Food and Drug Administration）discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy（US Food and Drug Administration, http://www.fda.gov/Medical Devices/Safety/Alerts and Notices/ucm393576.htm in 2014）. In the wake of recent ban on usage of power morcellation by US FDA, & recent studies on the incidence of ULMS we would like to review the facts and thoughts on ULMS & morcellation techniques.

We introduce a technique of in－bag morcellation, done on 33 consecutive patients for TLH & Lap Myomectomy thus avoiding spillage of tissues in the peritoneal cavity and spread of an undiagnosed disease or cancer or sarcoma.

CV–Dr Prakash Trivedi

- **Director**：Dr. Trivedi's Total Health Care Pvt. Ltd. & Aakar IVF Centre, Urinary Incontinence correction Centre, Mumbai.
- **Immediate Past President IAGE** 2013~15 Indian Association of Gynaecological Endoscopy
- **FOGSI President** 2015~16
- **Scientific Program Chair, AAGL Global MIG Conference** 1st time ever in Asia and in India from 2nd to 5th June 2016 to Mumbai.
- Regional Ambassador for the FIGO Adolescent, Preconception and Maternal Nutrition Initiative, 2015~18
- Prof. & Head of Dept. at Rajawadi Municipal Hospital, Mumbai
- Endoscopist and Urogynaecologist at Jaslok & BARC Hospital
- Vice President FOGSI 2008, Infertility Committee Chairperson 2003~07
- Published **8** outstanding teaching books, **15** educational CD & DVD.
- Guest articles in **30** books & **72** publications in National & International journal
- Received "Young Scientist Award" 1995 & "Senior Scientist Award" 2005 & Health minister award for research
- Pioneer in Gynaec. Endoscopic Surgery, Urogyn. Surg & IVF–ICSI Consultant & Performed > 30000 Gynaec Minimal Access Surgery

2）Robot assisted radical hysterectomy with complete resection of uterosacral ligament（Modified total mesometrial Resection, TMMR）for the cervical cancer

Yoon Soon Lee

Kyungpook National University Hospital Medical Center, Daegu, Korea

The ontogenetic compartment theory means that cancer growth is confined to compartment from a common primordium in embryonic development. Tumor spread may be through ontogenic compartment but inhibit at the compartment border.

Conception of TMMR procedure is not familiar to gynecologic oncologist, but Hòckel introduce the ontogenetic compartment theory, however most of gynecologic oncologist does not agree with his theory. This procedure is En bloc resection of the uterus, proximal vagina, and mesometrium, transection of the rectouterine dense subperitoneal connective tissue above the level of the exposed inf. hypogastric plexus and extended pelvic/periaorticlymphadenectomy preserving the sup. hypogastric plexus.

Our modified TMMR means additional complete resection of uterosacral ligament which insert to coccygeous and sacrospinous ligament complex or pyriformis, sciatic foramen, sacrum. It is difficult to identify the insertion area of uterosacral ligament, so we inject the methylene blue dye to cervix, and then identify the blue stained ligament more easily.

First separated mesoureter, IHP and Hypogastric nerve from uterosacral ligament, then cut at level of insertion to coccygeous and sacrospinous ligament complex or pyriformis, sciatic foramen or sacrum. After that cut the rectovaginal ligament with preservation of branches of rectal artery.

Whole procedures are performed by delicate movement of robotic system more easily.

We introduce our modified TMMR procedure with da Vinci robotic system.

CURRICULUM VITAE

Yoon S Lee has pioneered in laparoscopic oncologic surgery in the Korea.
He has experienced of in live surgery at foreign country about robot gynecologic oncologic surgery and single port laparoscopic radical hysterectomy. He is the first robotic surgeon who had experience of over 300 robotic surgeries in Korea. He had experience of 430 cases of robotic surgeries. And he has many lectures for laparoscopic radical hysterectomy and robot oncologic surgery for all around world. And he taught the techniques of the robotic radical surgery at his hospital for Asian Drs, from Japan and Twain, Turkey. He had published a book about single port surgery for the first time in the world."Mastering single port gynecologic surgery using by OCTOport" in year of 2014.

Kyungpook National University Medical Center, Gynecologic Cancer Center

Current appointment (position and institution):
Professor
Chief of Gynecologic Cancer Center, Kyungpook National University Medical Center, School of Medicine, Daegu, Korea

Short scientific biography:
1999. July; Visiting Professor at Dep. of Gynecologic oncology, Friedrich Schiller University, Jena, Germany
1996–1998; Research fellow in Washington University, Department of gynecologic oncology, St. Louis. USA
2000 to present; Professor in Kyungpook national university, school of medicine
1997–2000; Associated professor in Kyungpook national university, school of medicine
1993–1997; Assistant professor in Kyungpook national university, school of medicine

Main scientific publications:
Presentation; SGO Montz Symposium, Invited lecture
SGO 2012 Annual Meeting March 24–26, 2012, Texas, Austin

3）Minimally Invasive Surgery in Asia

Joo-Hyun Nam

Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

During the past three decade, the most dominant change in gynecologic surgery is minimally invasive surgery including laparoscopic and robotic surgery. Laparoscopic surgery has been proven to have many benefits over laparotomy in the surgical management of benign and malignant gynecologic diseases, such as less postoperative pain, less blood loss, better cosmetic outcome, shorter recovery time and hospital stay with less complications and morbidity. With accumulation of surgical experience and the advances of surgical techniques and instruments, laparoscopic surgery is becoming the preferred and standard surgical option for patients with even gynecologic cancers. According to the currently existing data in the literature reported by several expert surgical teams through the world, it was proven that laparoscopic surgery for gynecologic cancers is feasible and safe both surgically and oncologically. However, the main cause of limited use of laparoscopic surgery is difficulty in learning, in other words, stiff learning curve.

To maximize the benefits of minimally invasive surgery by reducing the number and size of laparoscopic ports, laparoendoscopic single-site surgery（LESS）in which procedures are performed through a multichannel single port made within the umbilicus was introduced and increasingly and widely used. It is potentially more advanced minimally invasive surgery, however, it is more difficult to learn.

Recently robotic surgery is introduced and becoming more and more popular because of short learning curve. Compared to the laparoscopic surgery, robotic surgery is much easier to learn even in difficult gynecologic cancer surgery because of dexterity of robotic arm and better 3-D surgical view. However it still has many disadvantages and limitations, such as no tactile sense and very high cost of Da Vinci system and instruments, particularly in developed countries. In Asia, still many middle and low income countries are not economically enough to run the robotic surgery considering cost-effectiveness and the finance of medical insurance system. To my speculation, laparoscopic surgery would be continuously the more dominant paradigm of surgical management of gynecologic diseases in a couple of decade in these countries.

`Brief Curriculum Vitae

Joo-Hyun Nam, M.D., Ph.D.

Dr. Joo-Hyun Nam is a professor of the Department of Obstetrics and Gynecology at University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Korea. He is the current president of ASGO（Asian Society of Gynecologic Oncology）and the President of AOFOG（Asia Oceania Federation of Obstetrics and Gynecology）and a council member of International Gynecologic Cancer Society (IGCS) a founding board member of Asia Pacific Association of Gynecologic Endoscopy and Minimally Invasive Therapy (APAGE). He was the president of Korean Society of Gynecologic Oncology (KSGO) and Korean Gynecologic Oncology Group (KGOG) and Korean Society of Gynecologic Endoscopy and Minimally Invasive Surgery（KSGE）and the chairman of Executive Board of Korean Society of Obstetrics and Gynecology（KSOG).
Dr. Nam graduated from Medical School of Seoul National University in Seoul, Korea and completed his residency at Seoul National University Hospital in 1980. He got the Ph.D. of medicine at Seoul National University in 1985 and took postdoctoral fellowship in the Division of Gynecologic Oncology at Yale University School of Medicine, New Haven, CT. USA for 2 years from 1988. He had an interest in laparoscopic surgery since 1990 from benign gynecologic diseases and extended to gynecologic cancers from 1997. He made his department the largest and best center for endoscopic and oncologic surgery in his country since he served as the chairman of department from 1998. Till now his group has performed more than 1200 laparoscopic radical hysterectomies in patients with cervical cancers and 1500 staging surgeries in patients with early endometrial and ovarian cancer.

He has published about 150 articles in peer review English journals and more than 250 articles in domestic journals.

Educational Seminar：
Cervical cancer prevention—HPV vaccination and screening

Safety and effectiveness of HPV vaccine — global understanding and promotion

Philip Edward Castle

Albert Einstein College of Medicine, USA

Human papillomavirus (HPV) is the necessary cause of cervical cancer, the third most common cancer and cause of cancer-related death in females worldwide. HPV also causes anal cancer as well as vaginal, vulvar, penile, and oropharyngeal cancer, latter for which there is no proven, effective method of screening. Two first-generation, U.S. Food and Drug Administration (FDA) approved prophylactic HPV vaccines prevent infections and disease caused by HPV16 and HPV18, the two HPV genotypes that cause approximately 70% of cervical cancer, and one of those vaccines also prevents HPV6 and HPV11, the two HPV genotypes that cause 90% of genital warts. A next generation vaccine, recently approved by the U.S. FDA, targets HPV16, 18, and 5 additional HPV genotypes that together causes approximately 90% of cervical cancer as well as HPV6 and HPV11. In clinical trials, these vaccines have shown high levels of efficacy (>90%) against *Pap-detected* precancerous lesions and infections caused by the targeted HPV genotypes in adolescent females and males and older females. Data indicate population effectiveness, and therefore cost effectiveness, is highest in HPV-naïve young females prior to becoming sexually active. Countries that implemented HPV vaccination before 2010 have already experienced notable decreases in population prevalence of targeted HPV genotypes and related anogenital diseases in women and via herd protection in heterosexual men. Importantly, after more 100 million doses given worldwide, HPV vaccine has demonstrated an excellent safety profile. With demonstrated efficacy, cost-effectiveness, and safety, universal HPV vaccination of all young, adolescent women, and with available resources at least high-risk groups of men, should be a global health priority. Failure to do will result in millions of women dying from avertable cervical cancers, especially in low- and middle-income countries (LMICs), and many thousands of women and men dying from other HPV-related cancers for which there are no other viable interventions.

In Japan, the rate of cervical cancer incidence in women under the age of 50 years is on the rise, possibly because these women are not undergoing screening and/or increased exposure to HPV in early adulthood due to changing sexual norms. Moreover, oropharyngeal cancer incidence rates in Japan, like the U.S. and Western Europe, have risen over the last decades, corroborating the secular trend in increased exposure to HPV. Unfortunately, HPV vaccination rates have plummeted to nearly 0% due to unfounded, unproven claims of serious adverse events. If the current trends continue, Japan may face an unprecedented high burden of *preventable* HPV-related cancers that is typically associated with LMICs.

Bio：Dr. Philip Castle

Dr. Philip Castle is a Professor of Epidemiology and Population Health at Albert Einstein College of Medicine (Bronx, NY, USA), Executive Director and Co-Founder of the Global Coalition Against Cervical Cancer (Arlington, VA, USA), and an Associate Investigator at the U.S. National Cancer Institute. He received his Ph.D. in Biophysics (1995) and M.P.H. in Epidemiology (2000) from the Johns Hopkins University. Dr. Castle's professional interests are (1) epidemiology of human papillomaviruses (HPV) and cervical/anogenital cancer ; (2) science and translation of cancer prevention strategies ; (3) cancer screening ; and (4) global health. He is a member of the Board of Directors of the American Society for Colposcopy and Cervical Pathology (ASCCP) and a panel and steering committee member of the American Society for Clinical Oncology's resource-stratified guidelines on the secondary prevention of cervical cancer. Dr. Castle has received (1) a Distinguished Scientific Achievement Award from the ASCCP (2010) and (2) The Arthur S. Flemming Award for Exceptional Achievement in Federal Government Service for Applied Science, Engineering and Mathematics (2010). Dr. Castle currently conducts cervical cancer prevention research and program development in the U.S., Mexico, El Salvador, Nicaragua, Brazil, Colombia, Peru, Haiti, Norway, Rwanda, Zambia, Cameroon, India, China, Vietnam, Australia, and Papua New Guinea.

IS-AC-1-1 Casein kinase I epsilon is a novel molecular target for c-Myc driven ovarian cancers

Tohoku University[1], Tohoku Medical Megabank Organization[2]
Masafumi Toyoshima[1], Kazuyuki Kitatani[2], Shogo Shigeta[1], Masumi Ishibashi[1], Junko Minato[1], Nobuo Yaegashi[1]

[Objective] The MYC oncogene is a central driver in many human cancers. Not only overexpression but gene amplification of c-MYC have been observed in epithelial ovarian cancers. We have explored a target molecule whose inhibition can selectively halt c-Myc driven cancers. [Methods] We carried out a high throughput siRNA screening and identified casein kinase I epsilon (CK1e) as a MYC synthetic lethal gene. We studied CK1e expressions in patients' samples and the prognosis based on the c-MYC states. We also investigated the effects of IC-261, a small molecule CK1e inhibitor, in in vitro and in vivo. All experiments were conducted on the approval of the ethic board at Tohoku University School of Medicine. [Results] CK1e expressions were significantly correlated with c-Myc expressions in ovarian cancer samples. High CK1e group showed significantly poor prognosis in only c-Myc high ovarian cancer patients. Both siRNA for CK1e and IC-261 treatment selectively inhibited c-Myc driven cancer cells through strong G2/M arrest. IC-261 administration showed a curative effect in mouse carcinomatous peritonitis model. [Conclusion] Through this functional genomics approach, we have identified CK1e as a new therapeutic target for c-MYC driven ovarian cancers. These results indicate rational combination treatments and biomarkers to aid therapeutic choices for molecularly defined patient populations.

IS-AC-1-2 EMT-related gene Snail inhibits anti-tumor immunity in ovarian cancer through recruitment of MDSC

Kyoto University
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[Objective] Epithelial-mesenchymal transition (EMT) is a key process in tumor invasion and metastasis, and recent studies on tumor microenvironment suggest that MDSC (myeloid-derived suppressor cells) suppress anti-tumor immunity via expression of CXCR2 ligands. The aim of this study is to explore the functional relationship between EMT and local immunity in ovarian cancer progression. [Methods] The expression of EMT-related gene Snail was analyzed using TCGA microarray 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, and local immunity were analyzed. [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. Flow cytometric analysis of mouse tumors showed that CD4+ and CD8+ T cells increased and MDSC decreased in number in HM1-sh-Snail group ($p<0.05$). In HM-1-sh-Snail, expression of CXCR2 ligands, CXCL2/3/5, were decreased ($p<0.05$). [Conclusion] EMT-related gene Snail plays an important role in ovarian cancer progression possibly via expression of CXCR2 ligands and recruitment of MDSCs.

IS-AC-1-3 Investigation for the antineoplastic effect of lovastatin on ovarian cancer using metabolomic analysis

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[Objective] Omics analysis recently has shown that metabolic abnormalities are involved in onset of many malignant tumors. 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 performed a metabolomic analysis to investigate the mechanism of action of lovastatin from a metabolic perspective. [Methods] Metabolites were analyzed with or without lovastatin in SKOV3 ovarian cancer cells by capillary electrophoresis coupled with mass spectrometry. The frequency of autophagy and apoptosis, which were found to have relationships with metabolites, and changes in resistance to antineoplastic agents were examined by quantitative RT-PCR, western blotting and cell count analysis. [Results] Production of ATP and GTP significantly decreased, and reduced and oxidized glutathione, an antioxidant, also decreased in lovastatin-treated cells compared to controls. Lovastatin treatment significantly increased expression of autophagy marker LC3A/B and apoptosis markers caspase-3 and PARP. Furthermore, lovastatin had inhibitory effects on cell growth in both paclitaxel- and carboplatin-resistant strains. [Conclusion] Lovastatin has an inhibitory effect on tumor cell growth probably due to regulation of glutathione, and it may be involved with autophagy, apoptosis and changes in resistance to antineoplastic agents.

IS-AC-1-4 Retrospective analysis on recurrent sites in 603 stage I ovarian cancer

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[Objective] Incidence of recurrence of stage I ovarian cancer (I-OC) was reported as 10%. There are few reports referring to recurrent sites. We analyzed the relationship between the staging laparotomy including lymphadenectomy (SL) and the recurrent sites of cases with I-OC. [Methods] We retrospectively examined 603 I-OC treated in our 4 institutions between 2001 and 2013. The recurrent sites were divided into 4 groups, A : peritoneal dissemination, B : hematogenous metastases, C : lymph node metastases, D : Others. We analyzed the incidence of those groups, the relations between SL and the others (non-SL), and the recurrent sites. [Results] The median age and follow-up period of 603 cases were 54 years old and 60 months. Seventy-one cases out of 603 cases had recurred (11.8%). Incidence of recurrent sites in A, B, C and D were 66.2%, 25.4%, 11.3% and 9.9%. Incidences of recurrence in SL and non-SL were 9.8% and 12.9%. Incidences of recurrence sites of A, B, C and D in SL were 77.2%, 22.7%, 4.5% and 9.0%, and those of non-SL were 61.2%, 24.5%, 14.3% and 10.2%. These showed a tendency of less lymph node metastasis in SL. [Conclusion] Peritoneal metastases were frequently observed in 66.2% of I-OC. These results suggested that SL+peritonectomy might be effective to reduce recurrence of I-OC. The staging laparotomy might contribute to reduce the risk of lymph node metastasis.

IS-AC-1-5 Proton pump inhibitors enhance the effects of cytotoxic agents in chemoresistant epithelial ovarian carcinoma

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[Objective] This study was designed to investigate whether proton pump inhibitors (PPI, V-ATPase blocker) could increase the effect of cytotoxic agents in chemoresistant epithelial ovarian cancer (EOC). [Methods] Expression of V-ATPase protein was evaluated in patients with EOC using immunohistochemistry, and patient survival was compared based on expression of V-ATPase mRNA from a TCGA data set. In vitro, EOC cell lines were treated with chemotherapeutic agents with or without V-ATPase siRNA or PPI (omeprazole) pretreatment. Cell survival and apoptosis was assessed using MTT assay and ELISA, respectively. In vivo experiments were performed to confirm the synergistic effect with omeprazole and paclitaxel on tumor growth in orthotopic and patient-derived xenograft (PDX) mouse models. [Results] Expression of V-ATPase protein in ovarian cancer tissues was observed in 44 patients (44/59, 74.6%). Higher expression of V-ATPase mRNA was associated with poorer overall survival in TCGA data. Inhibition of V-ATPase by siRNA or omeprazole significantly increased cytotoxicity or apoptosis to paclitaxel in chemoresistant (HeyA8-MDR, SKOV3-TR) and clear cell carcinoma cells (ES-2, RMG-1), but not in chemosensitive cells (HeyA8, SKOV3ip1). Moreover, the combination of omeprazole and paclitaxel significantly decreased the total tumor weight compared with paclitaxel alone in a chemoresistant EOC animal model and a PDX model of clear cell carcinoma. However, this finding was not observed in chemosensitive EOC animal models. [Conclusion] These results show that omeprazole pretreatment can increase the effect of chemotherapeutic agents in chemoresistant EOC and clear cell carcinoma via reduction of the acidic tumor microenvironment.

IS-AC-1-6 Magnetic resonance spectroscopy can be used to discriminate between benign endometriotic cysts and endometriosis-associated ovarian cancer

Nara Medical University
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[Objective] Recently, an iron-rich environment in endometriotic cysts is thought to play an important role in the pathogenesis of endometriosis-associated ovarian cancer (EAOC). The aim of this study was to investigate the clinical applicability of iron concentration measurement in endometriotic cysts and EAOC using magnetic resonance (MR) spectroscopy. [Methods] Samples were obtained from patients with benign endometriotic cysts (n=67) and EAOC (n=15), all of whom provided informed consent under permission of the ethical committee of the hospital. The amount of iron [Fe] was determined by specific spectrometry and a parameter R2 was determined in vivo and ex vivo by using MR spectroscopy. [Results] R2 values in vivo corresponded to those ex vivo, and were correlated with [Fe]. Thus, R2 values in vivo were demonstrated to reflect [Fe]. The mean R2 value and [Fe] in the malignant group were lower than those in the benign group. A ROC curve showed the cut-off R2 value with high sensitivity and specificity to differentiate transformation of endometriotic cysts. [Conclusion] This is the first study to present a new MRI technique, MR spectroscopy, which may estimate iron levels in vivo and discriminate between benign endometriotic cysts and EAOC. The lower iron levels in EAOC than those in endometriotic cysts suggest a consequence of an effective antioxidant defense of cancer cells.

IS-AC-2-1 Methylation analysis of DNA mismatch repair genes using DNA derived from peripheral blood of patients with endometrial cancer：epimutation in endometrial carcinogenesis

Keio University
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[Objective] Germline mutation of DNA mismatch repair (MMR) genes (MLH1, MSH2 and MSH6) is a cause of Lynch syndrome. Methylation of MLH1 and MSH2 has been detected in peripheral blood cell of Lynch syndrome patients with colorectal cancer. This germline methylation is referred to as epimutation, but has not been studied in patients with endometrial cancer. We examined to detect epimutation of patients with endometrial cancer. [Methods] The subjects were 196 patients with endometrial cancer. After approval of the institutional review board, we analyzed methylation of MLH1, MSH2 and MSH6 promoter regions of peripheral blood cell by methylation-specific PCR. Family history was analyzed in each case with epimutation. [Results] MLH1 epimutation was detected in 1/196 patients (0.5%), including in 1/55 (1.8%) with an onset age of less than 50. The patient with MLH1 epimutation developed endometrial cancer at 46 years old and complicated with colorectal cancer, but she did not meet the revised Amsterdam Criteria. No case had epimutation of MSH2 or MSH6. [Conclusion] MLH1 epimutation was detected in a patient with endometrial cancer and may be a cause of endometrial carcinogenesis. Our results indicate that it is important to check for epimutation in endometrial cancer patients without germ cell mutation of MMR genes.

IS-AC-2-2 Anti-tumor effect of inhibition of DNA damage response proteins, ATM and ATR, in endometrial cancer cells

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[Objective] Activation of DNA repair pathways is one of the factors for resistance to chemotherapy in cancer cells. Targeting DNA damage response (DDR) proteins, such as ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), might enhance the cytotoxic effects of chemotherapy. The objective of this study is to clarify the anti-tumor effect of inhibitors to ATM or ATR, combined with doxorubicin in endometrial cancer cells. [Methods] Four endometrial cancer cells (HEC-6, HEC-108, HEC-1B, HEC-50B) were treated with doxorubicin in the presence or absence of an ATM inhibitor (KU55933) or an ATR inhibitor (VE821). Their anti-tumor effects were evaluated by colony formation assay. The levels of phosphorylation of DDR proteins were analyzed by immunoblotting. [Results] The combination of doxorubicin and KU55933, but not VE821, suppressed the number of colony formation, compared with doxorubicin alone. Doxorubicin induced accumulation of p-ATM, p-Chk2 and γ-H2AX, but did not affect the levels of p-ATR and p-Chk1 in immunoblotting. The up-regulation of p-ATM, p-Chk2 and γ-H2AX by doxorubicin was cancelled by KU55933 in a dose dependent manner. [Conclusion] Increased levels of the p-ATM and p-Chk2 might be associated with resistance to doxorubicin. Combination of doxorubisin and an ATM inhibitor can be a promising therapy in endometrial cancer.

IS-AC-2-3 An analysis of short-term recurrent cases following medroxyprogesterone acetate (MPA) therapy for endometrial cancer and atypical endometrial hyperplasia

Keio University
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[Objective] Medroxyprogesterone acetate (MPA) therapy is a fertility preserving therapy for patients with endometrial cancer (EC) and atypical endometrial hyperplasia (AEH). The problem of this therapy is high recurrent rate. The aim of our study is to clarify the characteristics of cases with short-term recurrence (SR). [Methods] Our study recruited 96 cases (29 AEH and 67 EC) with intrauterine recurrence following MPA therapy from 1998 to 2011. MPA therapy was continued until tumor disappearance, and endometrial biopsy were performed every 3-4 months due to follow-up. We defined SR and long-term recurrence (LR) as recurrence within 6 months and after 12 months after initial MPA therapy. This study was approved by an ethical committee of our institution. [Results] The median treatment period and recurrence free interval (RFI) were 197 days (56-755) and 285 days (41-2171). SR and LR were occurred in 28 cases (29%) and 38 cases (40%). Polycystic ovary (PCO) was complicated more frequently in SR group than in LR group ($p=0.04$). The duration of re-MPA therapy for recurrent disease in SR group was longer than that in LR group ($p<0.01$). However the RFI following re-MPA therapy was no significantly difference between both groups. [Conclusion] SR following MPA therapy may be associated with PCO. Re-MPA therapy after intrauterine recurrence can be performed even in SR group.

IS-AC-2-4 The H3K9 Methyltransferase G9a Represses E-cadherin and is Associated with Myometrial Invasion in Endometrial Cancer

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[Objective] Emerging evidence suggests that G9a, a histone methyltransferase, is involved in tumor progression and metastasis. In this study, we demonstrate the correlation of G9a to endometrial cancer. [Methods] The differential expression of G9a in cancer and normal tissues was assessed using an array of 28 paired samples. Tissue specimens from 94 patients with endometrial cancer who underwent primary surgery were immunohistochemically evaluated for G9a and E-cadherin expression. To assess the biologic role of G9a in endometrial cancer, G9a was either stably knocked down or knocked down using a tetracycline-controllable system in endometrial cancer cells, followed by functional assays. [Results] Increased G9a expression was identified in endometrial cancer tissues, and its expression was specifically correlated with deep myometrial invasion. Cell invasiveness was inhibited by an RNAi-mediated knockdown of G9a in invasive endometrial cancer cells in vitro and in vivo. An important mediator of G9a-induced tumor invasion is the epigenetic silencing of E-cadherin. Knockdown of G9a restored E-cadherin expression by reducing H3K9me2 levels and decreasing CDH1 promoter DNA methyltransferase recruitment. Knockdown of RNAi-mediated E-cadherin substantially relieved the invasion suppression imposed by G9a suppression. A significant negative correlation between G9a and E-cadherin expression was observed in endometrial cancer (P=0.02). [Conclusions] This study provides the first clear evidence that G9a contributes to endometrial cancer progression.Mechanistic investigations suggest that E-cadherin repression mediates the effects of G9a. Targeting G9a-mediated epigenetic pathway dysregulation may be a therapeutic strategy for endometrial cancers.

IS-AC-2-5 Human papillomavirus (HPV) genotype is a prognostic factor of recurrence following loop electrosurgical excision procedure for high-grade cervical intraepithelial neoplasia (CIN 2-3) in menopausal women

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[Objective] This study was conducted to determine whether the human papillomavirus (HPV) genotype by the HPV DNA chip test (HDC) is predictive of recurrent high-grade cervical intraepithelial neoplasia (CIN2-3) following a loop electrosurgical excision procedure (LEEP) in menopausal women. [Methods] Between January 2007 and February 2013, 206 menopausal women with CIN2-3 were treated by a LEEP and followed with cytology, the hybrid capture II assay (HC2), and the HDC. Post-LEEP follow-up was performed at 3, 6, 9, 12, 18, and 24 months during the first 2 years and yearly thereafter. [Results] Of the 206 patients, the HC2 was positive in 199 patients (96.6%) and the HDC was positive in 201 patients (97.6%) before LEEP. The overall agreement between the HDC and HC2 was 99.0%. The area under the receiver-operating characteristic curve for HR-HPV viral load measured by the HC2 predicting recurrent CIN2-3 was 0.567 (P=0.335). Twenty-six (12.6%) patients developed a recurrence, and those who developed a recurrence tested positive for the same HR-HPV genotype before and after the LEEP. The same HR-HPV genotype by the HDC during the follow-up had a sensitivity and a negative predictive value of 100% in detecting recurrent disease. HPV-18 was significantly associated with recurrent CIN 2-3 ($P<0.05$). [Conclusions] In postmenopausal women, persistent infection with the same HR-HPV genotype, especially HPV-18, should be considered a risk factor for developing recurrent CIN2-3, and after LEEP such patients warrant special attention with intense follow-up.

IS-AC-2-6 Current situation of cervical cancer diagnosis, management and registration in three national tertiary hospitals in Cambodia

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[Objective] Three national tertiary hospitals in the capital are major service providers in Cambodia in terms of cervical cancer. The gynecology departments of these hospitals were reviewed and analyzed to identify areas to be improved in a joint project by Cambodia Ob/Gyn Society and JSOG. [Methods] The registration books in these hospitals were reviewed in Nov 2014 by JSOG members. Then 6 Cambodian Gynecology doctors in these hospitals validated and updated the results in Sep 2015. [Results] (I) In the three hospitals, about 2500 pap smear were taken in 2014. At least 500 colposcopy examinations were conducted in two hospitals with no aggregated colposcopy data in one hospital. Two hospitals are implementing punch biopsy and LEEP conizations (number not known), while one hospital conducted cryotherapy without taking punch biopsy. In the two hospitals, the numbers of cervical cancer cases managed in Gynecology and Oncology departments were 292 and 374 cases respectively. None of the three hospitals could give the total number of new cervical cancer cases managed in each hospital, mainly because advanced cases are managed in oncology units for radiation or chemotherapy without communicating with gynecologists. [Conclusion] Compared to the estimated number of the reproductive age women and cervical cancer cases (2 million, 1500 cases respectively), the number of diagnosis procedures provided in these hospitals is very low. Services should be expanded. Also, recording services and registration of cervical cancer should be strengthened.

IS-AC-2-7 The risk estimation of gestational trophoblastic neoplasia after cytogenetically defined hydatidiform molar pregnancy：A prospective cohort study

Chiba University
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[Objective] The incidence rates of gestational trophoblastic neoplasia (GTN) after partial moles (PHM) have been reported from 1% to 20%. This wide range is due to diagnostic uncertainty. This study aimed to clarify GTN rates after molar pregnancies, especially after PHM. [Methods] We recruited 328 participants for a molecular diagnostic study of suspicious molar pregnancy from 2007 to 2015. The institutional review board approved this prospective cohort study. Cytogenetic diagnosis was performed with multiplex short tandem repeat polymorphism analysis. [Results] Cytogenetic diagnosis was possible in 310 cases. Complete moles (CHM) (androgenetic), PHM (diandric monogynic triploid), and abortion (biparental diploid) occurred in 185, 54, and 71 cases. All cases progressed to GTN before hCG normalization and were classified as low-risk GTN. The incidence rates of GTN were 18% (30/163), 27% (6/22), 2% (1/54), and 0% (0/71) in homozygous CHM, heterozygous CHM, PHM, and abortion, respectively. Compared with that of homozygous CHM, the odds ratios of heterozygous CHM, PHM, and abortion were 1.66 (confidence interval：0.49–4.9), 0.084 (0.002–0.53), and 0 (0–0.26). [Conclusion] The cytogenetically diagnosed incidence rate of GTN after PHM is much lower than that after CHM, but it is not zero. Further studies are needed to elucidate the specific incidence rates, especially those after PHM.

IS-AC-3-1 Randomized Controlled Trial Comparing Two Different Regimes of Magnesium Sulphate in Severe Preeclampsia：PIPES Trial

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[Objective] To compare the efficacy and safety of "Standard Dhaka" regime with "Loading dose only" regime for seizure prophylaxis in severe preeclampsia. [Methods] This was a randomized open-label, parallel arm, trial with 1：1 allocation ratio conducted in the labour ward attached to the Department of Obstetrics and Gynecology, Jawaharlal Institute of Medical Education & Research, Pondicherry, India. Four Hundred and two women admitted with a singleton pregnancy complicated by severe pre-eclampsia according to the ACOG Criteria were randomized to Standard Dhaka regime (Loading dose of 10gm and maintenance dose of 2.5gm every 4th hourly, 5 doses) or loading dose only regime (Loading dose of 10gm and no maintenance doses). Primary outcome of the study was development of eclampsia within 48 hours of the loading dose. [Results] The incidence of eclampsia in the women who received "standard Dhaka" regime (Group A) was 3.48% (7/201) and that in the "Loading dose only regime" (Group B) was 1.49% (3/201) (relative risk=2.38, 95% confidence interval 0.61, 9.34, p=0.194). Women assigned to group B had similar rates of cesarean section (22.39% vs 23.88%), postpartum hemorrhage (2.99% vs 1.98%), coagulopathy (2.99% vs 1.49%), and acute renal failure (1.99% vs. 0.50%). Neonatal outcome such as Apgar score at 5 minutes (8.05% vs 5.03%) perinatal mortality (21.89% vs. 20.40%) were similar in both groups. [Conclusions] "Loading dose only" regimen offers the safety advantages of a single administration while retaining the efficacy simillar to "Standard Dhaka regime" in preventing eclampsia. Larger multicenter studies would be required to assess the impact and incidence of rare events before incorporation into routine clinical practice.

IS-AC-3-2 Hypoxia-independent upregulation of placental hypoxia-inducible factor-1α contributes to the pathogenesis of preeclampsia

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[Objective] Preeclampsia (PE) is known to be characterized by elevated placental hypoxia-inducible factor-1α (HIF-1α) levels. However, pathologic role of placental HIF-1α in PE remains largely unknown. Here, we examined the mechanisms underlying the elevation of placental HIF-1α and its role in PE. [Methods] Two independent PE mouse models induced by angiotensin II type I receptor agonistic autoantibody (AT_1-AA) or inflammatory cytokine LIGHT (tumor necrosis factor superfamily member 14) were conducted. *In vivo* siRNA-induced knockdown of HIF-1α was conducted to assess the role of HIF-1α. The research protocol was approved by the Institutional Committee. [Results] HIF-1α expression was elevated in the placentas of two PE models. Knockdown of placental HIF-1α by siRNA attenuated PE features induced by AT_1-AA or LIGHT in pregnant mice, including hypertension, proteinuria, and elevated circulating sFlt-1 levels. *In vitro* studies with human villous explants (HVE) showed that AT_1-AA or LIGHT induces HIF-1α expression in a hypoxia-independent manner. Moreover, increased HIF-1α was found to be responsible for AT_1-AA or LIGHT-induced elevation of Flt-1 gene and production of sFlt-1 in HVE. [Conclusion] Our data revealed that the elevated placental HIF-1α initially triggered by hypoxia-independent factors, such as AT_1-AA or LIGHT, plays a key role in the pathogenesis of PE.

IS-AC-3-3 Prediction of pre-eclampsia and its severity by soluble FMS-like Tyrosine Kinase 1 and Placental growth factor

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[Objective] Pre-eclampsia (PE) presents the greatest risk to the mother and her fetus with challenges in early diagnosis or prediction of PE and its severity. There is no reliable test for its prediction. It has been demonstrated that biomarkers ; soluble fms -like tyrosine kinase-1 (sFlt-1) and placental growth factor (PIGF) seem to play a critical role in the prediction of PE. The serum level of sFlt-1 is increased, PIGF concentration is decreased and sFlt-1/PIGF ratio is raised in women who will develop PE. The aim of this study was to evaluate the role of sFlt-1, PlGF and sFlt-1/PlGF ratio in prediction of PE and its severity. [Method] The study design is nested case control study. The study was carried out from January, 2013 to December, 2013 in Central Women's Hospital (CWH), Yangon and Insein General Hospital (IGH). The study population was 987 non PE primigravid women who were selected from the antenatal (AN) clinics at gestational age between 21 and 32 weeks. Blood was taken at the first appointment and serum samples were stored until testing. Clinical data including demographic information, risk factors for PE, blood pressure, proteinuria, and signs and symptoms of severe PE were recorded. The participants were followed up until postpartum 6 weeks. Fifty patients who developed PE were represented as 'cases'. Each woman with PE was matched according to maternal age and gestational age at blood sampling to one pregnant woman without PE. They were represented as 'control'. The levels of sFlt-1 and PlGF of total 50 pairs of cases and controls were analyzed using Enzyme Linked Immunosorbent Assay (ELISA). [Result] The marked increase in sFlt-1 concentration and sFlt-1/PlGF ratio before the onset of PE, accompanied by decrease in PlGF levels were detected in this study. In prediction of PE, there were antenatal sFlt-1 cutoff value 500pg/ml with sensitivity 74% and specificity 82% ; and sFlt-1/PlGF ratio cutoff value 3.6 with sensitivity 74% and specificity 82%. However, cutoff value of PlGF for prediction of PE was not valid because the Receiver Operator Characteristic (ROC) curve crossed the diagonal line. It has limited usefulness. For prediction of severe PE, there were sFlt-1 cutoff value 1275.75 pg/ml with sensitivity 91% and specificity 87% ; PlGF cutoff value 110pg/ml with sensitivity 91% and specificity 97% ; and sFlt-1/PlGF ratio cutoff value 14.79 with sensitivity 91% and specificity 97%. [Conclusion] This study demonstrated the marked increase in the sFlt-1 and sFlt-1/PlGF ratio with decreased PlGF with statistically significant results in predicting PE and severe PE. These findings supported the hypothesis of predicting the occurrence of PE and severe PE. Further prospective, longitudinal studies on larger number of women in which serial measurement of sFlt-1, PlGF and their ratio throughout pregnancy are needed for better assessment of the relevance of these biomarkers to predict PE and its severity. Prediction of women at risk of developing PE and severe PE will contribute to prevention, early diagnosis and treatment leading to reduction of maternal and perinatal morbidity and mortality.

IS-AC-3-4 Preeclampsia (PE) serum disrupts the autophagy/lysosome pathway cooperated with endoplasmic reticulum (ER) stress

University of Toyama
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[Objective] We have reported that impaired autophagy contributes to the shallow trophoblast invasion and poor vascular remodeling (1st step of PE). The aim of this study is to clarify the correlation between autophagy and dysfunction of placenta (2nd step of PE). [Methods] We used placental tissues and serums from PE patients with informed consent. Proteostat dye® is used for detecting aggregated proteins. [Results] We firstly found that the number of lysosome was significantly decreased ($p=0.037$), and aggregated proteins were increased ($p=0.021$) in the syncytiotrophoblast in PE placenta. Secondarily, ER stress inducers inhibited the lysosomal number and functions in a trophoblast cell line, suggesting that ER stress reduces autophagy and protein quality control. We then took notice of transcriptional factor EB (TFEB), a master regulator of autophagy and lysosome biogenesis. The expression of TFEB was significantly decreased ($p=0.005$) in the PE placenta than that in normal placenta. Finally, serum from PE patients suppressed the TFEB activation via hyper-activating mammalian target of rapamycin. [Conclusion] ER stress as well as PE serum cooperatively impaired homeostasis in PE placenta via suppressing autophagy and lysosome functions. As overexpression of TFEB is known to improve some neurodegenerative disease in mice model, TFEB activation would be a new therapeutic option for PE.

IS-AC-3-5 Lower diet intake of omega-3 polyunsaturated fatty acids (PUFAs) during late pregnant is associated with late preterm birth

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[Objective] Omega-3 PUFAs, including EPA and DHA, are well-known to have protective effects on inflammations and are also reported to reduce the incidence of preterm birth in mice model. The aim of this study is to elucidate the effect of intake of omega-3 PUFAs on the occurrence of preterm birth in pregnant women. [Methods] Under the approval by our ethics committee and informed consent, we conducted dietary questionnaire survey to 530 singleton pregnant outpatient women in our hospital. BDHQ (Brief-type self-administered diet history questionnaire) that is designed to obtain the information of nutrient and food intakes was used for the dietary survey. It was performed at each gestational trimester. Serum fatty acid levels were also measured. Obstetrical outcome in this series of pregnant women was investigated. [Results] Intake ratio of omega-3/6 PUFAs which was estimated by BDHQ paralleled serum ratio of that. The intake ratio at 3rd trimester in preterm birth women was significantly lower than that in full-term birth. By contrast, the intake ratio at 2nd trimester was not associated with the occurrence of preterm birth. [Conclusion] Lower diet intake of omega-3 PUFAs during 3rd trimester correlated to occurrence of late preterm birth. Sufficient intake of omega-3 PUFAs may provide pregnant women body composition resistant to inflammation-associated preterm birth.

IS-AC-3-6 Low-dose betamethasone infusions elicit partial lung maturation in a sheep model of pregnancy

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[Objectives] Antenatal steroid (ANS) therapy to improve outcomes for preterm infants is widely used, but is not FDA approved and there has been little optimization of dosing strategies. We aimed to determine the maternal and fetal pharmacokinetics of low-dose intravenous betamethasone phosphate (BETA) infusions in a sheep model of pregnancy. [Methods] 32 ewes with single fetuses (114 d gestation) had surgery to catheterize fetal and maternal jugular veins. Animals were recovered for 2 d, and randomized to receive two maternal jugular infusions (separated by 2 d) of either (n=4/dose) : i) saline, 0.125 mg/kg, 0.04 mg/kg, or 0.0125 mg/kg BETA over 3 h ; or ii) saline, 0.25 mg/kg, 0.08 mg/kg, or 0.025 mg/kg BETA over 12 h. Maternal and fetal plasma was sampled for 24 h during infusions. Fetal lung tissue collected for maturation analysis using qPCR. Plasma BETA levels were determined by mass spectrometry. [Results] Fetal betamethasone was only detectable in 0.125 mg/kg/3h or 0.250 mg/kg/12h animals. Maternal/fetal Cmax, T1/2α, and AUC0-inf values for 0.125 mg/kg BETA were 83/10.5 ng/mL, 2.2/6.1 h, and 577/109 ng/mL*h, respectively. Maternal/fetal Cmax, T1/2α, and AUC0-inf values for 0.250 mg/kg BETA were 60/8.2 ng/mL, 1.3/2.7 h, and 742/116 ng/mL*h, respectively. Relative to saline control, animals receiving 0.125 mg/kg and 0.25 mg/kg BETA had statistically significant increases in fetal lung compliance and surfactant protein-A mRNA expression. [Conclusions] Low-dose BETA infusions (0.125 mg/kg/3 h and 0.25 mg/kg/12h) achieved fetal lung maturation, suggesting the potential to refine existing high-dose clinical ANS therapy.

IS-AC-3-7 The effects of acute hypoxemia under magnesium sulphate administration on baroreflex in chronically instrumented fetal sheep

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[Objective] The purpose of this study is to investigate the effects of magnesium sulphate (MgSO4), which is used for the treatment of threatened premature delivery and eclampsia prophylaxis, on fetal baroreflex during normoxia or acute hypoxemia. [Methods] Eight chronically instrumented fetal sheep were assigned to either MgSO4 or saline administration group. Fetal baroreflex was induced using phenylephrine at 30 micro gram. The fetuses were exposed to normoxia or acute hypoxemia. We monitored their baroreflex, dividing into 2 sleep status : REM and NREM phases. Baroreflex was evaluated with changes in the fetal heart rate (FHR) to mean arterial pressure (MAP) ratio (dFHR/dMAP). [Results] In the saline group with acute hypoxemia, dFHR/dMAP increased during both REM and NREM phases compared with normoxia (REM, 2.72 vs 4.37 ; p=0.038 ; NREM, 3.15 vs 4.31 ; p=0.000). Meanwhile, in the MgSO4 group with acute hypoxemia, dFHR/dMAP significantly decreased compared with the one with normoxia (3.15 vs 1.36 ; p=0.001). [Conclusion] Fetal baroreflex significantly decreased in the group of MgSO4 with acute hypoxemia. We presume from this result that baroreflex-mediated bradycardia is likely to be underestimated in a fetus with hypoxemia after exposure to MgSO4 via the mother in the clinical settings.

IS-AC-4-1 Assignment of the direction and axis in single cardiac volume dataset without information of fetal position—Toward the virtual diagnosis of fetal cardiac lateralization disorders by 4D spatiotemporal image correlation technique

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[Objective] Spatiotemporal image correlation (STIC) is a powerful tool that can integrate the gated fetal cardiac images into a virtual heart for scanning. Moreover, it allows the transmission of the virtual heart (digital dataset) via the internet for tele-consultation. We carry out this prospective study to determine whether the fetal cardiac location, situs, ventricular looping, and ventriculo-arterial connection could be determined by the single volume dataset without the reference of fetal lying to the maternal abdomen. [Methods] This study is carried on by the approval of our institutional review board. We recruited the pregnancy with fetal lateralization defects as our study group. The control group consist the pregnancy with other forms of cardiac anomalies. The scanning gestations ranged from 20 weeks to 36 weeks of gestation. We scan the fetal heart in the duration of 12.5s with the scanning angle of 25 degrees during fetal quiescence. The 3D volume dataset was reoriented in 4D VIEW software (GE healthcare, United States). In brief, we reoriented the cardiac position in panel A, with cardiac apex in superior and the spine in the right. The interventricular septum was aligned in the Y-axis and the AV canal was aligned in X-axis. The navigation dot was set in the atrial septum primum. Then we accessed the heart in panel C. Since the inherent human axes have already set - the fetal spine is always at posterior and great vessels extend upward from heart, we are able to assign the directional information for the cardiac volume without reference of fetal lying in relation to maternal uterus. After determination of the left-right axis, we further identify the cardiac situs (position of right atrium) by the drainage of the inferior vena cava in relevant to body axis. The ventricular looping (location of right ventricle in compare to the body axis) is then determined by the location of moderator band. The vessels of aorta and pulmonary artery are further recognized by their characteristics. [Results] Totally 52 fetuses of lateralization disorders (including right atrial isomerism, left atrial isomerism, situs inversus, corrected transposition of great arteries, and certain double outlets of right ventricles) and 337 fetuses of other forms of congenital cardiac defects were recruited in this period. Of these patients, follow-up information was available in 38 fetuses in study group and 258 fetuses in the control group. The cardiac location, axis were correctly predict in 36/38 (95%) in the study group and 100% in control group before birth. The only 2 exceptions were 2 mesocardia of right atrial isomerism in which we were unable to determine the left- right axis before birth. Besides, we were able to assess atrio-ventricular connection in 31/38 cases in study groups and 213/258 cases of fetuses. Furthermore, we were able to describe ventriculo-arterial relationship in 26/38 cases of study group and 186/258 cases of control group. With these information, we are allowed to make the diagnosis by virtual scanning of fetal heart in subsequent 296 complex congenital heart diseases. [Conclusions] Assignment of directional information and axes of single fetal cardiac dataset is feasible solely by 4D STIC without additional information of fetal position in relevant to maternal position. This study highlights the potential of telediagnosis of fetal complex heart defects, especially for those diagnosis relying on the documentation of cardiac axis and atrio-ventricular, ventrculo-arterial relationship.

IS-AC-4-2 Fetal outcomes in pregnancies detected hypoplasia of nasal bone at second trimester of gestation

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[Objective] Nasal bone is an importan factor for predicting fetal aneuploidies including trisomy 21. This study is aimed to evaluate fetal outcomes in pregnancies diagnosed hypoplasia of nasal bone at second trimester of gestation. [Methods] A prospective study was carried out from January 1st 2013 to December 31 2014. All pregnant women were measured routinely nasal bone length following ultrasonography scanning at 16 to 26 weeks' gestation. The 5th percentile of nasal bone length was chosen as cut-off point of hypoplasia. Pregnancies diagnosed hypoplasias of nasal bone were performed an amniocentesis and followed up to the delivery. Fetal outcomes were recorded and analyzed in order to evaluate a relation between hypoplasia of nasal bone and fetal prognosis. [Results] A total of 38 fetuses (1.6%) were detected hypoplasia of nasal bone following measurement of nasal bone length in 2440 pregnancies. Most of these women (89.5%) were delivered healthy babies. 3 cases of them (7.9%) were terminated pregnancies because of trisomy 21 (2 cases) and osteogenesis imperfecta type 1 (1 case). Severe intra-uterine growth restriction was found in one case of hypoplasia associated with cleft lip (2.6%). [Conclusion] Fetuses with adverse outcomes had additional abnormalities determined in prenatal ultrasonography. It's necessary to perform a detailed scanning in case of hypoplasia of nasal bone before counseling fetal outcomes. Keywords : Fetal outcomes, hypoplasia of nasal bone, ultrasonography.

IS-AC-4-3 Association analysis of polymorphisms with high-risk group of gestational diabetes mellitus in a Japanese population

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[Objective] There is a paucity of data on genetic variants associated with gestational diabetes mellitus (GDM) in Japanese women. Therefore, we investigated whether risk variants for type 2 diabetes mellitus (T2DM) were genetically associated with GDM in a Japanese cohort. [Methods] With institutional review board approval, we reviewed a total of 299 Japanese women at our institutions with a singleton pregnancy who underwent a diagnostic 75g oral glucose tolerance test during late pregnancy. Of the T2DM risk variants previously reported, 45 single nucleotide polymorphisms (SNPs) in 36 candidates (Japanese minor allele frequency>30%) were genotyped using DNA from maternal peripheral blood samples. Logistic regression analyses were used to test for differences in genotype frequencies between women with GDM (n=171) and those without GDM (n=128). [Results] Three variants (one insulin sensitivity candidate and two insulin secretion candidates) had nominal associations with GDM. One of the three was a newly identified SNP associated with GDM. Regarding these three variants, women with five or more risk alleles had a 10.3-fold increased risk of GDM (p=0.0013, 95% confidence interval: 4.57-8.20) compared with those having no more than one risk allele. [Conclusion] T2DM risk alleles of three SNPs had cumulative effects on the development of GDM in this cohort of Japanese women.

IS-AC-4-4 Enhanced expression of contraction associated proteins and ion channels in myometrium of preterm mouse model with odontogenic *Porphyromonas gingivalis* infection

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[Objective] We previously presented that mice with the odontogenic *Porphyromonas gingivalis* infection (*P.g* mice) could be used as animal models for chronic inflammation-induced preterm delivery. This study aimed to investigate the mechanism of underlying increase in uterine contractility. We examined contraction associated proteins (CAPs) and ion channels including the P2X7 receptor, which was one of the receptor operated calcium channels and was previously reported to be enhanced by inflammation. [Methods] We examined the expression of the oxytocin receptor, connexin 43, the L-type Ca^{2+} channel, and the P2X7 receptor in the myometrium at day 18 of gestation using real-time PCR and western blot analysis. The uterine contraction was recorded in tissue organ bath systems and analyzed. [Results] The mRNA expression of the oxytocin receptor and connexin 43 were 5.4 and 3.2 fold elevated in the *P.g* mice. The expression levels of protein were also increased. The L-type Ca^{2+} channel and the P2X7 receptor were 2.5 and 1.7 fold elevated in the *P.g* mice. The concentration-response curves for oxytocin shifted to the left in the *P.g* mice, compared to those in normal mice. [Conclusion] The expression of CAPs, L-type Ca^{2+} channel and P2X7 receptor was enhanced, and the sensitivity to oxytocin was increased in the *P.g* mice. Enhanced contractility induces preterm delivery.

IS-AC-4-5 Do teenagers with sexually transmitted disease during pregnancy have an increased risk of preterm birth or chorioamnionitis?

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[Objective] Teen pregnancy in the United States continues to be a significant social and economic problem. Peoria County is one of three counties in Illinois with the highest rates of teen pregnancies and sexually transmitted infections (STIs). Prior studies have shown that both teenage birth and lower genital tract infection lead to higher risk of preterm birth. Our primary objective is to determine the prevalence of STI's (Gonorrhea, Chlamydia and Trichomonas) in pregnant teenagers, and compare preterm delivery and chorioamnionitis in teens with and without STIs. [Methods] We performed a retrospective cohort study by reviewing electronic medical records of females age 19 or younger with deliveries from 01/01/2012 to 12/31/14 at our tertiary referral center. Patients with multiple gestation were excluded. After descriptive statistics and univariate analysis, a multivariable logistic regression was used to examine the association between STIs and outcomes controlling for age, marital status, race, parity and smoking status. [Results] 562 charts were reviewed, 517 teens with live singleton births were identified. The rate of STIs was 17.2% (gonorrhea 3.5%, chlamydia 14.7%, trichomonas 3.3%). The rates of preterm deliveries and clinical chorioamnionitis were 18.4% (95/517) and 4.1% (21/517), respectively. STIs were not associated with preterm deliveries or chorioamnionitis ($p>0.05$). [Conclusion] Surprisingly, we did not find any significant association between STIs and preterm delivery in our population, contrasting prior studies not specific to teenagers. However a finding unique to our study was higher than anticipated rates of STIs in teen pregnancies.

IS-AC-4-6 The differential expression of microRNA between human first trimester villous and extravillous trophoblast cells：PCR array-based approach

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[Objective] Villous trophoblast (VT) differentiates into extravillous trophoblast (EVT)：this requires gene expression changes between VT and EVT, meaning that expression of microRNA (miRNA) naturally changes between the two. We demonstrated placental expression of placenta-specific miRNA clusters. We examined whether expression of miRNAs, especially placenta-specific miRNAs, change between VT and EVT. [Methods] We obtained informed consent and the approval of Ethics Committee. PCR-based array analysis was employed to examine the expressions of 756 miRNAs between VT (minced chorionic villi) and EVT (isolated from explanted chorionic villi) (10-11 weeks at legal abortion). [Results] Of 756 miRNAs, 160 were detected, of which 31 and 5 were originated from chromosome 19 cluster (C19MC) and C14MC miRNAs, respectively. Of 160, 29 (29/160：18%) showed statistically different expressions between the two, with all 29 down-regulated in EVT than VT, with 9 belonging to C19MC and 4 to C14MC miRNAs. The miR-100 and -145 expressions were markedly reduced：EVT expressed them less than 1/10 than VT. [Conclusion] Expression of 29 miRNAs including placenta-specific miRNAs changed between VT vs. EVT, with all reduced in EVT. While differentiating from VT into EVT, trophoblast cells lost some miRNA expression (especially placenta-specific miRNAs), thereby regulating corresponding gene expression.

IS-AC-5-1 Human induced pluripotent stem cells (iPS cell) differentiate to hCG-producing trophoblast (For elucidation of the various obstetrics and trophoblastic diseases)

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[Objective] The characteristics of the induced pluripotent stem cells (iPS cells) are useful for a disease study and treatment. However the model construction about the placental development of the human is difficult, so we haven't understood about it yet. This study tried differentiation to hCG-producing trophoblast, using these iPS cells to elucidate placentation. [Methods] The iPS cells on feeder were subcultured to the xeno-free environment, and we added BMP4 for about 10 days. We evaluate morphologic change and hormone level of culture media supernatant. After collecting cells, we extracted RNA and made cDNA to measure the gene expression of the trophoblast markers in RT-PCR. Further, immunohistochemistry was underwent about CDX2 and HCG. [Results] After about 5days incubation, a morphological change and the expression of trophoblast markers in RT-PCR was confirmed, and the hormone level of HCG and progesterone in supernatant were rose. Furthermore the CDX2 and HCG in the immunohistochemistry were positive. [Conclusion] Now we try to transfect a vector of the PPAR-γ gene to the iPS cells and differentiate to hCG-producing trophoblast. Then it will be transplanted to mouse to investigate a function in vivo and to construct placenta model. The differentiation of the trophoblast should greatly contribute to elucidation and treatment of the various obstetrical and trophoblastic diseases.

IS-AC-5-2 Exacerbation of endometriosis by dysfunction of regulatory T cells in mouse and human

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[Objective] Endometriosis is a chronic inflammatory disorder that is associated with the altered immune response. Regulatory T cells (Treg) play a key role in maintaining immune homeostasis. Here we demonstrate the role of Treg in endometriosis. [Methods] A mouse model of endometriosis was made by transplanting donor mouse uterine fragments into the abdominal cavity of recipient mice. Foxp3-IRES-DTR/GFP [FDG] C57BL/6 mice were used as Treg cell-depleted model. Endometrioma, endometrium, peritoneal fluid, and peripheral blood were obtained from women with and without endometriosis. Three Treg cell fractions (resting Treg, activated Treg, non-Treg) in human CD4+ cells were examined by FACS. This study was approved by the IRB and informed consent was obtained from each patient. [Results] In FDG mice, the number ($P<0.05$) and weight ($P<0.01$) of endometriotic lesions, and the serum level of IL-6 ($P<0.01$) were significantly increased compared with those in control mice. In women with endometriosis, the proportion of activated Treg in endometrioma ($2.4 \pm 1.7\%$, $P<0.01$) and endometrium ($2.0 \pm 1.1\%$, $P<0.01$), but not in peritoneal fluid or peripheral blood, was significantly decreased compared with that in women without endometriosis ($5.2 \pm 4.5\%$). [Conclusion] An enhanced inflammatory response caused by reduced activated Treg cells may be involved in the progression of endometriosis.

IS-AC-5-3 Identification the non-obstructive azoospermia-related genes in infertile male individuals

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[Objective] Male infertility represents one of the clearest examples of a complex disease with a substantial genetic basis. Numerous male mouse models, mutation screening and association studies reported over the last few years reveal the high prevalence of genetic causes of spermatogenic impairment, accounting for 10–15% of severe male infertility, including chromosomal aberrations and single gene mutations. However, a large proportion of infertile males are diagnosed as idiopathic, reflecting poor understanding of the basic mechanisms regulating spermatogenesis and sperm function. Furthermore, the molecular mechanisms underlying spermatogenic damage in cases of genetic infertility (for example Yq microdeletions) are not known. These problems can be addressed only by large-scale association studies and testicular or spermatozoal expression studies in well-defined alterations of spermatogenesis. This proposal will seek the genetic variations in non-obstructive azoospermia (especially in sertoli cell only) in patients by means of array Comparative genomic hybridization. Further to find those genetic disorders associated with human male infertility and present emerging and previously unrecognized genetic aspects. [Methods] First, we identified the novel genetic variation in human non-obstructive (especially in sertoli-cell only) type azoospermia by using NimbleGen Array CGH. Second, we elucidated the genetic variation between 24 sertoli-cell only azoospermia and 24 normal spermatogenesis testis specimens from patients receiving IVF/ICSI treatment by using real-time PCR. [Results and Discussion] We have attempted to contribute to the discovery of causative copy number variations (CNVs), which are important to understand the pathogenesis of sertoli cell-only syndrome (SCOS) azoospermia in Taiwanese populations. Moreover, the incidence for potentially susceptible loci mapping to known genes was high in our patient cohort and the highly recurrent microdeletion on Y q11.223 and q11.23 seems to be pathogenic. Our exploratory data provide information on CNVs for SCOS in Taiwanese populations. CNVs may be implicated in this form of male infertility. Several follow-up analyses are needed to assess the reproduction-related gene disrupted by CNVs identified by this pilot study. Deleted in azoospermia (DAZ) gene family identified on the Y chromosome is required for the completion of normal spermatogenesis. The role of DAZ in spermatogenesis remains unclear. There was a significant association between the type of testicular impairment and the expression of CDY1 and CDY2 transcripts. CDY2 was expressed whenever germ cells were present, but CDY1 major and especially CDY1 minor and short transcripts were identified almost exclusively when mature spermatids/spermatozoa were detected. The expression of CDY1 minor and short transcripts detected in aspirated specimens was less efficient than that in testicular tissue acquired by extraction. It is suggested that CDY2 is apparently required in the early stages of spermatogenesis, whereas CDY1 transcripts are required later on in the process. Microdeletion analysis using PCR helps determine the frequency and site of gene deletion and thus the testicular phenotype, and also contributes to the determination of an accurate prognosis and ultimately to valuable counseling for couples diagnosed with Y chromosome microdeletions. Because sperm retrieval is sometimes unsuccessful in SCOS, with the availability of assisted reproduction technology for infertile couples, a genetic etiology is critical for the well being of these prospective parents and their potential offspring. [Conclusion] The gene defect (DAZ1-4 Gene, CDY1 Gene, CDY1B Gene, GOLGA2LY1 Gene, CSPG4LYP1 Gene, BPY2 Gene) is identified from the clinic infertility SCOS men with spermatogenesis deficiency.

IS-AC-5-4 Clinical study of gasless Laparoscopic Adenomyosis Resection with Loop Electrosurgical Excision Procedure (LEEP) Combined with Drug Therapy

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[Objective] To explore the effects of gasless laparoscopic procedure and LEEP combined with GnRH agonist (GnRHa) and levonorgestrel intrauterine system (LNG-IUS) in the traetment of uterine adenomyosis to reserve the uterus of patients. [Methods] Sixty patients with adenomyosis severe enough for hysterectomy were prospectively studied in Shanghai Zhabei District Central Hospital and Shanghai 9th People's Hospital Affiliated to Shanghai Jiaotong University, School of Medicine, from August 2010 to July 2012. The patients all were consent-informed to receive gasless laparoscopic adenomyosis resection with LEEP and then GnRHa injection once a month for six months, and then to have LNG-IUS inserted in the uterus. All the patients were followed up at 1st, 3rd, 6th, 12th, and 18th mouth after operation. And the items such as uterine volume, hemoglobin and serum CA125 levels before and after treatment were observed and compared in the follow-up. The menstrual bleeding and dysmenorrhea were also observed and compared between those of the pre-treatment and those after menstrual recovery. [Results] All 60 patients of adenomyosis underwent successfully surgical procedure and GnRHa treatment six times, and 58 patients had LNG-IUS inserted in uterine cavity. The mean uterine volume decreased gradually and significantly from 244.4 ± 70.2cm^3 before surgery to 86.8 ± 13.2 cm^3 at the 6th month after surgery ($p<0.01$). The mean uterine volumes increased lightly at 12th month (103.8 ± 26.6 cm^3) and at 18th month (150.2 ± 32.8 cm^3) after surgery, either of which was still significantly far smaller than that before surgery ($p<0.05$). The level of hemoglobin returned to normal (107.5 ± 5.9 g/L) at the 18th month after surgery from 88.8 ± 11.7g/L before surgery. 41 patients were found with high serum CA125 level (66.5 ± 22.6 IU/ml) before surgery. The mean serum CA125 level in these patients reduced to normal (28.3 ± 6.7 IU/ml) at the 3th month after surgery, and remained still normal at the18th month. There were 55 patients with heavy menstrual bleeding among the 60 subjects. All the 55 patients had LNG-IUS inserted. The follow-up results showed that the menstrual bleeding turned to normal at the 1st menstrual period after the recovery of menstruation and that the menstrual bleeding remained nearly normal both at the 12th and the 18th month. There were 43 cases with dysmenorrhea among the 60 subjects. And 42 cases had LNG-IUS inserted. The mean visual analogue scale (VAS) scores of dysmenorrhea in the 42 cases were significantly lower at 1st period of menstruation recovery, at 12th month (2.3 ± 0.7) or at 18th month (2.6 ± 1.1, n=40) than that before treatment (7.2 ± 2.3) ($p<0.01$). The VAS score was significantly higher at 18th month than that at 1st period after menstrual recovery ($p<0.05$), but not significantly different from that at 12th month ($p>0.05$). [Conclusions] The gasless laparoscopic technique with LEEP could be effective in the resection of the uterine adenomyosis to reserve the uterus with severe adenomyosis. The surgery combined with treatment of GnRHa could cure the anemia, reduce serum CA125 level to normal within 3months. And the LNG-IUS insertion could maintain the curative effects. Therefore the combined therapy of gasless laparoscopic procedure with LEEP and GnRHa injection and LNG-IUS insertion could effectively treat the uterine adenomyosis and reserve the uterus, and need further studying clinically.

IS-AC-5-5 Fast track gynecologic laparoscopic surgery in Korean women

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Fast track surgery is not so popular in Korea, but it enhances healing process as well as early return to normal activity. Here we are aim to show the experience of the patients with gynecologic disease with fast track surgery. [Methods] There were one hundred and six cases of laparoscopic benign gynecologic surgery with general anesthesia from June 2009 to October 2010. All the patients were received the explanation of fast track surgery on preoperative consultation. Early ambulation was encouraged and regular meals were provided right after operation. Medical charts were reviewed retrospectively. [Result] Among 106 general gynecologic surgery, 61 laparoscopic cystectomy or oophorectomy, 23 laparoscopic hysterectomy, and 22 laparoscopic myomectomy was included. The entire patient went home within 24hour and 17 patients discharged same day. Most of cases were return the bowel movements in a day and additional pain killers were not required. Fourteen out of 17 patient with same day discharge received laparoscopic cystectomy. [Conclusion] Fast track gynecologic surgery is safe and eligible to Korean women. Preoperative counseling and active postoperative management is important for the success of fast tract surgery.

IS-AC-5-6 Efficacy of self-management of vaginal device for pelvic organ prolapse

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[Objective] Correcting vaginal device is an effective treatment for pelvic organ prolapse (POP) but complications can occur during long-term usage. We investigated the improvement of quality of life (QOL) for POP patients when they self-managed a vaginal ring pessary. [Methods] 49 patients who accepted self-management of a ring pessary (SM group) and 42 patients who refused self-care and chose to have the device managed by their attending physician (PC group) were recruited (IRB 2860). Outcomes including QOL assessment and complications were analyzed. QOL was assessed by the SF-36 questionnaire. [Results] The incidence of vaginal erosion in SM group (20.4%) was significantly lower than that in PC group (50.4%) ($P<0.01$). QOL analysis by SF-36 showed that scales of SM group versus PC group were ; physical functioning 74 ± 25 vs 59 ± 29 ; role physical 76 ± 20 vs 60 ± 26 ; bodily pain 67 ± 26 vs 60 ± 27 ; general health 58 ± 20 vs 49 ± 20 ; vitality 65 ± 19 vs 54 ± 24 ; social functioning 83 ± 20 vs 73 ± 28 ; role emotional 77 ± 26 vs 66 ± 31 and mental health 72 ± 19 vs 66 ± 20 ($p<0.01, <0.01$, 0.17, 0.02, 0.03, 0.06, 0.09, respectively). [Conclusion] Self-management of a pessary may improve the QOL of POP patients in regard to both physical and mental health, and can be achieved by introducing education in conservative management.

IS-MW-1-1 Oncogenes (K-ras and c-Myc) modulate tumor immune system and enhance peritoneal carcinomatosis in the ovarian cancer

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[Objective] Little is known whether oncogenes involve the modulation of tumor microenvironment (TME) favorable for cancer development. We here addressed the contribution of K-ras and c-Myc oncogenes in the TME of peritoneal carcinomatosis accompanied by disseminated ovarian cancer. [Methods] K-ras and c-Myc were stably introduced into murine ovarian cancer cell line, ID8, named ID8-Kras and ID8-cMyc. Each cell line was intra-peritoneal injected into mice. Concentrations of VEGF and inflammatory cytokines (IL6, TNFa) in ascites were assessed by specific ELISA. 3T3-L1, adipocyte cell line, was cultured with medium of each cell and expression of IL-6 in 3T3-L1 was assessed by RT-PCR. [Results] ID8-Kras and ID8-cMyc cells accelerated production of ascites compared with ID8 cell. VEGF concentration was higher in ID8-cMyc-induced ascites while IL-6 was higher in ID8-Kras-induced ascites when compared with the others. Medium from ID8-Kras promoted IL-6 expression in the 3T3-L1 adipocytes. [Conclusion] K-ras and c-Myc altered cancer-induced peritonitis (TME) in a different way. c-Myc induced VEGF secretion into ascites followed by angiogenesis. K-ras induced IL-6 secretion probably from adipocytes leading to severe inflammation. These oncogenes were involved in the characteristics of disseminated ovarian cancers through modulation of the TME.

IS-MW-1-2 Combination of MDM2 inhibitor and PI3K/mTOR inhibitor showed synergistic anti-tumor effect in ovarian clear cell carcinomas

The University of Tokyo
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[Objective] In ovarian clear cell carcinoma (OCCC), PI3K/mTOR signaling pathway is frequently activated, while p53 mutation is only detected in 10%. MDM2 inhibitor activates p53 by inhibiting the binding of MDM2 and p53. We aimed to elucidate whether dual inhibition of MDM2 and PI3K/mTOR suppresses cell growth in OCCC cells with wild-type p53. [Methods] We treated 7 OCCA cell lines with a MDM2 inhibitor, RG7112, and/or a PI3K/mTOR inhibitor, DS7423. Cell proliferation and apoptotic cell population were evaluated by MTT assay and Annexin-V assay. In vivo anti-tumor effect was analyzed by using a mouse xenograft model. [Results] Sensitivity to DS7423 was not distinct between p53 wild-type and p53 mutant OCCC cells. However, dose-dependent suppression of cell proliferation by RG7112 was only observed in cells with wild-type p53. The IC50 values of DS7423 were drastically decreased when combined with RG7112. Combination of RG7112 at 2.5μ M and DS7423 at 156nM increased the ratio of apoptotic cells up to 23% in OVTOKO cells. In mouse xenograft models, oral administration of combination DS7423 (3mg daily) and RG7112 (50mg daily) significantly suppressed the tumor growth, compared with each single agent alone ($p<0.05$). [Conclusion] Targeting both PI3K/mTOR pathway and MDM2 might be a promising therapeutic strategy in OCCC with wild-type p53, by synergistically causing the cytotoxic effect.

IS-MW-1-3 A novel biomarker that distinguishes early stage ovarian clear cell adenocarcinomas from benign endometriomas

Tokai University
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[Objective] While certain fraction of endometriomas can develop ovarian clear cell carcinoma (OCCC), there is currently no useful biomarker available for early detection of OCCC from endometriomas. The aim of this study was to describe the diagnostic utility of a novel biomarker for OCCC to distinguish from endometrioma. [Methods] After receiving institutional review board approval, more than 100,000 glycan structures of serum glycoproteins obtained from 134 pretreatment all stage epithelial ovarian cancer (EOC) patients (including 45 OCCCs) and 159 non-cancer control women (including 36 endometriomas) were explored for a mass spectrum approach. Diagnostic accuracy of identified biomarker was compared to the one of CA-125 by comparing area under curve (AUC) and positive/negative predictive values (PPV and NPV). [Results] A2160, a fully-sialylated alpha-chain of complement 4-binding protein, was identified as the candidate target marker. A2160 was significantly elevated in all stage OCCC compared to endometrioma. Diagnostic accuracy of A2160 (cutoff 1.6 U/mL) to distinguish early stage OCCC from endometrioma is significantly higher than that of CA-125 (cutoff 35 IU/L) : AUC for A2160 versus CA-125, 0.92 versus 0.67 ; PPV 95% versus 64% ; and NPV 85% versus 58%. [Conclusion] Our study suggested that A2160 may be a useful biomarker to distinguish early-stage OCCC from endometrioma.

IS-MW-1-4 Four pathological subtypes of high-grade serous adenocarcinoma of ovary, Fallopian tube and peritoneum indicate distinct clinical features and prognosis

Kyoto University
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[Objective] High-grade serous adenocarcinoma (HGSAC) is classified to 4 subtypes based on gene expression profiles. We identified pathological classification according to these subtypes : Immuno-reactive (IR), Mesenchymal Transition (MT), Solid and Proliferative (SP) and Well Differentiated (WD). The aim of this study is to identify distinct clinical findings among 4 pathological subtypes of HGSAC. [Methods] The clinical factors of 69 HGSAC cases (IR : 18, MT : 27, SP : 17, WD : 7), which were treated at our institution were analyzed retrospectively.IC was obtained from all participants. [Results] The origin of all IR cases was ovary or Fallopian tube ($p=0.0279$). IR cases showed significantly earlier stages and possessed less peritoneal dissemination, omental cake and distant metastasis compared with the other subtypes ($p<0.01$ for all). MT included more cases of peritoneal origin, advanced stages, peritoneal dissemination and distant metastasis ($p<0.05$ for both). SP cases tended to include larger amount of ascites ($p=0.0592$) and magnetic resonance images demonstrated that a larger proportion of SP cases (11 out of 16) shows solid appearance compared with the other subtypes (29 out of 52, $p=0.3562$). [Conclusion] The pathological subtypes of HGSAC show distinct clinical behaviors. These findings lead to development of novel diagnostic tools and therapeutic strategies based on precision medicine.

IS-MW-2-1 Branched-chain amino acids regulate insulin-like growth factor binding protein-1 production by decidua and influence trophoblast migration

Kyorin University
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[Objective] Insulin-like growth factor binding protein-1 (BP-1) is a major product of decidua and regulates extravillous trophoblast (EVT) migration. Branched-chain amino acids (BCAA) are known to regulate production of BP-1 in hepatic cells, however it is unknown whether BCAA also regulate BP-1 secretion in decidua. We examined possible changes in BP-1 production in decidua by BCAA and investigated its physiological effects on trophoblast cells. [Methods] Production of BP-1 by decidua was examined by immunoblot after incubation with/without BCAA. EVT migration was evaluated using the media conditioned by decidua. Phosphorylation of focal adhesion kinase (FAK) of EVT cells was also analyzed by immunoblot. The same experiments were repeated with adding RGD peptide, which inhibits BP-1 binding to $\alpha5\beta1$ integrin. [Results] EVT migration and phosphorylation of FAK was enhanced in the conditioned media, presumably due to existence of BP-1 in media. RGD treatment abrogated stimulating effects of the media on both. BCAA deprivation selectively decreased BP-1 secretion from decidua. The conditioned media deprived of BCAA had suppressive effects on EVT migration and phosphorylation of FAK. [Conclusion] We demonstrated that BP-1 directly stimulates EVT migration and that deprivation of BCAA decreased BP-1 production by decidua, thereby suppressing EVT migration, for the first time.

IS-MW-2-2 Epigenotype switch from maternal to paternal type at imprinted DMRs is associated with placental mesenchymal dysplasia

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Saori Aoki[1], Takashi Ohba[1], Hidetaka Katabuchi[1], Hidenobu Soejima[2]

[Objective] Placental mesenchymal dysplasia (PMD), a disorder of placental morphology characterized by placentomegaly and multicystic changes, is often associated with fetal growth restriction and death. A subset of PMDs demonstrate androgenetic/biparental mosaicism and Beckwith-Wiedemann syndrome, suggesting imprinting disruption. However, the etiology of PMD remains unknown. [Methods] We collected frozen placental tissues from 21 patients with PMD in Japan. Genetic analysis involved SNP arrays and whole-exome sequencing (WES). Epigenetic analysis consisted of bisulfite-pyrosequencing to quantitate DNA methylation of 57 imprinting-associated differentially methylated regions (DMRs). [Results] SNP array analysis showed androgenetic/biparental mosaicism in 15 PMD cases, while 6 had normal biparental inheritance. Several copy number variations (CNVs) were found, but since all have been seen in normal individuals they were unlikely to be pathogenic. WES identified no disease-associated variants. Almost all DMRs in mosaic cases had a paternal methylation pattern. In biparental cases, 19 DMRs showed aberrant methylation ; 18 had normally maternally methylated DMRs with hypomethylation, indicating a maternal-to-paternal epigenotype switch. [Conclusion] PMD may be caused not by the genetic abnormalities mentioned above, but by a maternal-to-paternal epigenotype switch at certain DMRs.

IS-MW-2-3 Altered Notch signaling via methylation of Delta-like ligand 1 in placental tissues with early-onset-preeclampsia

Juntendo University
Yota Shimanuki, Shintaro Makino, Atsuo Itakura, Satoru Takeda

[Objective] Notch signaling pathway has shown to be dysregulated in placentas with preeclampsia (PE), but there has been a lack of studies on methylation of Notch family genes in PE. We therefore investigated the methylation status of Notch 1 receptor and its ligand, Delta-like (DLL) 1 and expression of those proteins in placental tissues. [Methods] We executed methylation specific PCR and immunostaining for Notch 1 and DLL 1 with placental tissues from cases of PE and other placental disorders. This study was approved by the ethical committee of our hospital. [Results] The frequency of DLL 1 methylation was significantly higher with early-onset PE than the other groups. On gestational period-matched analysis, the rate of DLL1 methylation was significantly higher in the early-onset PE group than preterm birth group. Increase of syncytial knots and accelerated villous maturation were also most prominent in DLL 1 methylated placentas with early-onset PE. Expression of Notch 1 and DLL 1 in villous trophoblasts and endothelial cells was significantly lower in the early-onset PE as compared to preterm birth controls. [Conclusion] Altered Notch signaling via methylation of DLL 1 might play roles in the pathogenesis of early-onset PE. Assessment of DLL 1 methylation might offer an alternative approach for presymptomatic diagnosis and a biomarker for disease severity with this disorder.

IS-MW-2-4 The expression of C19MC microRNAs in mesenchymal stem cells primarily expanded from human placental tissues

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[Objective] Circulating placenta-specific C19MC miRNAs has been demonstrated to be the potential biomarkers of pregnant disorders. We investigated the expression of C19MC miRNAs in mesenchymal stem cells (MSCs) from various placental tissues. [Methods] This study protocol was approved by the IRB for Ethical, Legal and Social Issues. Normal placentas were obtained at the first and third trimester following written informed consent. We expanded MSCs primarily from chorionic villi (CV-MSCs) and chorionic plate (CP-MSCs) tissues. The expressions of C19MC miRNAs were measured by real-time RT-PCR, and normalized with the endogenous U6. [Results] Either CP-MSCs or CV-DCs positively expressed with MSC markers (CD44, CD73, CD90 and CD105), but negatively with hematopoietic markers (CD34 and CD45), confirmed the characterization of MSCs. The relative expression levels of miR-517a and -518b, two representative members of C19MC miRNAs were 0.00184 and 0.00525 in first trimester CV-MSCs, 11.5 and 8.03 in third trimester CV-MSCs, and 1.47 and 3.81 in third trimester CP-MSCs, respectively. [Conclusion] Placenta-specific C19MC miRNAs was clearly detected in MSCs from different placental tissues. Primarily expanded MSCs may serve as useful tools for uncovering the molecular mechanism on pregnant disorders.

IS-MW-3-1 Nuclear receptor coactivator-6 (Ncoa6) plays as a potent tumor suppressor of endometrial cancer

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[Objective] Nuclear receptor coactivator-6 (Ncoa6) plays an interesting role in regulating estrogen sensitivity in uterus by both up-regulating transcription of estrogen receptor alpha (ERα) and down-regulating ERα expression via ubiquitin-proteasome pathway. In this study, we pursed the role of Ncoa6 in the development of endometrial cancer (EMC). [Methods] We used 1) uterine specific Ncoa6 knock-out (KO) mice (PRcre/+ ; Ncoa6f/f), 2) uterine specific Ncoa6 and Pten KO mice (PRcre/+ ; Ncoa6f/f ; Ptenf/f), and 3) transplant model of uterine epithelial cells from PRcre/+ ; Ncoa6f/f ; Ptenf/f to SCID mice, to demonstrate if the loss-of-Ncoa6 promotes EMC development. Then, we performed mRNAseq to detect responsible gene targets of Ncoa6. Moreover, Ncoa6 expression in normal human endometrium and human EMC were compared in the database. [Results] We found that loss-of-Ncoa6 promoted 1) onset of EMC in aged PRcre/+ ; Ncoa 6f/f) mice, and 2) massive growth of EMC in PRcre/+ ; Ncoa6f/f ; Ptenf/f mice. Importantly, the strong promotion of EMC was observed in ovariectomized mice. Epithelial loss-of-Ncoa6 was sufficient for EMC promotion. The mRNAseq showed that Ncoa6 regulated several carcinogenic pathways. Down-regulation of Ncoa6 in human EMC was frequently observed in the database. [Conclusion] Our data strongly indicated that Ncoa6 could be a potent tumor suppressor of EMCs.

IS-MW-3-2 Retinoic acid receptor β : a potential therapeutic target in retinoic acid treatment of endometrial cancer

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[Objective] The effects of retinoic acid are mediated by the retinoic acid receptor (RAR), and RARα/RARβ especially acts as a tumor suppressor. However, little is known about its role in human endometrial cancer. [Methods] The effects of all-trans retinoic acid (ATRA) on cell proliferation, apoptosis and migration were analyzed in RL95-2 and Hec1A. We also carried out these assays with knockdown of RARα and RARβ. Furthermore we performed analyzed correlation between immunoreactivity of RARα/RARβ and clinicopathological factors endometrial cancer tissue. This study was approved by the Ethics Committee. [Results] We found inhibitory effects of ATRA on cell proliferation, apoptosis, and migration in RL95-2 cells, but not in Hec1A cells. RARα or RARβ knockdown individually could not cancel out the inhibition of cell proliferation by ATRA in RL95-2 cells, but simultaneous knockdown of RARα and RARβ could block its effect on proliferation. RARα and RARβ knockdown dose-dependently reduced the inhibition of migration by ATRA, but the effect was more pronounced with RARβ knockdown than with RARα knockdown. In immunohistochemistry, RARα expression was positively correlated with tumor grade, and RARβ showed the opposite tendency. [Conclusion]RA might have multiple anti-tumor effects and RARβ may be a potential therapeutic target in RA treatment for endometrial cancers.

IS-MW-3-3 17β-estradiol promotes cervical cancer progression by stimulating the production of myeloid derived suppressor cells from hematopoietic stem cells

Osaka University
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[Objective] We previously reported that cervical cancer (CC) patients displaying tumor related leukocytosis (TRL) have poor prognosis and that myeloid derived suppressor cells (MDSC) induced by tumor-derived G-CSF are involved in the mechanism. As younger age is known to be associated with poorer prognosis in CC patients, we speculated estrogen may play roles in the development of TRL, induction of MDSC from hematopoietic stem cells (HSC), and the progression of CC. [Methods] 1. Using HSCs isolated from the bone marrow of ICR mice, the in vitro effect of 17β-Estradiol (E2), ICI 182780 (ICI), or both on the proliferation of HSC were examined by BrdU Assay. 2. Using ovariectomized ICR mice, the effect of E2 on the number of HSC, MDSC and WBC in bone marrow, spleens, and peripheral blood was examined using flow cytometry. 3. Ovariectomized BALB/c nude mice were subcutaneously inoculated with estrogen receptor negative CC cells : HeLa. Then we treated the mice with E2 and examined the tumor growth and the mice survival. [Results] 1. Treatment HSC with E2 increased the number of HSC in vitro. ICI abolished the effect of E2. 2. Treatment mice with E2 increased the number of HSC, MDSC, and WBC. 3. Treatment mice with E2 promoted the growth of CC, leading to the decreased survival in mice. [Conclusion] E2 promotes CC progression by stimulating the induction of MDSCs from HSCs.

IS-MW-3-4 Cancer stem cell survives through the resistance to the ER stress-induced apoptosis by chemotherapeutics

The University of Tokyo
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[Objective] The objective of this study is to determine the degree of sensitivity of cancer stem cells to endoplasmic reticulum (ER) stress such as hypoxia and chemotherapy. [Methods] Cancer stem-like cells of cervical cancer cell line, SiHa, were isolated as sphere cells (CSC). Comparing between CSC and monolayer cancer cells (CC), we addressed the ER stress-mediated apoptosis pathways and the amount of apoptotic cells after ER stress by tunicamycin (TM), a stress inducer, or low-dose cisplatin (CDDP). [Results] TM-induced ER stress-mediated apoptosis occurred in CC whereas did not occur in CSC. Biochemical analysis revealed that CSC showed activation of PERK pathway during TM-induced ER stress while CC showed activation of IRE1 pathway. By PERK inhibitor treatment, CSC fell into the TM-induced ER stress-mediated apoptosis. By contrast, low-dose CDDP (with no cytotoxicity for SiHa) exposure induced ER stress-mediated apoptosis in CSC through IRE1 pathway, but not PERK. Then, combination of low-dose CDDP and IRE1 inhibitor induced dramatically ER stress-mediated apoptosis in CSC. [Conclusion] We concluded that cancer stem-like sphere cell (CSC) acquires the resistance of ER stress-mediated apoptosis by activating ER stress sensors (PERK or IRE1α). Inhibition of ER stress pathway, combined with chemotherapy, may be a novel therapeutic strategy targeting cancer stem cells.

IS-MW-3-5 Expression levels of C19MC-cluster microRNAs in complete hydatidiform mole and mature cystic ovarian teratoma

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[Aim] Complete hydatidiform mole (CHM) was composed of paternal alleles only (androgenic origin), while mature cystic ovarian teratoma (MCT) was maternal allele only (parthenogenic origin). To confirm that C19MC-cluster miRNAs are imprinted and expressed from paternal allele, we investigated the expression levels of C19MC in CHM and MCT. [Method] All samples were obtained after receiving written informed consent and the study protocol was approved by the IRB of our university. Tissue samples were obtained from 11 cases of CHM and 16 cases of MCT. The expression levels of C19MC microRNAs (miR-518b, -517a, -517c) were measured by quantitative real-time RT-PCR. The limitation of detection level by quantitative real-time RT-PCR was less than 50 copies/mL. [Results] The mean expression levels of C19MC microRNAs (miR-518b, -517a, -517c) in cases of CHM were 142254.7, 1301768.8 and 507473.9 copies/mL, respectively. On the other hand, the expression levels of C19MC microRNAs (miR-518b, -517a, -517c) in cases of MCT were all less than the detection levels. [Conclusions] The expressions of C19MC microRNAs were detected in androgenic samples, while those were not in parthenogenic samples, supporting the data that C19MC microRNAs are imprinted and expressed from paternal allele in human.

IS-MW-4-1 mRNA splicing is an emerging player of DNA damage repair and homologous recombination

The University of Tokyo
Michihiro Tanikawa

[Objective] Molecular elucidation of synthetic lethality and PARP inhibitor made an epoch for therapeutic modality for ovarian cancer. However their sensitivity mechanism is still controversial. DNA damage response (DDR), especially homologous recombination (HR) pathway, is closely correlated with the sensitivity and has been under intensive researches. In this study, we analyzed unpredicted roles of mRNA splicing in DNA damage and HR pathway. [Methods] Genome-wide siRNA screens were performed to search for novel HR factors, and we found that U2 snRNP splicing factors, known to be frequently mutated in several malignancies, constituted one of top hits along with established DNA repair factors. These splicing factors were further analyzed for their roles in DNA repair. [Results] HR assay showed strong HR deficiencies in cells devoid of splicing factors. In cells depleted with endogenous splicing factors, accumulation of BRCA1 and Rad51 at DNA damage sites were significantly impaired, and live cell imaging revealed the recruitment of splicing factors to laser-induced DNA damage sites. [Conclusion] Splicing pathway might contribute to DNA damage repair pathway by recruiting HR factors to DNA damage sites. This unpredicted role could explain molecular mechanism of BRCAness with intact HR factors and susceptible to PARP inhibitor, at least in part.

IS-MW-4-2 Clinical significance of sentinel lymph node metastases detected by ultrastaging of three different methods in endometrial cancer

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[Objective] We evaluated clinical significance of sentinel lymph node (SLN) metastases detected by ultrastaging (step section, serial section with immunohistochemistry (SS+IHC) and/or one-step nucleic acid amplification (OSNA)). [Methods] Two hundred seventy seven SLN from 77 patients were obtained with the approval of the institutional internal review board. Each SLNs was analyzed by 2 mm interval histopathological examination with H&E stain (2 mm method). For 11 patients diagnosed as negative by 2 mm method, SLNs were analyzed by SS+IHC. For the other 66 patients, SLNs were analyzed by 2 mm method and OSNA. Furthermore, we investigated the prognostic impacts of the SLNs metastases size. [Results] Metastases were detected in 31 (11.2%) SLNs by three method. ITCs was detected by SS+IHC in 2 SLNs (2 patients) of 38 metastases negative SLNs (11 patients) by 2 mm method. We compared the results of OSNA with 2 mm method. 2mm method revealed 26 positive (11 patients) and 213 negative SLNs (55 patients), while OSNA revealed 22 positive (10 patients) and 217 negative SLNs (56 patients). Two of 15 with SLNs metastases had macrometastases and did have recurrence and died. On the other hand, patients with micrometastases and ITCs, or with metastases positive by only OSNA had no recurrence. [Conclusion] Metastases could be detected efficiently by ultrastaging.

IS-MW-4-3 Expression of UCP2 predicts the efficacy of neoadjuvant chemotherapy for locally advanced uterine cervical cancer

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[Objective] We examined the correlation between UCP2 (uncoupling protein 2) expression and the efficacy of Neoadjuvant chemotherapy (NAC) for locally advanced uterine cervical cancer. [Methods] We reviewed 58 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=34), and another group in which NAC was ineffective and radiation therapy was performed (group B ; n=24). UCP2 expression was examined immunohistochemically in paraffin-embedded sections using the avidin-biotin peroxidase complex method. This study was approved by the Ethics Committee in our facility. [Results] The expression of UCP2 was significantly higher in the group B than in the group A (p=0.011). The overall survival of group A was significantly better than of group B ($P<0.01$). Cases were divided into two groups : one group in which UCP2 expression was low level (weighted score$\leq$4, n=21), and another group in which UCP2 expression was high level (weighted score$\geq$6, n=37). Low UCP2 expression group might be responsive to NAC than high expression group (p=0.038). [Conclusion] It is suggested that the expression of UCP2 may predict the efficacy of NAC as a treatment for locally advanced uterine cervical cancer.

IS-MW-4-4 Soluble VEGF receptor 1 (sFLT1) induces death of ovarian and colorectal cancer cells in a non-apoptotic way

Osaka University
Tatsuya Miyake, Keiichi Kumasawa, Noriko Sato, Tsuyoshi Takiuchi, Hitomi Nakamura, Tadashi Kimura

[Objective] Soluble VEGF Receptor1 (sFLT1) is an inhibitor of angiogenesis generated within living bodies, competing with angiogenic factors. VEGF family imbalance with sFLT1 levels leads to pathological states such as tumor growth. However, there has been no report of direct damage to sFLT1-treated tumor cells. This study was carried out to clarify how sFLT1 leads to injured cells. [Methods] We tried to elucidate the direct effects of sFLT1 on two ovarian cancer and one colorectal cancer cell lines. We exposed these cells to endogenous transfection or exogenous treatment of sFLT1 in two ways. The effect of sFLT1 on cell proliferation, cytotoxicity were examined by cell counting, LDH Release Assay. Soluble FLT-1 induced apoptosis was analysed using TUNEL staining, western blot, and FACS. We also tried in vivo experiments. [Results] The transfection of pLV-sFLT1 and the treatment with recombinant VEGFR-1 induced cytotoxicity, but didn`t increase caspase-3 activity, the number of TUNEL-positive cells, and Annexin V-positive cells. By FACS for Annexin V, transfection of sFLT1 increased the percentage of necrotic cells. In ovarian cancer model mice, recombinant VEGFR1 and bevacizumab groups showed significantly smaller tumors. [Conclusion] In this study, non-apoptotic cell damage was found to be induced by sFLT1. Soluble FLT1 could be a future therapeutic candidate for several cancers.

IS-MW-5-1 The improved management of obstetric hemorrhage can reduce the maternal mortality rate : A report from the Maternal Death Exploratory Committee in Japan

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[Objective] To clarify the problems related to maternal deaths in Japan, including the diseases themselves, causes, treatments, and the hospital or regional systems. [Methods] Women who died during pregnancy or within a year after delivery between 2010 and 2014 throughout Japan were analyzed. This study was approved by the ethics board of chief institution of the present study. [Results] Maternal deaths (n=213) were caused by postpartum hemorrhage (PPH ; 23%), brain disease (16%), amniotic fluid embolism (12%), cardiovascular disease (8%) and pulmonary disease (8%). It was difficult to prevent maternal deaths due to amniotic fluid embolism and brain disease. In contrast, half of the deaths due to PPH might had possibility to prevent, because the peak duration between the initial symptoms and initial cardiopulmonary arrest was 1–3 hours, but there were no cases of massive PPH in which cardiopulmonary arrest occurred within 30 minutes. 58% (98 cases) of maternal deaths still occur after maternal transport between medical facilities. In particular, 15 cases were transferred from a facility in which only one or two obstetricians were on duty or from a midwifery home. [Conclusion] The committee considered that the deaths of approximately half of the pregnant women died due to PPH in Japan were potentially preventable.

IS-MW-5-2 Prediction of adherent placenta with placenta previa using a novel scoring system

Kobe University
Kenji Tanimura, Masashi Deguchi, Mayumi Morizane, Hideto Yamada

[Objective] Adherent placenta (AP) is a life-threatening condition, and is often complicated by placenta previa (PP). We have devised an original scoring system for predicting AP complicated by PP (APPP), and conducted a prospective cohort study to evaluate the diagnostic accuracy of our scoring system (APPP score). [Methods] APPP score is composed of the following two components ; 1) past history of previous cesarean section, dilation and curettage, or other surgeries damaging endometrium ; and 2) imaging findings of ultrasonography and MRI. Each item is graded either 0, 1, 2, or 4 points, and then added up to yield a number between 0 and 24. If patients had score 8 or more, we suspected that they had APPP. The diagnostic accuracy of APPP score were estimated. This study was approved by the institutional ethic boards. The informed consent was obtained from all patients. [Results] The study included 104 pregnant women with PP, and 17 had APPP score 8 or more. Fourteen of the 17 actually had APPP. However, two women with APPP were overlooked by APPP score. APPP score yielded 88% sensitivity, 96% specificity, 82% positive predictive value, and 98% negative predictive value. [Conclusion] This prospective cohort study demonstrated that a novel scoring system might be useful for identifying patients at a high risk for APPP.

IS-MW-5-3 Brain damage-preventive effects of progesterone in a cerebral palsy rat model

Chiba University
Yoshimasa Kawarai, Hiroshi Ishikawa, Hirokazu Tanaka, Makio Shozu

[Objective] Neonatal cerebral palsy (CP) is caused by a series of brain damage repair processes after perinatal hypoxia/ischemia-reperfusion. Progesterone (P) promotes recovery from damage caused by brain trauma in adults. In this study, we used a CP rat model to investigate its brain damage-preventive effects. [Methods] Female rats on pregnancy day 18 were laparotomized, and blood flow in the uterine artery was cut off for 45 min. P (0.10 mg/d) or medroxyprogesterone acetate (MPA, 0.12 mg/d) was continuously administered subcutaneously to the offspring for 9 days from day 1 after birth. The rotarod test was used to assess motor coordination ability. Survival time (T) was defined as time during which they were able to stay on the rotarod and analyzed by using the Kaplan-Meier method. Furthermore, brain tissue was observed on microscopy. [Results] The hypoxia/ischemia treatment significantly shortened T. In the P group, T was restored to sham surgery level (log rank test, p=0.001), but not in the MPA group. The neuron count in the cortical and hippocampal CA1 region was decreased, as well as the oligodendrocyte count in the corpus callosum. These changes manifested at 5–50 days of age. P administration decreased these histological changes. [Conclusion] P administration after birth restored motor ability in the CP rats, showing that it may prevent brain damage with CP.

IS-MW-5-4 Effects of maternal positions on regional brain oxygen saturation during cardiac arrest and cardiopulmonary resuscitation in pregnancy：An animal experimental study

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[Objective] Cardiopulmonary resuscitation (CPR) during pregnancy requires particular patient positioning to minimize aortocaval compression. Regional brain oxygen saturation (rSO_2), a noninvasive form of cerebral oximetry, can predict return of spontaneous circulation during cardiac arrest, as well as the coronary perfusion pressure (CPP). In the present study, we investigated the correlation between rSO_2 and the optimal maternal position during cardiac arrest. [Methods] We used a swine that placed fetal mannequin in an abdominal cavity as a pregnant model. We evaluated the effect of supine with left uterine displacement position (LUD), supine position (SP), left-lateral tilt position (L-LT), and right-lateral tilt position (R-LT) on the 2-min interval CPP as well as the rSO_2 by using the INVOS™ system that monitors rSO_2 during chest compressions. [Results] In the LUD, SP, L-LT, and R-LT, the average CPP and rSO_2 were 50.0, 39.5, 40.0, 32.75 mmHg, and 68.5, 66.75, 64.0, 64.5% respectively. The highest and lowest CPP levels were accomplished with the LUD and R-LT, respectively ($p<0.05$). The rSO_2 in LUD was significantly higher than L-LT as well as R-LT ($p<0.05$). [Conclusion] The findings of this study suggest that LUD is the most optimal position under maternal CPR. R-LT might be avoided because of the resulting from low CPP and rSO_2.

IS-MW-6-1 Effects of a new quantitative analysis for preimplantation genetic diagnosis of mitochondrial DNA disorders

Keio University
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[Objective] Leigh syndrome is caused by a homoplasmic 8993T>G mutation in intracellular mitochondrial DNA (mtDNA) and the previous method for preimplantation genetic diagnosis (PGD) of the disease uses quantitative PCR which needs labor-intensive processes, such as plotting a standard curve based on the fluorescence intensity ratio of normal/mutant plasmid mtDNA clones. We aimed to assess the newly introduced quantitative method for PGD. [Methods] 1) Plasmid DNA mixed with 8993T and 8993G were prepared to each mutation ratios (0, 10, 25, 50, 75, 90, 100%) and heteroplasmic ratios were analyzed by pyrosequencing. 2) Whole genome amplification (WGA) using multiple displacement amplification, multiple annealing and looping based amplification cycles, were performed for each samples and were also analysed. This study was approved by the institutional review board. [Results] 1) Each samples were called as a heterozygous or homozygous for the mutation correctly. 2) Although the calculated rates of heteroplasmy samples were slightly lower than the known rate with either WGA, it was possible to assume that they were heteroplasmic, while the homoplasmy samples (0% and 100% mutation) were accurately quantified. [Conclusion] Pyrosequencing can be an analytical method for PGD of the disease. The biases observed were considered to be attributable to WGA itself or the forms of plasmid samples.

IS-MW-6-2 Hypoxic response mediated by hypoxia inducible factor-1α in uterine leiomyoma and myometrium

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[Objective] Although uterine leiomyoma enlarges in hypoxia, a hypoxic response has not been elucidated. We clarified whether hypoxia induces hypoxia-inducible factor-1α (HIF-1α) and HIF-mediated hypoxic responses in uterine leiomyoma and myometrium *in vitro*. [Methods] IRB at our facility approved protocols. We obtained consents from participants. We cultured primary leiomyoma and myometrial cells obtained from surgical specimens under hypoxia (1% oxygen) or normoxia, and extracted total RNA and protein. We performed RT-qPCR, immunoblotting, and Chromatin immunoprecipitation-qPCR to detect mRNA, protein, and HIF-1α binding to the promoter of HIF-target genes, respectively. [Results] Hypoxia induced a significant increase of HIF-1α protein, but a significant decrease of HIF-1α mRNA without any initial increase in leiomyoma and myometrial cells up to 6 h in a time-dependent manner. Hypoxia up-regulated mRNA expression of 9 out of 9 HIF-target genes. HIF-1α bound putative HIF response elements on the promoter of 3 out of 3 HIF-target genes. All of the hypoxic responses were attenuated in leiomyoma cells. [Conclusion] Hypoxia induces HIF-mediated hypoxic responses in both leiomyoma and myometrial cells. The attenuated responses in leiomyoma cells may reflect hypoxia tolerance of uterine leiomyoma. The hypoxia-induced decrease of HIF-1α mRNA is a unique character of uterus-derived cells.

IS-MW-6-3 Trophoblast specific conditional Atg7 knockout pregnant mice develop gestational hypertension

University of Toyama[1], Osaka University[2]
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[Objective] We have reported that impairment of autophagy in extravillous trophoblast of preeclamptic cases. But it is unclear whether impaired autophagy is cause or the effect. [Methods] Lentiviral vector mediated trophoblast-specific Atg7, which is one of the autophagy-related proteins, knockout system (cKO) was used. We also compared the phenotypes between cKO and systemic Atg7 knockout (sKO) mice. [Results] cKO mice developed gestational hypertension (GH) and cKO placentas weight was significantly lighter, whereas no significant differences were observed in urinary protein levels or fetal body weights. sKO mice stayed normotensive, and its placental weight and urinary concentration levels did not show significance. P62 immunostaining of placental sections revealed impaired autophagy was localized in giant trophoblasts and the spongiotrophoblast layer (Sp) in both cKO and sKO placentas. The ratio of Sp to total area was significantly reduced, suggesting that absence of autophagy reduced the number of spongiotrophoblast. Trophoblast invasion into the maternal decidua was significantly decreased and the wall/lumen ratio of the spiral arteries was significantly increased in cKO placentas, but not in sKO placentas. [Conclusion] We firstly showed that impaired autophagy induces the shallow trophoblast invasion and impairment of vascular remodeling, resulting in GH using cKO mice.

IS-MW-7-1 27-hydroxycholesterol promotes estrogen receptor positive breast cancer

Tokyo Medical and Dental University
Tomonori Ishikawa, Toshiro Kubota

[Objective] The risk of estrogen receptor (ER)-positive (+) breast cancer increases in postmenopausal women despite of the decline of circulating estrogen levels. Endocrine-based therapies against ER+ breast cancer with synthetic selective estrogen receptor modulator (SERM) are often resistance develops, suggesting that there are yet unknown, important ER-mediated mechanisms. We have reported the most abundant circulating oxysterol : 27-hydroxycholesterol (27HC) is the first identified endogenous SERM. The objective of this study is to investigate the impact of 27HC on ER+ breast cancer. [Methods] ER+ breast cancer progression by 27HC was determined with both proliferation assay in vitro and tumor xenograft model in vivo. Serum and tissue 27HC content of breast cancer patients was compared with healthy controls. The correlation of cyp27a1 and cyp7b1, which are 27HC producing and catabolizing enzyme respectively, with overall survival in ER+ cancer patients were examined by Kaplan-Meier curves. [Results] 27HC promotes ER+ breast tumor cell proliferation both in vitro and in vivo. 27HC contents is increased in ER+ breast cancer. Tissue expression of cyp7b1 reversely correlates with overall outcome. [Conclusion] 27HC actions as an endogenous SERM contribute to breast cancer progression. Strategies to lower 27HC may be complement approaches targeting cholesterol to prevent breast cancer.

IS-MW-7-2 The effect of soymilk on skeletal muscle atrophy and muscle weakness in estrogen deficient status

Nagasaki University
Yuriko Kitajima, Hideaki Masuzaki

[Objective] Estrogen deficiency may deteriorate various estrogen-sensitive tissues including skeletal muscle results in skeletal muscle atrophy and weakness. Although hormone replacement therapy is effective, side effects are worrisome. Soymilk contains isoflavone retains estrogenic property. In this study, we examined the effects of soymilk on skeletal muscle and satellite cells in mice model. [Methods] Six-week-old C57BL/6 female mice were ovariectomised (OVX). Sham operated mice were used as control (Sham). Mice received conventional food (C) or soymilk-rich food (22.7% of the conventional food was replaced by soymilk, S) for 3 months. Cross sectional area of TA was determined. Muscle strength was measured by grip test. Single myofiber associated with satellite cells were isolated and cultured for 3 days. Expression of Pax7, MyoD, Ki67, and myoG in these cells were evaluated. [Results] Although the area of TA muscle was significantly decreased in C, muscle atrophy was not observed in S similar to Sham. Accordingly, muscle strength was also significantly decreased in C but not in S or Sham. Proliferation and differentiation of satellite cells per myofiber were increased in S. [Conclusion] Our results may indicate protective effects of soymilk on muscle atrophy and weakness. Soymilk may be useful to maintain motor functions in female with estrogen deficiency.

IS-MW-7-3 Intraperitoneal inflammation enhances the formation of endometriosis in murine model

Tokushima University
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［Objective］ The aim of this study is to clarify the intraperitoneal inflammation progress the development of endometriosis in murine model. ［Methods］ We used C57BL/6J female mice in 8 weeks. After oophorectomy, estradiol（2μg/day）was injected subcutaneously for 7 days. The endometrium tissue was removed on 8th day. We implanted endometrial tissue and flesh blood（100μl/body）to recipient mice intraperitoneally as a control group. In another group, LPS（100μg/body）was injected intraperitoneally one day before the implantation. In the other group, the endometrium tissue, flesh blood（100μl/body）and LPS（100μg/body）was implanted at the same time. The number of lesion and the greatest dimension was measured in 15th day. As a next trial, we conducted the analysis of the concentration of inflammatory cytokines in ascites. We injected LPS（50μg/body）into the abdominal cavity of mice. Then abdominal irrigation was done with saline（1ml）after 2, 6 hours, 1, 3, 5, 7 and 10days of injection. The outcome measures are TNFα, MIP−2, and IL−6. ［Results］ The endometrial lesions are significantly formed in the mice which was implanted blood, endometrial tissue, and LPS at the same time. TNFα and IL−6 reached the maximum level in 2 hours, and MIP−2 did in 7days after injection. ［Conclusion］ LPS causes inflammation, and it progresses the development of endometriosis.

ISP-1-1 Pretreatment leukocytosis predicts clinical outcome in cervical cancer

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[Objective] To analyze the prognostic values of pretreatment leukocytosis in patients with cervical cancer in comparison with various risk factors. [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 Hyogo cancer center. Progression-free survival (PFS) and overall survival (OS) were compared between the leukocytosis group (>9,000/μl) and the non-leukocytosis group. Survival curves were 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] Of a total 2,266 patients, 1,305 had stage I, 578 had stage II, 256 had stage III, 127 had stage IV. Pretreatment leukocytosis was observed in 318 patients (14%). Multivariate analysis revealed that age (HR ; 1.7, $p<0.001$), advanced stage (HR ; 4.8, $p<0.001$), histology (HR ; 2.0, $p<0.001$) and pretreatment leukocytosis (HR ; 1.5, $p<0.001$) were independent predictors of decreased OS. In patients with stage I–III, leukocytosis group showed significantly shorter OS (I : $p<0.01$, II : $p<0.05$, III : $p<0.01$) and significantly shorter PFS (I : $p<0.05$, II : $p<0.05$, III : $p<0.01$) than non-leukocytosis group. [Conclusion] Pretreatment leukocytosis is the independent prognostic factor in patients with cervical cancer.

ISP-1-2 A retrospective analysis of neoadjuvant chemotherapy in the treatment of uterine cervical cancer

Shikoku Cancer Center
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[Objective] Neoadjuvant chemotherapy (NAC) for cervical cancer has been used in clinical practice so far, whereas its indication and efficacy remain controversial. Therefore, we have retrospectively investigated the clinical data of cervical cancer patients underwent NAC in our hospital. [Methods] A total of 90 patients treated with paclitaxel plus cisplatin followed by surgery was assessed for treatment progress and response using RECIST and Kaplan-Meier method. [Results] The age range was 24–74 (median 49), and FIGO stage were IB1 : 20 patients, IB2 : 15, IIA : 6, IIB : 38, IIIA : 1, IIIB : 5, IVB : 5. Total response rate was 85.6% (CR : 34 patients, PR : 43, SD : 12, PD : 1), and that of 56 patients with squamous cell carcinoma (SCC) and 34 with non-SCC were 90.7% and 82.4%, respectively. Seventy-nine patients underwent radical hysterectomy. Adjuvant chemotherapy was performed in 77 of 90 patients and 24 patients were followed by radiation. The median follow-up duration was 6.0 years, and there were no significant differences in survival rates between SCC and non-SCC (PFS : $P=0.935$, OS : $P=0.180$). [Conclusion] The patients with SCC well responded to NAC and most of them completed surgery. A prospective study limiting the cell type and clinical stage may lead to reveal its efficacy on survival.

ISP-1-3 The role of G-CSF-induced myeloid-derived suppressor cells (MDSC) in the induction of cancer stem-like cells in cervical cancer

Osaka University
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[Objective] To investigate the role of G-CSF-induced myeloid-derived suppressor cells (MDSC) in the induction of cancer stem cells (CSC) in uterine cervical cancer and its mechanism. [Methods] ALDH (aldehyde dehydrogenase) activity was employed as a marker of CSC. The stemness of ALDH-high population in ME180 cervical cancer cell line was first confirmed. We next established ME180 cell lines stably transfected with G-CSF expression vector (ME180-GCSF) or control vector (ME180-control). Then, we investigated the MDSC and ALDH-high ME180 cells in tumors obtained from ME180-GCSF-bearing mice and ME180-control-bearing mice. To demonstrate that MDSC induces the stemness in ME180 cells, ME180 cells were co-incubated with MDSC. To explore the mechanism by which MDSC induce the stemness, the protein array was performed. [Results] ALDH-high ME180 cells have stem cell properties and show resistance to radiotherapy and chemotherapy. MDSC and ALDH-high ME180 cells were more frequently observed in ME180-GCSF-derived tumors than in ME180-control-derived tumors (MDSC : 2.4% vs. 0.68%, ALDH-high cells : 1.2% vs. 0.38%). Co-incubation of ME180 cells with MDSC increased the number of ALDH-high ME180 cells. We identified a MDSC-derived cytokine that plays a key role in the induction of the CSC. [Conclusion] MDSC induced by tumor-derived G-CSF increases the number of CSC in uterine cervical cancer.

ISP-1-4 HER2 as a Novel Therapeutic Target for Cervical Cancer

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[Objective] Although surgery and radiation represent the current standards for the treatment of cervical cancer, there is no effective therapy for metastatic or recurrent cases. In this study, we sought to establish a patient-derived xenograft (PDX) model using human cervical cancer tissues and apply it as part of a therapeutic strategy. [Methods] Small pieces of human cervical cancer were meticulously grafted under subrenal capsules of BALB/C-nude mice within two hours after surgery. Grossly visible and fresh tumor tissues in developed PDX tumors were serially transplanted for subsequent generations. Phenotypic and genetic features were compared between patient and PDX tumor tissue using H&E staining, array-comparative genomic hybridization (aCGH) and targeted next-generation sequencing (NGS) analysis. [Results] Of the 21 patient samples collected, 16 were successfully engrafted into mice and resulted in PDX models (engraftment rate=76.2%). Serially passaged PDX tumors retained both histopathologic and genetic features of the original tumors. Among nine molecularly profiled cervical cancer patient samples, one HER2-amplified tumor was detected by aCGH and targeted NGS. We confirmed HER2 overexpression in the tumor and serially passaged PDX tissues. Moreover, co-administration of trastuzumab and lapatinib in the HER2-overexpressing PDX significantly inhibited tumor growth compared to the control ($P<0.05$). [Conclusion] We established histopathologically and genomically homologous PDX models with human cervical cancer tissue using subrenal implantation. We propose using HER2 inhibitor-based therapy for HER2-amplified cervical cancer refractory to conventional therapy.

ISP-1-5 Genome-wide gene expression profiling of cervical cancer in Xinjiang women by oligonucleotide microarray and detection of apoptosis genes c-IAP1, Bcl-xl, Bcl2

The People's Hospital of Xinjiang Uyghur Autonomous Region, China
Gulan Tuohetimulati, Mayinuer Niyazi, Wang Ling

[Objective] To use gene chip technology searched related gene to analyze differences of Cervical cancer-changing spectrum, to validate apoptosis-related gene, explore the pathogenesis of Uyghur Cervical cancer (Cc) and the relationship with clinicopathological parameters. [Methods] Affymetrix genome-wide oligonucleotide microarray was used of expression Porfiling for 5 Cc and 5 normal cervix. Genes with differential expression were identified by analytic tools of bioinformatics and functional genomics. Real-time quantitative (PCR), immunohistochemistry were used to validate expression of genes : Bcl2, Bcl-xl, c-IAP1 in 45 Cc and 21 normal cervical. [Results] The relationship expression these genes with clinicopathological and prognostic parameters. The genome-wide expression profiling showed that expression of 1326 genes was increased by at leased 2-fold in Cc over normal cervix, while expression of 1432 genes was decreased by at least 2-fold in cc over normal cervix. Apoptotic pathways were over-expressed in Cc. The anti-apoptotic genes c-IAP1 of the IAP family and Bcl-xl of the Bcl2 family were expressed at high levels in Cc, while the anti-apoptotic gene Bcl2 was expressed at low level in cc. Validation of microarray data was done at both mRNA and protein levels, which further demonstrated the following. [Results] The mRNA of anti-apoptotic genes c-IAP1, Bcl-xl were expressed at high levels and Bcl2 were expressed at low levels in Cc. The protein expression level of anti-apoptotic genes c-IAP1, Bcl-xl were high and Bcl2 was low in cc. [Conclusions] (1) Proving the occurrence of invasive cervical cancer is a multistep genetic pathways regulated more complex process of biological molecular marker spectrum of cc and screening of marker gene, to study the molecular mechanism of Cc occur in Xinjiang It is helpful to get further understanding on the molecular mechanism of development and signal transduction pathway for study of common differentially expressed genes between them. (2) Cc tissue of IAP family and Bcl2 family anti-apoptotic proteins high expression may play an important role in cc anti-apoptotic mechanisms, these genes can be used for cc early diagnosis and monitoring, for molecular targeted therapy also has important guiding significance. Key words : Apoptosis ; Microarray ; Expression profilling ; Cervical cancer ; Bcl2 ; Bcl-xl ; C-IAP1

ISP-1-6 Methylation of HPV16 genome CpG site in L1 and LCR are associated with HPV persistent infection and cervical cancer development in Uyghur women

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[Objective] To obtain detailed methylation information in HPV16 genome Cpg site in L1 and LCR, to evaluate the relationship between HPV16 L1, LCR methylation levels and HPV persistent infection, cervical cancer occurrence and development. [Methods] HPV (+) (n=300) women did HPV genotypes test and biopsy under colposcope detecting pathological diagnosis and dividing five pathological levels (persistent infection, transient infection, CIN1, CIN2- 3, cervical cancer) in Xinjiang people's hospital. Using ROC curve analysis to evaluate the value of HPV16 methylation to diagnose CIN2+ and predict HPV persistent infection ; Immune histochemical method to inspect the expression of L1 protein in the 5 pathological levels ; Multiple real-time PCR to detect HPV16 E2/E6 ratio to indicate the physical state. [Results] High methylation in 13 CpG sites of L1 increased the risk of CIN2+, the highest value of OR was 9.89 for site 6650 ; AUCs of 13 CpG sites in L1 for the diagnosis of CIN2+ were between 0.756 to 0.862, the highest value is site 6650 with the AUC of 0.862 ; High methylation of site 6389, 6457, 6581, 6650, 6796, 7034 increased the risk of persistent infection, $P<0.05$, the strongest risk estimate site was site 6389 (OR : 13.33, 95%CI : 3.95-28.08) ; AUCs of these sites in L1 for the prediction of HPV persistent infection were between 0.656 to 0.943, the highest value is site 6389 with the AUC of 0.943 ; The methylation rate of site 31, 37, 43, 52 and 58 in LCR were statistically significant differences among five level of pathological lesions and as the disease progresses, methylation rates were on the rise ; high methylation in these CpG sites increased the risk of CIN2+, the strongest risk estimate site was site 58 (OR : 5.71, 95%CI : 2.54-12.84), AUCs of these CpG sites for the diagnosis of CIN2+ were between 0.640 to 0.848, the highest value of site is site 58 with the AUC of 0.848 ; methylation rate of CpG sites in promoter, E2BS3 and E2BS4 was on the decline with increase of proportion of integrated status in CIN 2-3 and cervical cancer, the difference was statistically significant, $P<0.05$. methylation rate of CpG sites in cervical cancer of integrated status were between 11.50% to 14.25%. [Conclusion] Methylation rates of HPV16 L1 has high value to predict HPV persistent infection, cervical cancer lesion progress ; The methylation of CpGs in the promoter region was common in HPV16 LCR region, which indicated the methylation of promoter is very important in the regulation of transcription. Key words : Cervical carcinoma ; methylation ; L1 ; Long control region ; Uyghur

ISP-1-7 Contribution of STAT3 to the resistance of TRAIL-induced apoptosis in cervical cancer

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[Objective] The sensitivity of TNF-related apoptosis inducing ligand (TRAIL)-induced apoptosis differs among various cells including cervical cancer cell lines. The aim of this study is to investigate the potential pathways to improve the sensitivity and seek out the potential therapeutics for cervical cancer, focusing on Stat3 which is a novel target of cancer therapy. [Methods] Expressions of death receptor (DR) 5 and survivin of CaSki and SiHa were measured using RT-qPCR. Then the pSTAT3 level was analyzed using Western blotting. The effect of STAT3 inhibitor on TRAIL-induced apoptosis of SiHa was assessed by Annexin V. After pretreatment of resveratrol (RVT), which is a natural product to suppress STAT3 pathway, TRAIL-induced apoptosis of SiHa was asessed by Annexin V. [Results] SiHa was resistant to TRAIL-induced apoptosis. There was no significant difference between CaSki and SiHa regarding the expression of DR5 and survivin although pSTAT3 expressed higher in SiHa. Inhibition of STAT3 by STAT3 inhibitor and RVT both dramatically enhanced TRAIL-induced apoptosis of SiHa supressing pSTAT3. [Conclusion] It is suggested that STAT3 would play a central role in resisting the TRAIL-induced apoptosis of cervical cancer. The therapeutics like RVT which can suppress STAT3 activation could be promising strategies for the treatment of cervical cancer.

ISP-1-8 Regeneration of Cervical Reserve Cell-like Cells from Human Induced Pluripotent Stem Cells (iPSCs) : A Novel Method in the Field of Gynecologic Research

The University of Tokyo
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[Objective] Cervical reserve cells are the origin of cervical cancer and investigating the characteristics of cervical reserve cells can be of help to understand cervical cancer stem cells (CSC) s features. In this study, we developed a method for regeneration of cervical reserve cell-like properties from human induced pluripotent stem cells (iPSCs) (induced reserve cell-like cells ; iRCs). [Methods] Using human iPS cells (201B7 ; kindly provided from Dr. Shinya Yamanaka), we induced intermediate mesodermal cells and cultured these cells on collagen IV-coated plates. P63, CK17, CK8 and CK5 were used as reserve cell markers by immunofluorescence. CK7, AGR2, CD63, MMP7 and GDA were used as squamocolumnar junction (SC junction) markers by RT-PCR. ERα, ERβ and CA125 were used as Mullerian duct -derived cell markers by RT-PCR. For confirming the bluripotency of iRCs as epithelial progenitor cells, we applied air-liquid interface and 3D-embeded culture method. [Results] About 70% of iRCs are positive for reserve cell markers. IRCs also expressed SC junction markers. IRCs expressed CA125. iRCs formed glandular epithelial-like cells in 3D-embedded culture and got rather pseudostratified than properly stratified in air-liquid interface culture. [Conclusion] We proposed a new method for gynecologic research by generating cervical reserve cell-like cells from iPSCs.

ISP-2-1 Mixed Endometrial Stromal and Smooth Muscle Tumors of the Uterus Associated with Uterine Tumor Resembling Ovarian Sex-cord Tumor

Oita University
Chiharu Mizoguchi, Harunobu Matsumoto, Kentaro Kai, Kaei Nasu, Hisashi Narahara

[Introduction] Mixed endometrial stromal (ES) and smooth muscle (SM) tumor is composed of a prominent component of smooth muscle and endometrial stroma. We report here a case of mixed ES and SM tumor which was composed of leiomyoma, low-grade ES sarcoma (ESS) with sex-cord like differentiation, and uterine tumor resembling ovarian sex-cord tumor (UTROSCT). [Case] A 63-years-old multiparous Japanese woman was referred to our institution complaining of recurrent atypical genital bleeding, anemia, and pointed out intrauterine tumor detected by hysteroscopy. Endometrial Pap smear was negative and tumor markers were within normal range. Magnetic resonance imaging demonstrated a 3.4 cm diameter solid tumor in her uterine cavity. Subsequently, she he underwent abdominal total hysterectomy and bilateral adnexectomy. Pathologically, the tumor was consisted of leiomyoma with necrosis, CD10-positive low-grade ESS, and CD10-negative UTROSCT. The component of ESS has extensive necrosis and the mitosis of 20/10 high power fields. She undergoes routine post-treatment surveillance without adjuvant therapy. [Discussion] Mixed ES and SM tumors should be distinguished from leiomyoma, ESS, and UTROSCT. At present, standard treatment protocol is not determined because natural behavior of this tumor is unclear. Careful follow-up is necessary for the possibility of recurrence.

ISP-2-2 Repeated resections of the tumor extend the survival of the patients with leiomyosarcoma：two case reports

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Uterine leiomyosarcoma (LMS) accounts for one-thirds of sarcomas that occurs in the uterine body. However the incidence of LMS is low, standard therapy has not been established. Clinical findings of LMS are similar to uterine fibroids, even if the possibility of sarcoma was suspected in MRI image, so preoperative definitive diagnosis is difficult. LMS has a tendency of metastasis by hematogenously regardless of it's stage, and prognosis is poor. Median survival time is as short as 31 months, the only effective treatment is complete resection.This time, we report two cases of LMS that achieved long term survival by performing repeated tumor resections for the post-operative recurrences. Case 1：In 2006, a 50-year-old woman underwent laparoscopic uterine myomectomy due to uterine fibroids. The postoperative pathological diagnosis was LMS. She underwent 6 times resective surgeries for recurrences after the primary surgery during 9 years. Case 2：In 1985, a 26-year-old woman underwent abdominal hysterectomy due to uterine malignant tumor. The postoperative pathological diagnosis was LMS, so she was treated with adjuvant combination chemotherapy and performed 5 times resective surgeries for the recurrences. These patients are still alive.When the recurrence of LMS seems to be resectable, it should be better to perform tumor resection. It was thought to contribute improve prognosis.

ISP-2-3 Pazopanib for recurrent or advanced uterine leiomyosarcoma：a case series

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Pazopanib, a multitargeted tyrosine kinase inhibitor, has activity in patients with soft-tissue sarcoma. We retrospectively assessed the outcomes and adverse events of pazopanib in three patients with recurrent or advanced uterine leiomyosarcomas, using the Response Evaluation Criteria in Solid Tumors (ver 1.1) to assess tumor responses. Case 1：A 62-year-old woman relapsed and received many treatments over five years. In subsequent treatment with pazopanib (800 mg) orally once daily for 2 months, the sum of her tumor diameters increased by 21.2% vs. by 43.7% after cessation. She died of the disease. Case 2：A 47-year-old woman had multiple lung metastases which progressed on her initial treatment. In subsequent treatment with pazopanib for 3 months, the sum of her tumor diameters increased by 46.8% vs. by 81.9% after cessation. She died of the disease. Case 3：A 75-year-old woman had a recurrent pelvic tumor that was surgically removed. A tumor again recurred and she received pazopanib, which has been inhibiting tumor growth and stabilizing the disease for 7 months. No patients had serious adverse events. The tumors of two of these patients enlarged suddenly after ending pazopanib treatment. The prognosis of recurrent uterine leiomyosarcomas is poor, thus disease control is important. Therefore the decision to discontinue pazopanib therapy requires careful consideration.

ISP-2-4 Prognostic impact of ovarian preservation and hormonal therapy in low-grade endometrial stromal sarcomas

The University of Tokyo
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[Objective] Low-grade endometrial stromal sarcoma (LG-ESS) is generally positive for ER and PR. The aim of this study is to investigate the prognosis of LG-ESS and its correlation with hormonal status. [Methods] We retrospectively investigated 12 cases of LG-ESS in our hospital under approval of our ethics committee. The median follow-up period is 102 months. Four patients underwent surgery with ovarian preservation. Four patients received MPA and/or an aromatase inhibitor (AI) for recurrent tumors as adjuvant therapy. We analyzed the correlation between prognosis and characteristics, including hormonal status. [Results] The median age was 43, and 9 (75%) were pre-menoposal. All the 4 cases with ovarian preservation recurred after primary surgery. However, only 2 patients (25%) recurred in 8 patients with hysterectomy and bilateral salpingo-oophorectomy. Although age, gravidity, parity, tumor size, and stage were not associated with recurrence, ovarian preservation was significantly associated with recurrence ($p=0.01$ by t-test). All the 3 recurrent patients with MPA and/or AI treatment showed long overall survival (OS) (12-25 years), and one stage IV patient with adjuvant MPA is free of recurrence for 47 months. [Conclusion] Ovarian preservation is indicated to increase the risk of recurrence in LG-ESS. Inversely, MPA and/or AI treatment may contribute to extend OS.

ISP-2-5 Efficacy of PET/CT for the differentiation of uterine sarcomas from leiomyoma

Juntendo University
Soshi Kusunoki, Tsuyoshi Ota, Takafumi Ujihira, Kazunari Fujino, Yasuhisa Terao, Satoru Takeda

[Objective] We respectively analyzed the efficacy of the PET/CT for the diagnosis of uterine sarcomas. [Methods] The patients were divided into sarcoma group (n=21) and leiomyoma group (n=20) retrospectively, which were suspected malignancy by MRI with high intensity area on T1-weighted images, heterogeneous high-signal intensity on T2- weighted images and/or the enhancement on contrast-enhanced MRI. All patients were measured the maximum standardized uptake values (SUVmax) of all lesions by PET/CT. We calculated the optimal cutoff value. Informed consent was obtained from all of the patients. [Results] The median SUVmax of uterine sarcomas and leiomyoma were 12 and 4.1, which were significantly different. The cutoff of SUVmax greater than 7.1 was able to exclude leiomyoma, with 85% sensitivity and 84.2% specificity (area under the curve 95%). [Conclusion] PET-CT is a good diagnostic tool for uterine sarcomas with an optimal cutoff value of SUVmax 7.1.

ISP-2-6 Uterine Leiomyosarcoma Tumorigenesis in Lmp2-deficient Mice : Involvement of Impaired Anti-oncogenic Factor IRF1

Dept. of Immunology, Shinshu University
Takuma Hayashi

[Objective] Uterine leiomyosarcoma (Ut-LMS) is a highly metastatic smooth muscle neoplasm. We previously reported that Lmp2-deficient mice spontaneously developed Ut-LMS, which implicated this protein as an anti-oncogenic candidate. IRF1 has been shown to play roles in the immune response, and tumor suppression. The aim of this study was to elucidate the molecular mechanism of sarcomagenesis of Ut-LMS using human and mouse uterine tissues. [Methods] The expressions of the IFN-g signal molecules, IRF1 and IRF2, STAT1, and LMP2, -3, -7 and -10 were examined by western blot analysis, electrophoretic mobility shift assay and immunohistochemistry with human and mouse uterine tissues. Physiological significance of IRF1 in sarcomagenesis of Ut-LMS was demonstrated by xenograft studies. [Results] In the present study, several lines of evidence indicated that although treatments with IFN-g strongly induced the activation of STAT1 as a transcriptional activator, its target molecule, IRF1, was not clearly produced in Lmp2-deficient uterine smooth muscle cells (Ut-SMCs). [Conclusion] Defective expression of IRF1 in the IFN-g-induced signaling molecules may result in the malignant transformation of Ut-SMCs. The modulation of LMP2 may lead to new therapeutic approaches in human Ut-LMS. These experiments were conducted in accordance with institutional ethical guidelines.

ISP-2-7 ATP7A is a promising therapeutic target for uterine leiomyosarcoma

Osaka University
Mamoru Kakuda, Shinya Matsuzaki, Yusuke Tanaka, Tomomi Takata, Eiji Kobayashi, Yutaka Ueda, Kiyoshi Yoshino, Tadashi Kimura

[Objective] Resistance to platinum drugs remains a significant problem in uterine leiomyosarcoma (LMS). We investigated the role of ATP7A in the resistance to platinum drugs in LMS using both in vitro and in vivo models. [Methods] The expression of the typical platinum transporters (MDR1, MRP2, ATP7A, and ATP7B) was examined in LMS cell lines using Western blotting analysis. ATP7A expression was investigated by immunohistochemistry (IHC) using clinical samples of LMS. IC50 values to cisplatin were measured in SK-LMS cells, SK-LMS-ATP7A-suppressed cell line (SK-LMS-7A cells), which permanently transfected PRS ATP7A shRNA vector. We established xenografted mice by inoculating SK-LMS cells and SK-LMS-7A cells, and examined in vivo platinum sensitivity with cisplatin for both tumors. (approved by IRB) [Results] The expression of ATP7A was identified in the SK-LMS cells. ATP7A expression was identified in 70% (14/20) of the LMS clinical samples using IHC. The IC50-values to cisplatin improved from 17 mM to 4.3 mM after the suppression of ATP7A in SK-LMS-7A cells. A significant anti-tumor effect of cisplatin was observed in SK-LMS-7A xenografted mice than in SK-LMS xenografted mice. We also identified omeprazole as an inhibitor of ATP7A in vitro. [Conclusion] ATP7A is associated with platinum resistance. Omeprazole acting as an inhibitor of ATP7A can be a therapeutic agent for LMS.

ISP-3-1 "Smartscopy" as a new device to identify the precancerous diseases of the uterine cervix：a pilot study

Osaka University
Yusuke Tanaka, Yutaka Ueda, Mamoru Kakuda, Satoshi Kubota, Satoko Matsuzaki, Satoshi Nakagawa, Tomomi Takata, Shinya Matsuzaki, Eiji Kobayashi, Kiyoshi Yoshino, Tadashi Kimura

[Objective] Colposcopy is a definitive procedure to diagnose the precancerous diseases of the lower genital tract. However, the traditional colposcopy has some disadvantages of being large, heavy and expensive. The purpose of the study is to develop a cost-effective, simple yet reliable device similar to the currently available colposcopies. [Methods] The institutional review board of our institution approved the present study. We used iPhone 5S (Apple Inc. USA) as a new device to inspect the uterine cervix for 10 patients with abnormal cervical cytology, and named it Smartscopy. Dr. A inspected the cervix using Smartscopy, and Dr. B inspected the cervix using colposcopy for the same patient. Whether the maximal smartscopic abnormality correlates to the maximal colposcopic abnormality was evaluated. The site of biopsy was determined on the basis of the colposcopic findings. [Results] Although the concordance between the maximal smartscopic and colposcopic abnormality was confirmed in seven of the 10 patients (70%), all cervical intraepithelial neoplasia (CIN) lesions were detectable by Smartscopy. Smartscopy can reveal the cervix as clearly as colposcopy, especially in acetowhite epithelium. [Conclusion] The pilot study showed the high sensitivity of Smartscopy to diagnose CIN. In terms of the cost and the size, Smartscopy may be utilized in countries with low medical resources.

ISP-3-2 Possibility of less radical treatment for patients with early invasive uterine cervical cancer

Sapporo Medical University
Kim Miseon, Shinichi Ishioka, Saori Kon, Youko Nshizawa, Sakura Takada, Masahito Mizuuchi, Miyuki Morishita, Toshiaki Endo, Tsuyoshi Saito

[Objective] Radical trachelectomy (RT) with lymphadenectomy has become a standard treatment modality for patients with early invasive uterine cervical cancer who hope for preservation of their fertility. However, pregnancy after RT has high risks of preterm birth. We studied the possibility of more conservative RT and the application of RT for patients with higher clinical stages. [Methods] Medical charts and operative specimens of 42patients with RT and 64patients with radical hystelectomy (RH) were studied retrospectively. Tumor size, the distance between the margin of the cancer and the internal Os, parametrial invasion, lymph node metastasis, and their obstetrical and oncological prognoses were investigated. [Results] The average distances were 37,29,18.7, and14mm for patients with stage 1A2, 1B1 (＜2cm), 1B1 (＞2cm), and 1 B2, respectively. When amputatation was done 10mm below the internal OS, all 10 patients with 1A2, 57 of the 58 patients with 1B1 (＜2cm), 19 of the 33 patients with 1B1 (＞2cm), and 1 of the 5 patients with 1B2, had a cancer-free margin＞10 mm. Furthermore, patients with stage 1A2 had a cancerfree margin 10mm even if we amputated the cervix 20mm below the internal OS. Parametrial invasion was detected in 2 cases of stage 1B1. [Conclusion] Simple trachelectomy 20mm below the internal Os might be possible for stage 1A2.The present method would be the best for stage 1B1 (＜2cm).

ISP-3-3 Robot-assisted laparoscopic radical hysterectomy：Comparison with 3D and 2D laparoscopy；one surgeon's experience at Shanghai OB/GYN Hospital

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Jichan Nie, Xishi Liu

[Objectives] Many studies have demonstrated the advantages of robotic assistance in overcoming the drawbacks of conventional two-dimensional (2D) laparoscopy. High-quality three-dimensional (3D) vision systems are now available for laparoscopic surgery and may improve surgical performance relative to 2D laparoscopy. It is unclear whether 3D laparoscopy is superior to 3D robotic systems. The purpose of this study was to investigate perioperative results of robot-assisted laparoscopic radical hysterectomies and pelvic lymphadenectomies in the early stage cervical carcinoma patients and compare with both 3D and 2D laparoscopic radical hysterectomy groups. [Methods] A total of 97 patients underwent radical hysterectomy and pelvic lymphadenectomy for early stage cervical carcinoma management. All cases (37 robot-assisted, 30 cases 3D laparoscopy and 30 with 2D laparoscopy) were operated by the same surgeon at Shanghai OB/GYN Hospital, Fudan University Shanghai Medical College between February and September 2015. All cases were reviewed to compare demographics, peri-operative variables such as mean operative time, estimated blood loss, lymph node counts, complications and follow-up results. [Results] The mean operating times (skin-to-skin) for patients undergoing robot-assisted laparoscopic radical hysterectomy, 3D and 2D laparoscopic radical hysterectomy were 193.43 ± 37.34, 124.70 ± 61.13 and 153.07 ± 30.84 min respectively. Patients receiving 3D laparoscopy had shortest operative time, followed by those undergoing 2D laparoscopy and then robot-assisted laparoscopic radical hysterectomy ($p<0.05$ for both). Estimated blood loss was significantly reduced in 3D laparoscopy compared to robot-assisted surgeries and 2D laparoscopy (224.0 ± 98.02ml vs. 328.38 ± 222.2 ml and 280.0 ± 162.73 ml ($p<0.05$), respectively). The mean number of patients undergoing robot-assisted laparoscopic radical hysterectomy, 3D and 2D laparoscopic radical hysterectomy removed lymph nodes was22.42 ± 3.72, 21.68 ± 3.41 and 21.65 ± 3.75 respectively ($p=0.623$)；and the mean length of hospital stay was 10.51 ± 3.42, 10.28 ± 2.05 and 9.70 ± 2.37 days, respectively ($p>0.05$). Intraoperative and early postoperative complications were not significantly different between the 3 groups (5.4% for robot, 6.67% for 3D；and 3.33% for 2D, P=0.089). [Conclusions] Use of the 3D laparoscopy by a single surgeon significantly enhances the possibility of achieving better intraoperative results in all patients undergoing radical hysterectomy. Patients of cervical cancer may not really benefit from robot systems if 3D laparoscopy is available. Nevertheless, further studies are necessary to better comprehend the role of 3D laparoscopy and robot-assisted surgeries in modern gynecology.

ISP-3-4 Genital bleeding during curative radiotherapy in cervical cancer

Kagoshima Medical Center[1], Kagoshima University[2]
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[Objective] Atypical genital bleeding is the most common and serious manifestation in patients with cervical cancer. Clinical characteristics of genital bleeding is unknown during radiotherapy treatment. [Methods] A total of 338 cervical cancer patients who underwent radiotherapy with/without concurrent chemotherapy between 2007 and 2013 were retrospectively analyzed. All patients were to be treated with curative intent, and no patient had undergone radical hysterectomy. Complete clinical data were collected by reviewing inpatient charts and radiotherapy records. [Results] 41 patients (13.9%) required hemostatic intervention because of increased genital bleedings. FIGO stage3B was the most common stage with 27 patients, stage1B 3 patients, stage2A 1 patient, stage2B was 8 patients, stage 3A was 1 patient, and stage 4A was 1 patients. 13 patients had genital bleeding prior to radiotherapy treatment, and 28 patients began to show genital bleeding during treatment. All bleeding was treated using gauze packing with 8 patients undergoing blood transfusions. No radiation was delayed due to bleeding, and all patients completed treatment with a result of 8 recurrances and 5 deaths. [Conclusion] Bleeding from the tumor during initial treatment was managed with gauze, and treatment was unaltered so it unlikely affected the prognosis.

ISP-3-5 Is lympho vascular space invasion the significant risk factor for recurrence in early cervical cancer without lymph node metastasis?

Aichi Cancer Center
Yusuke Shimizu, Mika Mizuno, Shinji Kondo, Masahiko Mori, Asuka Uno

[Objective] To evaluate the risk of lympho vascular space invasion (LVSI) and treatment outcomes in cervical cancer patients with TNM stage pT1bN0. [Methods] 305 patients who underwent radical hysterectomy (RH) including pelvic lymph node dissection (PLND) with patient's IC between 2001 and 2012 were retrospectively evaluated with patient's IC. All patients had received no postoperative therapy. [Results] Median follow-up time of 5.7 years (range 0.2-16.3 years), 14 (4.5%) patients had disease recurrence and 4 (1.3%) had died of the disease. There were 167 (55%) patients with LVSI and 138 (45%) without LVSI. 5-year recurrence-free survival (RFS) rates were 97.5 and 97.8%, respectively. Age, tumor size, LVSI, histological sub-type, and the number of dissected lymph nodes were analyzed. In univariate analysis, only tumor size differed in PFS (p=0.002). Multivariate analysis demonstrated that only tumor size (>2cm) was a significant prognostic factor for recurrence (hazard rate 8.523, 95%CI 1.842-39.476, p=0.006). When stratifying for presence of LVSI, tumor size significantly related to 5-year PFS (LVSI+, p=0.008, LVSI-, p=0.075). [Conclusion] LVSI alone may not be the prognostic factor of patients with stage pT1bN0 in cervical cancer. The routine postoperative therapy following RH including PLND may be unnecessary for these patients with<2m tumor size regardless of the presence of LVSI.

ISP-3-6 Postrecurrence oncologic outcome of patients with uterine cervical carcinoma

Nagoya University
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[Objective] To estimate and overview the long-term clinical outcome of patients with recurrent uterine cervical carcinoma (RCC). [Methods] From 1998 to 2014, 740 patients with cervical carcinoma was initially treated in our institute. Of all, 156 patients who experienced recurrence were analyzed. The end point was the postrecurrence survival (PRS). This study was approved by the ethics committee of our institute. [Results] The median age was 54.5 (20-88) years. Consequently, 83 patients died of the disease. The median PRS time of all patients was 28.4 months. The 1, 3, and 5-year PRS rates of patients were 75.2, 42.8, and 33.9%, respectively. The prognosis of patients without surgery was significantly poorer than that of those with surgery (P=0.0132). In multivariable analysis, the recurrence site and absence of surgery were significantly poorer prognostic indicators for PRS [Surgery (+) vs. Surgery (-)] : hazard ratio, 0.534 : 95% confidence interval, 0.306-0.920 ; P=0.0237 : [Pelvis vs. Distant/extra-pelvis LN] ; hazard ratio, 1.768 : 95% confidence interval, 1.113-2.796 ; P=0.0160). [Conclusion] The long-term clinical outcome of patients with RCC was extremely poor. Aiming to improve the prognosis of these patients, useful therapeutic approaches including new generation antineoplastic agents are anticipated in the near future.

ISP-3-7 Obstetrical outcome and complications during pregnancy after fertility-sparing abdominal trachelectomy for cervical cancer

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[Objective] We herein evaluated the obstetrical outcome and complications during pregnancy after abdominal trachelectomy for cervical cancer. [Methods] We started to perform abdominal trachelectomy from 2005. This clinical study was approved by IRB and a fully informed consent was obtained from each patient. Medical records of patients who underwent trachelectomies were reviewed. [Results] We performed total 151 abdominal trachelectomies (radial 89 cases ; semi-radical 48 cases ; simple 14 cases). The median age of patients was 33 years-old and median postoperative follow-up period was 53 months. Though one case experienced recurrence at preserved cervix, no patients died after treatment. Sixty-one patients attempted to conceive after trachelectomy. A total of 20 pregnancies were achieved in 15 women, therefore, the pregnancy rate among patients who attempted to conceive was 25%. Eleven babies were delivered by cesarean section between the 23rd and the 37th weeks of gestation. Four babies were delivered at term. Five cases of pPROM were observed. Varices appeared around the utero-vaginal anastomotic site in 5 cases. [Conclusion] Our data showed that oncological outcome was excellent, however, pregnancy rate was low and pPROM and premature delivery were frequently observed. Improvement of pregnancy rate and prevention of complications during pregnancy are issues for the future.

ISP-3-8 Treatment of early stage cervical non-squamous cell carcinoma (NSCC) : clinical significance of preoperative tumor markers and postoperative macro and/or micro lymph node metastasis

Tokai University Hachioji Hospital[1], Tokai University[2]
Yuki Hirano[1], Toshinari Muramatsu[1], Chisato Noji[1], Hiroki Ishii[1], Yuki Uda[1], Yumiko Goto[1], Taro Sugiyama[1], Hironobu Maeda[1], Mikio Mikami[2]

[Objective] Cervical non-squamous cell carcinoma (NSCC) has a poor prognosis. We examined the outcome in stage I/II, and determined the clinical significance of preoperative markers and postoperative lymph node (LN) metastasis. [Methods] We treated 31 stage I/II NSCC patients with patient's IC. These comprised 25 adenocarcinoma, 5 adenosquamous carcinoma, and 1 small cell carcinoma. CEA, CA125 and CA19-9 markers were compared between stages. LN dissections were performed in the pelvis. [Results] Tumor marker for cases at stage IB and stage II were as follows : CEA, 3.0 ± 1.0 and 8.2 ± 2.5ng/ml (p=0.0337) ; CA125, 17.7 ± 4.8 and 95.7 ± 47.8U/ml (p=0.0468) ; and CA19-9, 22.3 ± 9.4U/ml and 410.7 ± 300U/ml (p=0.1041). All 5 year survival rate was 65.4%. Disease-free survival was 100%, 79.4% and 25.4% for stage IA, IB and II. 17 cases at stage IB showed postoperative lymph node metastasis (LN+). Stage II were all at stage IIB, and 4 were LN+. 9 patients died. 4 of the 5 LN+ patients had recurrence and died within two years. 4 LN- patients died, including 2 cases at stage IB1 and one case at stage IIB. 6 cases of pelvic recurrence, 2 of multiple lung metastases, and 1 of para-aortic lymph node metastasis. [Conclusion] Stage I/II NSCC patient was a significant difference in the levels of CEA and CA125 markers between these stages. The LN+ group showed recurrence at an early stage.

ISP-3-9 Outcome of minimally invasive surgery by using sentinel lymph node biopsy in cervical cancer

Tohoku University
Asami Toki, Hitoshi Niikura, Satoshi Okamoto, Chiaki Hashimoto, Izumi Sato, Shogo Shigeta, Keita Tsuji, Hideki Tokunaga, Tadao Takano, Kiyoshi Ito, Yoh Watanabe, Nobuo Yaegashi

[Objective] The purpose of this study was to clarify the incidence of recurrence rate and lymphedema in patients with cervical cancer who underwent sentinel lymph node (SLN) biopsy alone without SLN metastases. [Methods] This study included 70 patients with operable cervical cancer (FIGO Stage IA1-IIA1) scheduled for surgery at our institution between May 2006 and Aug 2015. Patients who had any positive metastasis SLNs and/or couldn't be detected bilateral SLNs were performed complete pelvic lymphadenectomy. Patients who had no metastasis for SLNs were omitted systematic lymphadenectomy. The present study was approved by the ethics committees. [Results] The detection rate of bilateral SLNs was 90% (63/70). Nineteen (27.1%) of 70 cases had LN metastasis, finally. Intraoperative frozen section identified correctly 16 of 19 metastatic patients. False negative rate was 6.1% (3/49). Forty-eight patients underwent SLN biopsy alone without systematic pelvic lymphadenectomy, and none of them have experienced a lymph node recurrence in the pelvic cavity. Symptomatic lymphedema 2 years after operation was identified in 3 (8.3%) of 36 patients who underwent SLN biopsy alone and in 6 (50%) of 12 patients who underwent systematic lymphadenectomy. [Conclusion] The minimally invasive surgery by SLN biopsy seems to be safe and effective for detecting key lymph node and decreasing lymphedema.

ISP-4-1 A Case of Lymphoepithelioma-like Carcinoma in the Uterine Cervix

Oita University
Masakazu Nishida, Kanetoshi Takebayashi, Harunobu Matsumoto, Kaei Nasu, Hisashi Narahara

Lymphoepithelioma-like carcinoma occurring in the reproductive organs is a rare variant of squamous cell carcinoma, and this tumor of the uterine cervix accounts for 0.7% of all primary cervical uterine neoplasms. Associations with Epstein-Barr virus (EBV) and human papilloma virus (HPV) have been demonstrated in some studies. Some investigators suggested that EBV has an important role in the initiation of lymphoepitheliomalike carcinoma in Asian women. Here we report the case of a 45-year-old Japanese woman, gravida 2 and parity 2. She was admitted due to severe atypical genital bleeding caused by uterine cervical cancer. Over 60-mm tumor was detected at the uterine cervix, and no distal metastasis or swallowing of lymph nodes was revealed by magnetic resonance imaging and a computed tomography scan. The cervical cancer stage FIGO Ib2 was diagnosed, and a radical hysterectomy was performed for this malignant tumor. The in situ hybridization for EBV was negative. HVP infection was strongly suspected because the squamous cell carcinoma was observed macroscopically in the uterine cervix. The prognosis of uterine lymphoepithelioma-like carcinoma is thought to be better than those of other cervical cancer types, but careful follow-up at fixed intervals is recommended. The patient has been followed up for 4 months since her surgery, and no evidence of recurrence has been detected.

ISP-4-2 Small Cell Carcinoma of the Uterine Cervix

Oita University[1], Iwanaga Ladies Clinic[2]
Satoshi Eto[1], Kentaro Kai[1], Kaei Nasu[1], Masakazu Nishida[1], Shigeaki Iwanaga[2], Hisashi Narahara[1]

[Introduction] Small cell carcinoma of the uterine cervix (SCCC) is a rare histological entity that has a poor prognosis. There is a paucity of information about SCCC during pregnancy. We report the case of a patient with SCCC who underwent a radical hysterectomy during pregnancy. [Cases] A 33-year-old Japanese woman with genital bleeding and an abnormal Pap smear result at 15 weeks' gestation was referred to our institution. A speculum exam revealed a 5.4-cm-dia. mass in the cervix, and a cervical biopsy revealed SCCC. Magnetic resonance imaging and contrast-enhanced computed tomography demonstrated a tumor confined to the cervix, swelling of intra-pelvic lymph nodes, and no distant spread. She was diagnosed with SCCC, Stage IB2. We performed a radical hysterectomy with pelvic lymphadenectomy at 18 weeks' gestation (pT1b2N1M0). She refused adjuvant chemotherapy and irradiation and has been undergoing routine post-treatment surveillance. She is healthy without disease 2 months after the surgery. [Discussion] To determine the optimal management of SCCCs, the context of the aggressive behavior of SCCCs should be considered. A radical hysterectomy during pregnancy should be listed among the treatment options for SCCC patients complicated with pregnancy.

ISP-4-3 Uterine cervical adenocarcinoma metastasizing concurrently to eutopic and ectopic ovaries : a case report

Dokkyo Medical University
Kaori Kiuchi, Kiyoshi Hasegawa, Mariko Watanabe, Anriko Kanamori, Tatsuko Nagai, Nobuaki Kosaka, Ichio Fukasawa

Ectopic, a designation that includes supernumerary ovaries and accessory ovaries, ovary is a rare gonadal anomaly. We encountered a patient with a metastasis to such an anomaly. A 43-year-old woman was diagnosed with stage IIb cervical adenocarcinoma with suspicion for a right ovarian malignancy. She underwent laparotomy after completing 3 cycles of neoadjuvant chemotherapy. Intraoperative inspection revealed 2 normal ovaries, but an ovary-like structure was identified attached to the fimbriae of the left Fallopian tube. A cystic tumor, 12 cm in diameter, developed from this structure, which was not connected to the infundibulopelvic ligament. The mass was pulled and elevated into the right pelvis by omental adhesions. Pathological examination revealed that both the left eutopic ovary and the ovary-like structure contained endometrioid adenocarcinoma metastases. The ovary-like structure contained spindle-shaped theca cells, which were positive for inhibin ; therefore, this structure was defined as ovarian tissue. The final diagnosis was uterine cervical endometrioid adenocarcinoma with metastases to the pelvic lymph nodes and to left eutopic and ectopic ovaries (pT2a2N1M0). There have been no previous descriptions in the English literature of uterine cervical adenocarcinoma metastasizing concurrently to unilateral eutopic and ectopic ovaries.

ISP-4-4 Clinical outcomes of CIN3 after cervical conization with positive surgical margins

University of the Ryukyus
Tomoko Nakamoto, Tadaharu Nakasone, Yoshino Kinjo, Yoshihisa Arakaki, Akihiko Wakayama, Wataru Kudaka, Yutaka Nagai, Yoichi Aoki

[Objective] The aim of this study is to evaluate the clinical outcomes of patients who were treated by cervical conization for CIN3 and histologically confirmed positive surgical margins. [Methods] From January 2006 to December 2012, the patients who went through cervical conizaion for CIN3 were retrospectively identified. The patient data include age, follow-up period, rate of abnormal pap after conization, and the details of additional treatment. [Results] Of 305 patients who underwent cervical conization for CIN3, 45 patients had positive surgical margins. The mean age was 38 years, and the mean follow-up was 36 months. 3 patients went through immediate hysterectomy, and 42 patients were followed-up conservatively. Abnormal pap was confirmed in 15 patients (35.7%) with mean follow-up of 8 months. 9 patients went through additional surgical treatment including re-conization in 5 patients, hysterectomy in 3, and one had IB1 disease at the time of recurrence and went through radical hysterectomy. 2 patients who went through hysterectomy were found to have IA2 and IB1 disease in the hysterectomy specimen. [Conclusion] Even if surgical margin is positive in the cone specimen, about 60% of patients are conservatively treated with no sign of recurrence. However, there are few cases in which invasive cancer is found at time of recurrence ; therefore prudent examination is necessary.

ISP-4-5 The retrospective analysis of the patients with positive surgical margin who underwent the uterine cervical conization

Osaka City University
Reiko Tasaka, Takeshi Fukuda, Takuma Wada, Masaru Kawanishi, Kenji Imai, Makoto Yamauchi, Mari Kasai, Yasunori Hashiguchi, Tomoyuki Ichimura, Tomoyo Yasui, Toshiyuki Sumi

[Objective]We analyzed the patients who underwent the conization with positive surgical margins. [Methods]A retrospective analysis was performed with a total of 303 patients who underwent the conization in our hospital from January 2008 to December 2012. [Results] Positive surgical margins were found in 31 patients (10.2%), of these cases 6 were found in the vaginal side (19.4%), 23 were in the cervical canal side (74.2%) and 2 were in both sides (6.4%). Concerning about menstrual status, positive margins were found in 10 of 40 cases (25%) and 21 of 263 cases (8.0%) in postmenopausal and premenopausal patients respectively (p=0.004). Concerning about diagnosis, positive margins were found in 0 cases (0%) in moderate dysplasia, 6 cases (5.8%) in severe dysplasia, 7 cases (5.1%) in CIS/AIS and 17cases (34%) in invasive cancer (P<0.001). In patients with positive margins, all 6 patients with severe dysplasia underwent only follow-up without cytological abnormality, only 1 out of 7 patients with CIS needed partial resection and revealed remaining severe dysplasia and 9 out of 13 patients with invasive cancer who underwent hysterectomy revealed remaining cancer. [Conclusion] The sufficient resection is needed in conization especially for postmenopausal and/or invasive cancer patients. Even if positive margins were found, the careful follow-up might be viable in patients with CIN.

ISP-4-6 Surgical management for early-stage cancer of the uterine cervix

Tokuyama Central Hospital
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[Objective] The aim of this study was to examine retrospectively as for the surgical treatment for early-stage cancer of the uterine cervix and the outcome. [Methods] Patients with pathologically proved CIS, AIS, and microinvasive cancer (FIGO stage 1A1) were selected. Between 2005 and 2012, 180 CIS, 7AIS, and 78 1A1 patients underwent laser conization and hysterectomy was added to 37 of CIS, 6 AIS, and 44 of 1A1 patients.(approved by IRB) [Results] Of the patients with CIS, 136 patients underwent conization and 3 of the 10 patients with positive margins received hysterectomy. Of the patients with AIS, 4 patients underwent conization followed by hysterectomy. Among the 4 patients with negative margins, one had residual disease. Of the patients with 1A1, 57 patients underwent conization. Among the 42 patients with negative margins, 19 had conservative treatment and 23 underwent hysterectomy. There were residual disease in 3 of these 23 patients. Among the 15 patients with positive margins, 3 had conservative treatment, 3 underwent re-conization and 9 did hysterectomy. There were residual disease in 2 of these 12 patients. All patients are free of disease. [Conclusion] These results suggest that laser conization can be a suitable treatment for CIS. However, careful attention must be taken when we preserve the uterus by laser conization for the patients with AIS and 1A1.

ISP-4-7 Effect of Body Mass Index (BMI) on Treatment Outcome of Patients with Cervical Cancer (IB1 to IVA)

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[Objective] To investigate the effect of body mass index (BMI) on treatment outcomes of patients with cervical carcinoma. [Methods] This retrospective cohort study included all patients with cervical carcinoma (IB1 to VIA) who were treated at Samsung Medical Center between April 1996 and December 2007. [Results] A total of 1003 patients with cervical cancer were enrolled in this study. The median follow up time was 52 months (range, 1 to 181 months). The 5-year overall survival rate was 86.3%. There were 174 (17.3%) recurrences or progressions and 124 (12.4%) deaths during the study period. The median age and BMI of patients were 50 years (21 to 85 years) and 23.6 kg/m^2 (15.4 to 38.5), respectively. In univariate analysis, compared to normal weight (BMI 18.5-24.9 kg/m^2) and overweight (BMI>25 kg/m^2), a BMI<18.5 kg/m^2 was associated with decreased progression and overall survival. However, such association was not statistically significant. In multivariate analysis, higher BMI was significantly associated with better overall survival (HR ; 0.941, 95% CI ; 0.892-0.933). Complication rates were not different based on the BMI. [Conclusion] Cervical cancer patients with lower BMI at pre-treatment had diminished overall survival.

ISP-4-8 Conservative Treatment in Women with Adenocarcinoma In Situ of the Cervix

Chonnam National University Medical School, Munhwa Woman Hospital, Gwangju, Korea
Ho Sun Choi, U Chul Ju, Woo Dai Kang, Seok Mo Kim

[Objective] To study outcomes and follow-up in women with adenocarcinoma in situ (AIS) of the uterine cervix and significance of human papillomavirus (HPV) genotyping for AIS recurrences. [Methods] Records of AIS cases diagnosed between 1995 and 2014 were reviewed. Clinical and histopathological data were analyzed. [Results] Mean age at diagnosis was 44 years. Diagnosis was established using cytology and biopsy. Primary treatment for 87 patients was loop electrosurgical excision procedure (LEEP). The follow-up time was 18-60months. Three (5.4%) recurrences were found after conservative treatment in 56 patients. AIS with coexisting carcinoma in situ and AIS alone were detected in 33 patients (59%) and 23 patients (41%). 2 (8.7%) recurrences in AIS alone group and 1 (3.0%) recurrence in coexisting carcinoma in situ group occurred. High-risk HPV positivity was detected in 77 (89%) of 87 patients, with HPV-16 and HPV-18 being the most commonly occurred subtype (84%). 3 recurred women have same HPV genotype with negative cytology for long time. [Conclusions] There is a small risk of recurrences after conservative therapy with LEEP when resection margins are negative in women with AIS. Patients should be given the options of hysterectomy or conservative therapy with strict long term follow-up. HPV genotyping was important value to find recurrences.

ISP-5-1 Co-testing with cytology and HPV in cervical cancer screening in Japanese population

Iwate Medical University[1], Shimane Prefectural Central Hospital[2], Hokkaido University Graduate School of Medicine[3], Jichi Medical University, Saitama Medical Cener[4]
Yuri Sasaki[1], Osamu Iwanari[2], Sharon Hanley[3], Ryo Konno[4]

[Objective] To determine the value of cytology and HPV co-testing for cervical cancer screening in Japan. [Methods] In total, 4,887 women who underwent routine cervical screening between January 2005 and December 2006 were enrolled. All participants provided written IC before entering the study. Women aged ≥20 years at baseline and cytology-negative were followed-up until December 2011 (n=2,474). Progression to CIN2+/CIN3+ was compared between the HPV-positive and HPV-negative groups using the Kaplan-Meier, the log rank and a Cox proportional hazards analysis. [Results] Progression to CIN2+/CIN3+ was higher in the HPV-positive group compared to the HPV-negative group ($p<0.001$). Incidence rates of CIN2+ and CIN3+ were 10.0 (95%CI：5.1-19.7) and 6.7 (95%CI：2.9-15.3), respectively per 1000 person-months in the HPV-negative group compared to 102.3 (95%CI：59.0-177.2) and 68.2 (95%CI：34.8-133.7), respectively in the HPV-positive group. Relative risk of progression to both CIN2+ and CIN3+ was 10.2 times higher in the HPV-positive group. [Conclusion] Co-testing with cytology and HPV might be a suitable strategy for primary cervical cancer screening in Japan. While, HPV-positive women require more careful follow-up due to the increased risk of progression to CIN2+ lesions, screening intervals could be increased to>2 years for women HPV negative, cytology negative.

ISP-5-2 Clinical outcome of atypical squamous cells of undetermined significance：an institutional experience

Kyoto Prefectural University
Kyoko Akashi, Taisuke Mori, Hiroshi Matsushima, Shiori Umemura, Kaori Sasamoto, Tetsuya Kokabu, Hiroshi Tatsumi, Haruo Kuroboshi, Morio Sawada, Jo Kitawaki

[Objective] To extract clinical problems we evaluated the outcomes of patients who had been diagnosed atypical squamous cells of undetermined significance (ASC-US) in cervical cytology. [Methods] A retrospective single-institution following-up study was performed in 334 cases from 232 patients (3.3% of total cytology specimens) who had been diagnosed ASC-US (including 19 patients after conization and 4 patients after radiation therapy) from January 2012 to July 2015. A total of 209 clinically intact patients were selected for the following analyses. [Results] While 148 patients (70.8%) were tested for high-risk human papilloma virus (HR-HPV) and 95 patients (64.2%) were come to positive, 61 patients (29.2%) were not tested. The number of patients progressed over CIN3 were 10, to CIN2 were 25, to CIN1 were 38. None of HR-HPV negative patients progressed to CIN3. Two patients were diagnosed with invasive cancer by the first colposcopy. There were 33 patients (22.2%) dropped out from our follow-up, including 16 patients positive for HR-HPV and 15 untested patients. [Conclusion] We confirmed the importance of accurate diagnosis by colposcopically biopsy and HR-HPV test in the cases of ASC-US. Clinical efforts would be required to prevent patients with the risk from being untreated.

ISP-5-3 Accuracy of initial postoperative cytology and high risk HPV (HRHPV) test for detection of recurrence of cervical intraepithelial neoplasia (CIN) after cervical laser vaporization

Keio University
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[Objective] The aim of this study was to examine the accuracy of cytology and HRHPV test for detection of recurrence of CIN after laser vaporization. [Methods] The subjects were 77 patients with CIN2/3 underwent vaporization from Apr. 2013 to Dec. 2014. Cytology was performed every 6 months postoperatively. Biopsy was performed after cytologic diagnosis of HSIL or ASC-H. Following LSIL or ASC-US, biopsy was performed if abnormal cytology was repeated. CIN 2 or higher in biopsy was diagnosed as recurrence. HRHPV test was performed simultaneously with initial postoperative cytology. This study was approved by the institutional review board, and all patients gave informed consent. [Results] The results of initial postoperative cytology of 77 patents were NILM : 50, ASC-US : 4, ASC-H : 3, LSIL : 6, and HSIL : 14. HPV was detected in 39 postoperatively. Ten patients were recurred during the observation (9-26 months). In initial cytology, the sensitivity and specificity were 100% and 73.5% for detection of recurrence with abnormal cytology (=>ASC-US), 100% and 55.9% for HPV-positive cases, and 100% and 79.4% for detection of=>ASC-US and HPV-positive cases. [Conclusion] Initial postoperative cytology had high sensitivity for detection of recurrence. Although HPV test had relatively low specificity, a combination of cytology and HRHPV test might increase the specificity and improve risk assessment.

ISP-5-4 The pathologic analysis of LSIL and ASCUS

Inha University, Incheon, Korea
Eunseop Song, Sukyung Jung, Shina Jang, Jeongok Kim

[Objective] Aim : To now the pathologic profile of LSIL and ASCUS. [Methods] From 1997 to 2015, Data of LSIL and ASCUS at cervical smear, which had been done at a single institution, were reviewed retrospectively. Every punch biopsy had been done under the guide of colposcopy. Pathologic results, age, and ways of follow-up were analyzed. [Results] For 19 years, there were 295patients with LSIL and 173 with ASCUS. The age distribution was between 17 to 80 years old (43±10). The distribution of punch biopsy, done within 2 weeks after cervical smear, was like these : there were 210 cervicitis (45%), 196 CIN 1 (42%), 21 CIN 2 (4%), 39 CIN 3 (8%) and 2 cancers. The distribution of management after punch biopsy, done within 2 weeks, was like these. 362 patients underwent observation only (77%), 88 cone (18%). Among patients who had undergone cone, 7 had undergone hysterectomy, 1 underwent intracavitary radiation (ICR) after hysterectomy, and 1 underwent concomitant chemoradiation after hysterectomy. 17 patients had been undergone hysterectomy as a first treatment. Among these group, 1 patient underwent radiotherapy including ICR. 1 patients was lost during follow-up. [Conclusion(s)] When the cytologic results were LSIL or ASCUS, 87 percents of the punch biopsy results were cervicitis or CIN 1. But 12 percent were worse than CIN 1 and needed further management. There were 2 cases of malignancy. Even though most of LSIL and ASCUS need not urgent management, we have to be very careful about malignancy.

ISP-5-5 How do we estimate monitoring HPV infection and efficacy of HPV vaccine in Japan?

Fujita Health University[1], Keio University[2]
Yutaka Torii[1], Takashi Iwata[2], Daisuke Aoki[2], Takuma Fujii[1]

[Objective] In clear cell carcinoma of the ovary (CCC), the critical molecular events include mutations in ARID1A and upregulation of IL-6 signal. It was reported that coexistent ARID1A-PIK3CA mutations could promote carcinogenesis through sustained IL-6 overproduction in a CCC mouse model. We aimed to identify the IL-6/ARID1A expression signature associated with patient characteristics in stage I CCC. [Methods] Immunohistochemical analyses for IL-6/ARID1A were performed in 138 stage I CCC cases with Ethics Review Committee approval. We investigated the correlation between IL-6/ARID1A expression and either age, CA125, CRP, ascites cytology, rupture, stage, endometriosis, or prognosis. [Results] High IL-6 expression (60-100%) was found in 31% and correlated with poor prognosis (OS, p=0.034 ; PFS, p=0.043). However, there was no significant association between IL-6 expression and any of these clinicopathological parameters. Although ARID1A loss was found in 54% and correlated with stage (IA+IC1 vs. IC2+IC3 ; p=0.02) and ascites cytology (p=0.05), there was no relationship between ARID1A loss and prognosis. There was no correlation between high IL-6 and ARID1A loss. [Conclusion] IL-6 expression may be useful prognostic marker in stage I CCC. There was no evidence that ARID1A loss could be possible reason for IL-6 overexpression.

ISP-5-6 HPV self-sampling is effective for engaging non-responders in cervical screening and identifying cervical abnormalities

Hokkaido University[1], Hokkaido Cancer Society[2]
Sharon Hanley[1], Dong Peixin[1], Hiromasa Fujita[2], Hidemichi Watari[1], Noriko Kobayashi[1], Masataka Kudo[1], Noriaki Sakuragi[1]

[Objective] We investigated whether HPV self-sampling may be an effective way to increase cervical cancer screening in women who had not used free cervical cancer screening coupons (non-responders). [Methods] In total 7645 non-responders from city X aged 20-42yrs were randomized into three groups : control group (n=955), call-recall group (n=956) and invitation to SS group (n=5736), from which 570 women (10%) requested a self-sampling kit. [Results] In all, 79 (8.3%) and 127 (13.2%) of women in the control and reminder groups, respectively, underwent screening. In the SS group, 392 (68.8%) underwent SS. Compared to the control, both reminder letters (RR=1.62, 95%CI 1.23-2.10) and receiving a self-sampling device (RR=8.31, 95%CI 6.68-10.34) significantly increased screening uptake. Compared to a reminder letter, receiving a self-sampling device also increased uptake (RR=5.38, 95%CI 4.53-6.60). In the SS group, 36 women (9.2%) tested HPV positive and 21 (58%) underwent a Pap smear. Abnormal cytology rates were 57.1% in the SS group compared to only 5.6% and 7.6% in the control and reminder group, respectively. [Conclusion] SS is effective for increasing screening uptake in non-responders. It is also effective for identifying those most at risk for future cervical disease and engaging them in preventative services.

ISP-5-7 Initial viral load in cases of single human papillomavirus 16 or 52 persistent infection is associated with progression of later cytopathological findings in the uterine cervix

Nagasaki University
Daisuke Hamaguchi, Kiyovori Miura, Shuhei Abe, Shoko Miura, Kentaro Yamasaki, Koh-ichiro Yoshiura, Hideaki Masuzaki

[Objective] The aim of this study was to investigate the relationship between viral load in single HPV 16 or 52 persistent infection and the progression of later cytopathological findings in the uterine cervix. [Methods] Cervical cytology and HPV genotyping tests were repeated within 3-6 months in 305 women with oncogenic HPV. Twenty-four cases of single HPV 52 persistent infection and 24 cases of single HPV 16 persistent infection were identified. Cases with later cytopathological findings showing progression were defined as the progression group, while those with no change or regression were the non-progression group. Relative HPV DNA loads were determined by quantitative real-time polymerase chain reaction and expressed relative to human ALB DNA. Differences between the two groups were evaluated. [Results] The median relative HPV 52 DNA load was 2.211 in the progression group and 0.022 in the non-progression group (P=0.003). The median relative HPV 16 DNA load was 4.206 in the progression group and 0.103 in the non-progression group (P=0.001). The relative HPV 52 DNA load was significantly lower than the HPV 16 DNA load in the cervix in patients with single HPV infections (P=0.019). [Conclusion] HPV 52 and 16 DNA loads assessed by quantitative real-time methods may be useful short-term markers for identifying women at high risk for progression of cervical cytological pathology.

ISP-5-8 A presence of HPV-16 or HPV-18 genotype as a reliable predictor of residual disease in a subsequent hysterectomy after loop electrosurgical excision procedure for cervical intraepithelial neoplasia (CIN) 3

Chonnam National University Medical School, Korea
Seok Mo Kim, U Chul Ju, Woo Dae Kang

[Objectives] This study was conducted using the HPV DNA chip test (HDC), in order to determine whether the human papillomavirus (HPV) genotype is a predictor of residual disease in a subsequent hysterectomy following a loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN) 3. [Methods] Between January 2002 and February 2015, a total of 189 patients who underwent a hysterectomy within 6 months of LEEP caused by CIN3 were included in this study. We analyzed their epidemiological data, pathological parameters, high-risk human papillomavirus (HR-HPV) load as measured by the hybrid capture II assay (HC2), and HR-HPV genotype as measured by the HDC. A logistic regression model was used to analyze the relationship between covariates and the probability of residual disease in subsequent hysterectomy specimens. [Results] Of the 189 patients, 92 (48.7%) had residual disease in the hysterectomy specimen, CIN 2 in 7 patients, CIN3 in 79 patients, IA1 cancer in 5 patients, and IA2 cancer in 1 patient. Using multivariate analysis, the results were as follows ; cone margin positivity (OR=2.43 ; 95% confidence interval [CI], 1.18-5.29 ; $P<0.05$), HPV viral load $\geq$ 220 RLU (OR=2.98 ; 95% CI, 1.38-6.43 ; $P<0.01$), positive endocervical cytology (OR=8.97 ; 95% CI, 3.81-21.13 ; $P<0.001$), and HPV-16 or HPV-18 positivity (OR=9.07 ; 95% CI, 3.86-21.30 ; $P<0.001$). [Conclusions] The HPV-16 or HPV-18 genotype is a reliable predictive factor of residual disease in a subsequent hysterectomy following a LEEP for CIN3.

ISP-5-9 Correlation studies between HPV persistent infection, cervical cancer occurrence and development and HPV16 L1 and LCR methylation levels

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[Objective] We investigated type-specific persistent infection state of HPV in Uyghur women, to explore persistent infection associated risk factors. We selected HPV (+) and HPV (-) women who attended the cervical cancer screening from 2012 to 2013 in Xinjiang people's hospital outpatient as objects were done by questionnaire survey, HPV (+) did genotypes test and biopsy under colposcope detecting pathological diagnosis, to follow-up the women of chronic cervicitis for 12 months. [Methods] Pyrophosphate sequencing technology to detect positioning and quantitative methylation levels of L1, LCR in HPV16 (+) groups of five pathological levels (persistent infection, transient infection, CIN1, CIN 2- 3, cervical cancer). Logistic regression to analyses its influencing factors. [Results] We found type-specific HPV persistence in Uyghur was 25.5%, HPV16 (48.00%), HPV18 (31.03%), HPV58 (28.30%), HPV52 (23.40%), HPV45 (21.43%) were the most frequently persistent types among major types. Viral load>1000 pg/ml compared in 1≤HPV≤100 (OR：2.40,95%CI：1.11-5.15), HPV16 infection compared to non-HPV16 infection (OR：4.81,95%CI：2.63-8.18) increased the risk of type-specific HPV persistent infection；Multivariate analysis showed that compared to the transient infection, postmenopause (OR：2.41,95%CI：1.23-2.89), non condoms (OR：3.85,95%CI：1.68-4.58) increased the risk of type-specific persistent HPV infection. Methylation rates of 13 sites in L1 were statistically significant differences among 5 pathological lesions groups and as the disease progresses. [Conclusions] Uyghur with HPV16 positive, high viral load, menopause, no-condom will likely increase risk from a transient into the persistent infection, Should strengthen follow-up of the crowd. Methylation rates of HPV16 L1 has high value to predict HPV persistent infection, cervical cancer lesion progress. Key words：Cervical carcinoma；methylation；L1；Long control region；Uyghur

ISP-5-10 Comparative Study of the effect of cervical cancer screening by Liquid-Based Cytology and High-Risk Human Papillomavirus detection in Inner Mongolia

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Xian-Zhi Duan, Yan-Bo Song

[Objective] To investigate the effect of cervical cancer screening by liquid-based cytology and high-risk human papillomavirus (HPV) detection in Inner Mongolia, and provide scientific data for the selection of primary screening technologies of cervical cancer in Inner Mongolia. [Method] From 2012 to 2014, 30,118 women aged 20-70 were screened by the Thinprep liquid-based cytology (TCT) and the Cervista HPV detective method for cervical cancer in Inner Mongolia. Those with abnormal cytological results or HPV infection were referred to colposcopy examination, and biopsy was taken for pathological confirmation. [Results] The positivity of cytologyand HPV infection was 5.54% and 23.18%, respectively. A9 group were the most common infective HPV types, with a positive rate of 7.77%. The predominated infective HPV types were the same for the Han nationality and Mongolian. Both the total HPV infection rate and A9 group HPV infection rate were positively associated with the grade of cytological abnormity. The positivity of A9 HPV type was increased by the pathological grades. The agreement (84.71%) between TCT and Cervista for the detection of high grade cervical intraepithelial neoplasia (CIN2+) was very good. The two methods worked as supplementary for each other. Twenty-six cases were detected by the HPV test while missed by the TCT, and 19 cases with negative HPV results were found by TCT. The combination of the two methods increased the detective rate of CIN2+ from 84.71% to 98.47% ($P<0.05$). [Conclusion] The agreement between TCT and Cervista for the detection of CIN2+ was very good. TCT and Cervista can be used as effective methods for cervical cancer screening in various areas with different health resources, and their combination can increase the accuracy. Key words：Liquid-based cytology；Cervista HPV detection；Cervical cancer；Screening；Inner Mongolia

ISP-6-1 Necessity of para-aortic lymphadenectomy in endometrial cancer with intermediate and high risk

Showa University
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[Objective]To assess the necessity of para-aortic lymphadenectomy in endometrial cancer with intermediate and high risk of recurrence. [Methods] 50 patients with endometrial carcinoma of intermediate or high risk of recurrence who were treated by combined pelvic and para-aortic lymphadenectomy between 2006 and 2015, were subjected, and were classified by pathology of metastasis to para-aortic lymph node. [Results] Metastasis to para-aortic lymph node was detected in 13 cases (30%). 8 cases had metastasis above the inferior mesenteric artery (IMA) among 11 cases with metastasis to left side. 5 cases were metastasis below and above IMA among 7 cases with metastasis to right side. Metastasis to pelvic lymph node, high-grade histopathology (endometrioid grade 3, serous and clear), invasion to adnexa, vagina and cervix, and lymphavascular invasion in cases with metastasis to para-aortic lymph node were significantly more frequent than in no metastasis to para-aortic lymph node cases. [Conclusion] The metastasis to para-aortic lymph node was related with pelvic metastasis, high-grade histopathology, invasion to adnexa, vagina and cervix, and lymphavascular invasion. As there is a case of metastasis only to para-aorta lymph node, combined pelvic and para-aortic lymphadenectomy is recommended as treatment for patients with endometrial carcinoma of intermediate or high risk of recurrence.

ISP-6-2 Retrospective analysis of justification for omission of lymph node dissection in uterine endometrioid cancer stage IA (endometrioid adenocarcinoma grade 1 and 2)

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[Objective] Therapeutic significance of retroperitoneal lymph node dissection (RPLND) in endometrioid adenocarcinoma (EA) has not been established. The present study aimed to clarify the possibility to omit RPLND in EA stage IA. [Methods] For cases of endometrial cancer stage IA and EA in which surgery was performed from 2006 to 2014, we retrospectively examined presence or absence of RPLND, disease-free survival (DFS) and overall survival rate (OS) in dissected group and non-dissected, with approval of our IRB. [Results] 67 cases were not performed with RPLND and 84 cases were done with only pelvic lymph node dissection. In 26 cases, pelvic lymph nodes and para-aortic lymph nodes were dessected. A pelvic lymph node metastasis was detected in two cases of EA G1. There was no difference in DFS and OS between dissection group and non-dissected group. In other two cases, the recurrence in the dissection group were observed. Their retroperitoneal lymph nodes were not recurred, but recurrences in the lung and vagina were detected. [Conclusion] It is concluded that RPLND is not always necessary for the low possibility of retroperitoneal lymph node metastasis in cases of endometrial cancer stage IA and EA. RPLND might be omitted under condition of no lymph-node swelling in preoperative imaging and intraoperative observation.

ISP-6-3 Novel approach to predict lymph node metastatic state of uterine endometrial cancer, toward reduction of lymphedema caused by irrelevant lymphadenectomy

Juntendo University[1], Juntendo University Shizuoka Hospital[2], Juntendo University Nerima Hospital[3], Kyushu University[4]
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[Objective] Lymphadenectomy in stage I endometrial cancer (EM ca) does not improve survival but increases the risk of side effects including lymphedema. While many studies were performed with aiming at predicting lymph node metastatic state (LN+/−), no effective methods have been established. Here we challenge the problem by genome-wide survey of RNA species. [Methods] After approval of the Ethical Committee, Of 97 EM ca tissues collected, 5 patients with LN+ and 10 patients with LN− diagnosed endometrioid adenocarcinoma G1 with less than 1/2 muscle invasion were chosen for transcriptome analysis, where CAGE (Cap Analysis of Gene Expression) was employed. qRT-PCR was employed to investigate a limited number of genes. [Results] The CAGE led us to identify two genes as promising candidates, and qRT-PCR experiments confirmed their association with LN+/− states. On of the markers, a novel promoter of TACC2, is highly expressed in cancer tissue with LN+, and the other is highly expressed in LN− reciprocally. Their combination shows significant difference in relative expression between LN+/− states ($p<0.001$), and effective discrimination of the two states (AUC=0.917). [Conclusion] We propose a novel approach to predict LN+/− state based on novel RNA markers, which may enable us to stratify patients, choose accurate personalized treatment, and improve QOL by reducing irrelevant lymphadenectomy.

ISP-6-4 Outcomes of patients with low-risk endometrial cancer surgically staged without paraaortic lymphadenectomy based on intraoperative evaluation

Osaka University
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[Objective] Some surgeons perform paraaortic lymphadenectomy (PAND) for all endometrial cancer. However there is some controversy in performing PAND for low-risk patients. The objective of this study was to evaluate the survival outcomes in patients treated without PAND. [Methods] From 2006 to 2013, 246 patients were surgically treated without lymphadenectomy for low-risk stage I endometrial cancer. Low-risk cancer was defined as following condition by intra-operative diagnosis based on frozen-tissue microscopic evaluation : 1) G1 or G2 endometrioid histology and 2) myometrial invasion<50%. Medical records were retrospectively reviewed for pathological diagnosis, adjuvant treatment, recurrence, and mortality. [Results] Recurrence, and disease-specific mortality were low. 44 of 246 patients (17.9%) were upstaged based on final pathology. 11 of 246 patients (4.5%) experienced recurrence with mean time to recurrence of 17.2 months. Among the 11 recurrent cases, two patient recurred at paraaortic lymph nodes (0.81%). These patients were treated chemotherapy and alive with disease for 23 months and 40 month after recurrence. Five year overall survival was 97.1%. [Conclusion] In condition with proper intra-operative pathological diagnosis, omission of PAND could be reasonable for low-risk disease.

ISP-6-5 Comparative study of laparoscopic surgery versus laparotomy for early-stage endometrial cancer

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[Objective] We started laparoscopic surgery for early-stage endometrial cancer with an approval of medical ethics committee in March 2010. The aim of this study was to retrospectively compare surgery-related complications and survival outcomes between patients' groups treated with laparoscopy and laparotomy. [Methods] From March 2010 through August 2015, we performed laparoscopic surgery in 111 cases and laparotomy in 158 cases. Preoperative assessment of the patients were ; endometrioid adenocarcinoma G1 or G2, invasion less than one half of the myometrium, and no distant/lymphatic metastasis. We evaluated surgery-related complications and analyzed recurrence-free and overall survival using Kaplan-Mayer or Long-rank test. [Results] Laparoscopic group experienced fewer complications compared with laparotomy group (11.7% vs 37.3% ; $p<.001$). During the observation period of median 10 months and 33.5 months in each group, there was no death in both groups. Recurrence rate was 1.8% (2 cases) in laparoscopic group and 6.3% (10 cases) in laparotomy group. There was no significant differences in recurrence-free survival and overall survival. [Conclusion] Survival outcome of laparoscopic surgery for early-stage endometrial cancer is not inferior to that of laparotomy. Laparoscopic surgery is the good alternative for early-stage endometrial cancer.

ISP-6-6 Outcome of laparoscopic surgery compared to laparotomy for early stage endometrial carcinoma

The University of Tokyo
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[Objective] Laparoscopic (L-) surgery for early stage endometrial carcinoma has become prevalent.We evaluated accuracy of preoperative diagnosis, safety and postoperative course of L-surgery for endometrial cancer. [Methods] We performed L-surgery (hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy : H+SO+PLA) in 13 endometrial cancer patients, with preoperative diagnosis as stage IA, grade 1. Informed consent was obtained from all patients. We retrospectively reviewed pathological diagnosis and surgical factors in these patients (L group), compared with 61 endometrial cancer patients (LA group) with same diagnosis as L group treated by laparotomy (H+SO+PLA) during 2010-2014. [Results] Preoperative and postoperative diagnoses were same in all the 13 cases. Surgical time, blood loss and length of hospital stay were significantly smaller in L group than LA group (301 min vs. 332 min, 109 ml vs. 843 ml, and 12 days vs. 9 days, respectively, $p<0.05$). Mean duration of drainage tube in Douglas' pouch and number of excised lymph nodes were not significantly different (4 days vs. 6 days, and 39 vs. 36, respectively). No perioperative complication was observed in L group. [Conclusion] Preoperative diagnosis was consistent with the postoperative diagnosis. L-surgery might be a less invasive surgical procedure in endometrial cancer, without decreasing the quality of PLA.

ISP-6-7 Impact of obesity on the surgical outcomes of early stage endometrial cancer : comparison of laparoscopic surgery and laparotomy

Osaka Rosai Hospital
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[Objective] Although surgical step is more difficult in obese case, laparoscopic surgery is the candidate of surgical intervention that can minimize the adverse effect of obesity. [Methods] Among 191 cases of endometrial cancer staged surgically between January 2010 and June 2015, 168 cases (90 cases of laparotomy and 78 cases of laparoscopic surgery) of pT1-2 cases were analyzed retrospectively. Use of laparoscope for surgical intervention was approved by IRB. [Results] Overall survival was not significantly different between laparoscopy and laparotomy groups. Post operational hospital stay was significantly shorter (laparoscopy vs. laparotomy=5.3 ± 2.7 days vs. 9.2 ± 5.7 days), and average amount of blood loss was smaller (89ml vs. 290ml) in laparoscopic group. Post operational hospital stay and complication rate increased according to the subgroups of increased BMI (8.2 ± 3.2, 13 ± 11, 17 ± 7.7days and 9.6, 23, 75% according to BMI : -30, 30-40, 40-) of laparotomy group, but this was not the case in laparoscopic group (5.3 ± 3.0, 4.6 ± 0.8, 4.3 ± 0.6days and 4.7, 0, 33%). SSI and ileus was the complication of laparotomy group that require longer hospitalization. [Conclusion] Laparoscopic surgery was superior to laparotomy in shorter hospital stay, especially in morbid obese cases. Laparoscopic surgery can replace laparotomy in early stage of endometrial cancer in cases of normal sized uterus.

ISP-6-8 The usefulness of hysteroscopic inspection with transcervical resection (TCR) for endometrial malignancy

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[Objective] The aim is to evaluate the diagnostic usefulness of transcervical resection (TCR) in patients with suspected endometrial cancer. [Methods] We reviewed the records of 69 patients who underwent TCR for suspected uterine malignancy from 2004 to 2015 in accordance with ethical guidelines at our hospital. We addressed correlation between hysteroscopic findings and the final diagnosis. We also compared the pathological diagnoses by TCR with those by fractional curettage. [Results] The distribution of diagnosis by TCR specimen was atypical endometrial hyperplasia complex (AEMHc) in 19 (28%), atypical polypoid adenomyoma (APAM) in 7 (10%), and endometrial carcinoma (EC) in 12 cases (17%). Evaluation of hysteroscopic inspection revealed that irregular vessels were found in 57% of the AEMHc cases, and in 78% of the EC cases. Notably, all resected specimens of white or desquamation lesions were diagnosed as endometrial cancer, even in cases with negative preoperative pathological findings. 72% of false negative cases (not diagnosed by fractional curettage) contained benign endometrial polyps and/or submucosal uterine fibroids, and TCR-targeted biopsy could give more accurate diagnosis. [Conclusion] The precise endometrial evaluation with TCR might be useful for improving the accuracy of diagnosis and subsequent appropriate treatment plan for early endometrial cancer.

ISP-6-9 A retrospective comparison of the safety of definitive radiotherapy in elderly and non-elderly women with uterine cancer

Hiroshima University
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[Objective] This study compared the safety of definitive radiotherapy (RT) in women＞70 years old (elderly group : A) and women＜70 years old (non-elderly group : B) with cervical cancer. [Methods] Forty-nine cases of cervical cancer (group A, 21 ; group B, 28) were treated during 2010-2014 using concurrent chemoradiotherapy (CCRT) or RT. The progressive stages I, II, III, IV for group A were 3, 6, 6, 6, and for group B were 1, 6, 14, 7, respectively. Acute and late toxicities (grade 3-4) were evaluated retrospectively. [Results] The median age in group A was 76 (range, 70-89) years and in group B was 53 (range, 27-69) years. CCRT was used in 14 cases in group A and 25 cases in group B. RT was used in 7 cases in group A and 3 cases in group B. Platinum was used in 10 cases in group A and 15 cases in group B. Taxane and platinum were used in 4 cases in group A and 10 cases in group B. Acute hematological toxicities in CCRT were 57% in group A and 48% in group B. Neutropenia was significantly different between groups (A vs. B : 57% vs. 24% p=0.03). In group A, 5 cases used G-CSF, and 2 needed blood transfusion. Acute and late non-hematological toxicities were not significantly different between groups. One case in each group could not complete RT due to toxicities. [Conclusion] Both group A and group B cases were treated using the same CCRT with appropriate treatment for the toxicities.

ISP-6-10 Combined large cell neuroendocrine carcinoma and endometrioid adenocarcinoma of the endometrium : A case report and survey of literature

Oita University
Harunobu Matsumoto, Kaei Nasu, Kentaro Kai, Masakazu Nishida, Tomoko Hirakawa, Hisashi Narahara

This report describes a case of primary large cell neuroendocrine carcinoma (LCNEC) of the endometrium combined with endometrioid adenocarcinoma. [Case] 51-year-old woman was admitted because of suspected uterine tumor. An endometrial specimen collected by curettage showed adenocarcinoma. MRI and CT scan showed endometrial hypertrophy. There were no findings that suggested lymph node metastasis or distal metastasis. The patient underwent abdominal radical total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymphadenectomy, and subtotal omentectomy. Polypoid tumor was found in the endometrium. The histological examination showed LCNEC and endometrioid adenocarcinoma (G1) of the endometrium. The tumor metastasized to the right ovary. The patient was diagnosed as stage IIIA. The patient received monthly irinotecan/cisplatin therapy for 6 cycles. The patient has been well without evidence of disease for 20 months. [Conclusion] Primary LCNEC of the endometrium is rare and only 14 cases are reported. In view of the limited number of the cases, it is difficult to establish an evidence-based therapeutic regimen. At this point, the standard modality of treatment is similar to that of endometrial adenocarcinoma : surgical resection, radiotherapy, and chemotherapy. In most reported cases, regimens of chemotherapy designed for lung neuroendocrine carcinoma were selected.

ISP-6-11 A Case Report of Combined Large Cell Neuroendocrine Carcinoma and Endometrioid Carcinoma of the Endometrium：Shared Gene Mutation Signature between the Two Histologic Components

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[Case report] A 61-year-old Japanese woman was diagnosed with FIGO Stage IB endometrial cancer with combined with Grade1 EC and LCNEC. The metastasis of lymph nodes in right bronchopulmonary area, mediastinum and brain were also found. Finally, she developed pleuritis and epicarditis carcinomatosa and died of cancer 51 months after the surgery. [Background] Gene alterations in uterine NE-carcinomas are still not understood. We examined gene alterations in the mutation-hotsopts of selected 50 cancer-associated genes. [Results] The EC and LCNEC components shared identical alterations in PTEN, PIK3CA and FGFR3. PTEN alteration was almost homozygous R130G missense single-base substitution (SBS). PIK 3CA was heterozygous for a missense SBS resulted in R88Q. Only the EC contained another missense heterozygous SBS on FGFR3 resulted in A374T. Both the EC and LCNEC components had heterozygous SBS on CTNNB1, but the EC contained G34R whereas the LCNEC contained T41A. In addition, both components had unique mutations each other, but with low allele frequency estimated less than 5%. The EC contained a H83Y mutation on CDKN2A and a T41A mutation on CTNNB1. On the other hand, the LCNEC had a R140W mutation on IDH2. [Conclusions] The gene mutation signature strongly supported the idea that the two components derived from a common precursor lesion or the LCNEC was originated from the pre-existing EC.

ISP-6-12 Endometrial Metastasis from Primary Rectal Carcinoma

Oita University
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[Introduction] Metastases to the uterine endometrium from an extra genital site are a rare event. As in primary endometrial carcinoma, abnormal uterine bleeding is the most common symptom of such metastases. The misdiagnosis of another original cancer as a primary endometrial carcinoma should be avoided. Here we report a case of endometrial metastasis from a primary rectal carcinoma. [Case] A 63-year-old Japanese woman was admitted to our hospital with postmenopausal abnormal uterine bleeding. Endometrial cytology revealed an adenocarcinoma. Endometrial sampling showed multiple fragments of proliferative endometrial tissue mixed with irregular glands lined by atypical cells with elongated, hyperchromatic nuclei and solid sheets of neoplastic cells. The neoplastic glands were positive for CDX2 and CK20 and negative for CK7. The tumor was histologically diagnosed as metastatic endometrial carcinoma originating in the rectum. The endometrial metastasis was treated solely by tumor removal. [Discussion] Although rare, extra genital sites should be considered as possible primary sites of metastatic endometrial carcinoma. In addition to the clinical history, a thorough histological examination including immunohistological staining is necessary to diagnose metastatic carcinoma.

ISP-7-1 MicroRNA let-7c contributes to acquired resistance to paclitaxel in endometrial serous carcinoma

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Izumi Sato[1], Yoh Watanabe[2], Fumihiko Suzuki[1], Hideki Tokunaga[1], Hitoshi Niikura[1], Satoru Nagase[3], Nobuo Yaegashi[1]

[Objective] Endometrial serous carcinoma (ESC) is a rare phenotype of endometrial carcinoma known for the poorest prognosis in gynecological cancers. One of the reasons of miserable clinical course of ESC is acquired chemo-resistance, because there are few choices of chemo-agent. Thus, the objective of this study is to investigate mechanisms of paclitaxel resistance from the aspect of microRNA (miRNA). [Methods] ESC cell line USPC1 and paclitaxel (PTX) resistant cell line (USPC 1/PTX-R) derived in our laboratory were used. Expression of let-7c was examined by qRT-PCR in drug resistant cells and compared with their parental cell. Alteration of drug-resistance was analyzed after let-7c precursor transfection. Moreover we searched for the possible target of let-7c including HMGA2, Bcl-xl and other candidate. [Results] The expression of let-7c was decreased in USPC1/PTX-R. After let-7c precursor transfection to USPC1/PTX-R, the decreased resistance for PTX was observed compared with negative control. [Conclusion] Let-7c contributes to acquired resistance to PTX in ESC.

ISP-7-2 The histone methyltransferase, SUV39H2, is a potent target of anti-cancer therapy in endometrial cancer

The University of Tokyo
Kenbun Sone, Katsutoshi Oda, Shinya Oki, Makoto Takeuchi, Chinami Makii, Osamu Wada-Hiraike, Kei Kawana, Yutaka Osuga, Tomoyuki Fujii

[Objective] Dysregulation of epigenetic machinery, especially the process of histone methylation, has been considered as one of key regulators for human carcinogens. However, little is known about functions of histone modifications, except for H2AX as a marker of the DNA damage response. [Methods] Endometrial cancer cell lines (n=11) and clinical endometrial cancer samples (n=52) were used in this study under approval of our ethical committee and informed consent. We performed quantitative real-time PCR (q-PCR) to evaluate expression of a histone methyltransferase, SUV39H2, and analyzed the relationshipt between SUV39H2 expression and methylation status of H2AX. [Results] The q-PCR revealed that SUV39H2 is overexpressed (>2-fold) in 11 out of 11 (100%) endometrial cancer cell lines and in 11 out of 52 (21%) clinical samples, compared with a control (immortalized endometrial cell line or normal endometrium). We found that SUV39H2 methylated lysine 134 on histone H2AX. The production of γ-H2AX was significantly reduced by introduction of mutant SUV39H2 (Lys134Ala). Furthermore, knockdown of SUV39H2 significantly increased the sensitivity to both irradiation or cisplatin/doxorubicin in the cancer cell lines. [Conclusion] Targeting histone methyltransferases, such as SUV39H2, might be a novel anti-cancer therapy in endometrial cancer.

ISP-7-3 Development of minimum invasive endometrial cancer detection method by targeting methylated DNA of cervical mucus

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[Objective] Endometrial cytology has a problem that the patients have painful. We aimed at developing minimum invasive endometrial cancer detection method using cervical mucus specimens. [Methods] With the approval of our institutional review board, written consent was obtained. 1) Quantitative PCR was performed using Marker-X which is one of the genes we have confirmed as specifically methylated in endometrial cancer. Methylation ratio (methylated Marker-X DNA/total Marker-X DNA) of DNA extracted from endometrial cancer tissue (n=69) and normal endometrium (n=35) was compared. In addition, the ability to discriminate endometrial cancer has been examined in ROC curve analysis. 2) Methylation ratio of Marker-X in cervical mucus specimens from 6 patients with endometrial cancer and 4 patients with normal endometrium was examined. [Results] 1) Methylation ratio of Marker-X of endometrial cancer was significantly higher ($P<0.0001$) compared to normal endometrium. ROC curve analysis showed moderate accuracy (AUC=0.894). 2) Using cervical mucus specimens, average methylation ratio of Marker-X was higher (14.8% vs. 4.7%) in endometrial cancer compared to normal endometrium. [Conclusion] These results suggest that measuring DNA methylation ratio of Marker-X from cervical mucus specimens may have possibility to be minimum invasive endometrial cancer detection method.

ISP-7-4 Mutation of any DNA mismatch repair gene can cause lower uterine segment cancer with Lynch syndrome

Keio University
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[Objective] Lynch syndrome is a hereditary disease that is caused by a mutation in a DNA mismatch repair (MMR) gene. Carcinoma arising from the lower uterine segment (LUS) is associated with Lynch syndrome harboring germline mutations in *MSH2*. In this study, we examined the correlation between carcinoma of the LUS and mutations of MMR genes in Japanese patients with endometrial cancer. [Methods] We examined 935 patients who were diagnosed with endometrial cancer and underwent hysterectomy. The patients were classified into those with LUS or non-LUS carcinoma. The clinical and pathological characteristics, results of microsatellite instability (MSI) analysis, methylation of *MLH1*, and immunohistochemical staining with anti-MMR protein antibody were compared between the two groups. This study was conducted after approval by the institutional review board. [Results] Carcinoma of the LUS was present in 18 cases, which accounted for 1.9% of all the endometrial cancer cases. One of the 18 cases (5.5%) met the Amsterdam II Criteria and 1 met the revised Bethesda guidelines. In these patients, we observed germline mutations in *MLH1* and *MSH6*. [Conclusion] Our results show that carcinoma of the LUS can occur in a patient with mutations of *MLH1* and *MSH6*, as well as *MSH2*. This suggests that germline mutation of any MMR gene can cause carcinoma of the LUS.

ISP-7-5 Significance of p53 expression in background endometrium in endometrial carcinoma

Occupational and Environmental Health University
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[Objective] The p53 signature (p53S) has been proposed to be a marker of the earliest phase of endometrial serous carcinogenesis. [Methods] The 225 endometrial carcinomas were available for review. Expression of estrogen receptor (ER)-alpha, Ki-67 and p53 was studied by immunohistochemistry. DNA sequence analysis for TP53 exons was made for p53S. The study was approved on ethical issues. [Results] he mean age of 22 patients with p53S was 64.2 years. The median labeling index (LI) of ki-67 for p53S was 4.0% (range : 0.0% to 21.0%). All p53Ss were positive for ER-alpha. The 225 noncancerous endometrium samples were divided into two groups, comprising 34 hyperplastic and 191 non-hyperplastic endometrium tissues. In the hyperplastic group, p53S was found to be associated with two grade 1 endometrioid tumors in premenopausal women with Lynch syndrome. In the non-hyperplastic group, p53S and endometrial intraepithelial carcinoma (EIC) were associated with 12 (7.9%) and zero (0.0%) of 152 endometrioid adenocarcinomas and eight (20.5%) and 20 (51.3%) of 39 non-endometrioid adenocarcinomas. A p53S with endometrioid adenocarcinoma showed TP53 wild type. A p53S with serous carcinoma showed a TP53 missense mutation in exon 5 at codon 183. [Conclusion] p53S is thought to be partly responsible for a latent precancerous lesion of non-endometrioid tumors, including carcinosarcomas.

ISP-7-6 Regulation of autophagy and its potential as a therapeutic target in endometrial cancer cells

The University of Tokyo
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[Objective] Autophagy is a major cellular catabolic process, which can promote cancer growth by fueling cellular metabolism. However, the relationship between autophagy and endometrial cancer has not been elucidated. We investigated the potential roles of autophagy in endometrial cancer cells by modulating autophagy with two drugs, anti-malarial chloroquine (CQ) and a famous polyphenol, resveratrol (RSV). [Methods] Ishikawa endometrial cancer cells were treated with CQ or RSV or combination of them. Genetic autophagy inhibition was performed by siRNAs to ATG5 and ATG7. Cell proliferation and apoptosis were analyzed by MTT assay and annexin-V staining, respectively. The level of autophagy was evaluated by LC3-II accumulation in western blotting and immunofluorescence. [Results] Both CQ and RSV suppressed cell proliferation in a dose-dependent manner, with apoptosis induction. However, autophagy was upregulated by RSV, whereas it was downregulated by CQ. Knocking down either ATG5 or ATG7 attenuated cell proliferation by inhibiting autophagy. Combination of CQ and RSV more robustly suppressed cell growth and induced apoptosis, compared with either CQ or RSV alone. [Conclusion] Both CQ and RSV showed anti-tumor effect, but the effect of RSV can be attenuated by the upregulation of autophagy. Thus, combination of CQ and RSV might be an attractive therapeutic option in endometrial cancer.

ISP-7-7 Survivin inhibitor-Sepantronium bromide, is a potent, novel molecular-targeted therapy against endometrial cancer

The University of Tokyo
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[Objective] Survivin, an anti-apoptotic protein, is up-regulated in most of malignant tumors. Sepantronium bromide is a small molecule which inhibits survivin. Despite several clinical trials in human cancers, effectiveness of this compound against endometrial cancer has not been reported. In our study, anti-tumor effects of Sepantronium bromide against endometrial cancer was investigated. [Methods] We analyzed the expression of survivin by immunoblotting and immunohistochemistry using 16 endometrial cancer cell-lines and 110 clinical specimens respectively with approval of our IRB. Cell viability assay was performed to assess anti-proliferative effects of Sepantronium bromide. Cell-cycle and apoptosis were analyzed by flow cytometry and Annexin V assays respectively. We also knocked down survivin by siRNAs to confirm its effect. [Results] Survivin was up-regulated in 12 of 16 (75%) endometrial cancer cell lines and abundantly expressed in 81 of 110 clinical samples (73%) by Western blotting and IHC respectively. The agent potently inhibited proliferation of all analyzed cell lines, arrested the cell-cycle at G1-phase and induced caspase-mediated apoptosis in a dose-dependent manner. Knockdown of survivin by siRNAs induced apoptosis by 60%. [Conclusion] The results suggest that survivin inhibitor, Sepantronium bromide, can be a potent, novel molecular-targeted therapy against endometrial cancer.

ISP-8-1 Basic HLH type of transcriptional factors, BHLHE40 and BHLHE41 suppress epithelial-to-mesenchymal transition of endometrial cancer cells by inhibiting SP1 function

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[Objective] We studied the impact of the transcriptional factors, BHLHE40 and BHLHE41 (BHLHEs) in human endometrial cancer (HEC) cells. [Methods] HEC specimens, which were surgically removed under patients' informed consents, were examined for mRNA and protein levels of BHLHEs. BHLHEs expression was manipulated in HEC cell lines. *In vitro* cell invasion assay of the manipulated cells was performed. Expression of the epithelial-to-mesenchymal transition (EMT) markers was also examined. Reporter assay was applied to identify the critical regions of TWIST1 promoter, which were regulated by BHLHEs. [Results] BHLHEs expression levels were higher in early stage of HEC tissues compared with those of advanced cases. BHLHEs expression in HEC cells resulted in suppression of *in vitro* cell invasion. The transcription factor, SP1 was critical for the transcription of TWIST1, a well-known EMT effector. BHLHEs suppressed TWIST1 transcription by competing with SP1 for binding to the TWIST1 promoter. The inhibitor of SP1, WP631 effectively inhibited TWIST1 expression and *in vitro* cell invasion. [Conclusion] Our data suggested that both BHLHEs suppress cell invasion by inhibiting EMT in HEC cells. BHLHEs are promising markers to predict the aggressiveness of each HEC cases, and molecular targeting strategies involving BHLHEs and SP1 may effectively regulate HEC progression.

ISP-8-2 Histone methyltransferases/demethylases are novel targets of anti-cancer therapy in endometrial cancer

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[Objective] Dysregulation of histone methyltransferases/demethylases in human cancer has been reported for a decade, however the roles of these alterations in cancer progression have not been well characterized, especially in endometrial cancer. The aim of this study is to elucidate the methyltransferases/demethylases dysregulated in endometrial cancer. [Methods] We screened 14 methyltransferases/demethylases, which was reported to be overexpressed in various types of human cancer. We analyzed the expression of these genes by quantitative real-time PCR (q-PCR), using 11 endometrial cancer cell lines and 50 clinical endometrial cancer specimens, under informed consent and approval of our ethics committee. The effect to cell proliferation by knocking down specific histone methyltransferases was evaluated by MTT assay. [Results] Q-PCR revealed that 9 out of 14 histone methyltransferases/demethylases were overexpressed in＞80% of endometrial cancer cell lines, compared with a control. Among them, 8 histone methyltransferases/demethylases were also overexpressed in＞40% of clinical samples. Knocking down these methyltransferases by siRNA suppressed cell proliferation in MTT assay. [Conclusion] Various types of methyltransferases/demethylases are overexpressed in endometrial cancer. These genes might be novel candidates for molecular target therapies in endometrial cancer.

ISP-8-3 Clinical impact of DNA mismatch repair status in endometrial carcinomas

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[Objective] Endometrial carcinoma is the most common malignancy in women with Lynch syndrome (LS) caused by mismatch repair (MMR) deficiency. The aim of this study was to elucidate the clinical impact of MMR status in unselected endometrial carcinomas. [Methods]Under approval by the institutional ethical committee, we analyzed immunohistochemical expressions of MLH1, MSH2, MSH6, and PMS2, and MLH1 promoter methylation in primary endometrial carcinomas from 221 consecutive patients. All patients provided informed consent. Tumors were categorized as sporadic or probable LS (PLS) based on these results. [Results] Sporadic group was significantly associated with older age, obesity, deep myometrial invasion, and advanced stage (p=0.008, 0.01, 0.02 and 0.03), while PLS was significantly associated with early stage and LS-associated multiple cancer (p=0.04 and 0.001). PLS showed significantly better overall survival (p=0.038). This trend was stronger in advanced stage than in early stage (p=0.14 vs. 0.49). In the subset receiving adjuvant therapies, PLS showed trends towards favorable disease-free survival by contrast with patients receiving no adjuvant therapies showing no such trend (p=0.12 vs. 0.85). [Conclusion] Analyzing MMR status and searching for LS may identify a group of patients with favorable survival and higher sensitivity to adjuvant therapies.

ISP-8-4 The characteristics of LAMC1 expression patterns associated with the clinical features of endometrial cancer

Keio University
Haruko Kunitomi, Yusuke Kobayashi, Kouji Banno, Ryuichiro Okawa, Kenta Masuda, Megumi Yanokura, Eiichiro Tominaga, Mamoru Tanaka, Daisuke Aoki

[Objective] Specific laminin expression profiles are related to cancer proliferation and metastasis. Upregulation of *LAMC1*, which encodes laminin-γ1, is of particular note because this is related to aggressive behavior of cancer cells of various origins. This is the first study to analyze the impact of LAMC1 expression on the clinical features of endometrial cancer. [Methods] The subjects were patients with endometrial cancer (EC), atypical endometrial hyperplasia (AEHC) or a normal endometrium (NE) who underwent hysterectomy during January 2008 and December 2011 at our institute. The study included 28 cases of EC, 9 of AEHC, and 16 NE. LAMC1 immunostaining was evaluated as negative or positive. Patient characteristics and clinical outcomes were obtained retrospectively from clinical records. This study was approved by our institutional review board. [Results] LAMC1 expression was significantly elevated in EC compared to AEHC and NE ($p < 0.001$). Compared to type 1 EC, type 2 EC indicated LAMC1 expression more frequently ($p=0.0005$). There was no relationship between expression of LAMC1 and FIGO surgical stage. LAMC1 expression tended to have a negative impact on progression-free and overall survival. [Conclusion] LAMC1 expression is related to aggressive tumor behavior in endometrial cancer.

ISP-8-5 The function of YBX2 on endometrial cancer stem cell

Juntendo University[1], Kyushu University[2]
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[Objective] Among the endometrial cancer cells, there are side population cells (SP cells) which show low Hoechst 33342 intake and cancer stem cell-like function. Intranuclear transcription factor YBX2 is one of the cancer testis antigens, which exists on testis, ovary, germ cells, and also cancer cells. In this study, we aim to clarify the function of YBX2 in the secure process of stem cell function on endometrial cancer cells. [Methods] We established YBX2-positive Ishikawa cell lines. We analyzed the gene expression associated with stemness and isolated SP cells from IK-YBX2cells. We sought cell-cycle analysis, chemosensitivity assay, and microarray on the IK-YBX2 cells. [Results] In IK-YBX2 cells, the ratio of SP cells and the expression of ALDH1 were up-regulated. IK-YBX2 cells had resistance of anticancer drugs and led to cell cycle delay. We found that another cancer testis antigen (CTA45) was overexpressed in IK-YBX2 cells. We down-regulated CTA45 in IK-YBX2 cells using shRNA. Among them, expression of ALDH1 and self-renewal ability were decreased. Finally, we investigated expression of CTA45 in human endometrial cancer tissues by immunohistochemistry. The level of CTA45 expression was enhanced in high-grade and/or advanced stage. [Conclusion] We conclude the expression of YBX2 is essential for the stem cell-like phenotype. CTA45 is also important factor for stemness.

ISP-8-6 Isolation and characterization of cancer stem-like cells from primary human endometrioid adenocarcinoma

Sapporo Medical University
Yuta Tabuchi, Tasuku Mariya, Takuya Asano, Takahumi Kuroda, Masahito Mizuuchi, Seiro Satohisa, Mizue Teramoto, Ryoichi Tanaka, Masahiro Iwasaki, Tsuyoshi Saito

[Objective] Cancer stem cells (CSCs) are defined as subpopulation of cancer cells and endowed with higher tumorigenicity, self-renewal and differentiation ability. Recent analysis revealed that CSCs are resistant to standard cancer therapies. Therefore, eradication of CSCs is essential to cure cancer. However, most of the analysis of CSCs were performed using cancer cell lines not primary human samples, and the results may not reflect primary tumors. In this study, we tried to isolate and analyze primary CSCs from endometiroid adenocarcinoma sample. [Methods] We cultured primary endometrioid adenocarcinoma cells in two conditions. One is a culture in floating condition using low-attachment plate and non-serum medium (sphere culture), and the other is an adhesive culture in serum containing medium (serum culture). Sphere culture cells and serum culture cells were analyzed by limiting dilution and mouse xenograft assay. [Results] A limiting dilution analysis revealed that sphere culture cells showed significantly higher sphere-forming ability than that in serum culture cells. In mouse xenograft assay, sphere culture cells showed significantly higher tumorigenicity than that in serum culture cells. [Conclusion] These results indicate that primary sphere culture cells are enriched with CSCs, and reasonable source to analyze endometrioid adenocarcinoma CSCs. Further analysis are ongoing.

ISP-9-1 A new educational program of operative procedure with a slim and rigid hysteroscopy

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Akio Tokudome[1], Toshimichi Oki[2], Chie Oki[1], Yuji Orita[1], Hideki Yamazaki[1], Tsutomu Douchi[1]

[Objective] There are a lot of educational programs for laparoscopic surgery. However, educational program for operative hysteroscopy is very rare. In this study, we made some programs for a hysteroscopic polypectomy and myomectomy. We studied a usefulness of our program. [Methods] The most important point is how to keep clear view and manage forceps. The former is hardly reproduced, but the latter is easily done. Grasping forceps include picking up, drawing, pushing and tearing. These procedures can be reproduced to pick up "Paprika kind" model through an opened hole with 3–4mm diameter. Scissors forceps include cutting and detaching. These techniques can be reproduced in "Buried corn in clay" model. We studied similarity between practical hysteroscopic procedures and these models. [Results] Protocol of hysteroscopic polypectomy was made of followings ; scissors cutting of steal of endometrial polyp, crow or grasp forceps grasping and tearing and drawing. Only "Paprika kind" model covered all steps of polypectomy. On the other hand, hysteroscopic myomectomy includes specific and additional following steps ; detachment of fibroid from endometrium and myometrium. These were very similar to detach corn kind from clay with scissors and grasping forceps. [Conclusion] These two programs were useful to acquire the skill of operative hysteroscopy.

ISP-9-2 Use of YouTube videos to learn laparoscopic hysterectomy

Osaka Railway Hospital
Koji Kumagai, Masahiro Sakai, Takayoshi Maeda

[Objective] Live operations are very important for novices in laparoscopic surgery. However, they may not always be able to observe a sufficient number of surgeries at their hospital. There are several videos on laparoscopic surgery available on a video-sharing web site called YouTube. We examined the usefulness of YouTube videos for novices to learn the various techniques involved in laparoscopic hysterectomy. [Methods] We searched the YouTube website using the key word "laparoscopic hysterectomy," and found 176,00 videos. We selected 112 videos based on the upload date (＜4 years since upload) and the number of views (＞700). In each video, we examined the laparoscopic hysterectomy techniques performed. [Results] The nationality of the physicians included Indian (29%), American (11%), Ukrainian (10%), Turkish (8%), Italian (7%), and others (35%). The mean video playback time was 11 min (range, 1–171 min). The uterine size was smaller than a fist in 72% videos. With regard to port placement, 42% used the diamond approach, 38% used the parallel approach, and 20% used other methods. Ultrasonic device, bipolar system, and colpotomizer were used in 37%, 29%, and 81% of the videos, respectively (some videos used a combination of these devices). [Conclusion] YouTube videos could be useful for novices to learn the various techniques involved in laparoscopic hysterectomy.

ISP-9-3 Dilemma in Diagnosis and Management of Huge Broad Ligament Myoma

Fatima University Medical Center, Philippines
Verlyn Zuniega-Cruz, Ma Lourdes R. Abeleda, Richard Jordias

Giant extrauterine fibroids are known to arise from the uterus but very rarely are they located in broad ligament. Its incidence is＜1%. This is a case report of a broad ligament myoma in a 39 year old Gravida 2 Para 2 (2002) who presented with abdominal enlargement for five months. Transvaginal ultrasound showed subserous myoma cannot totally rule out broad ligament myoma. On Exploratory Laparotomy, a huge broad ligament myoma was found. Total Abdominal Hysterectomy followed by myomectomy was done. Hence, we are presenting a rare case of leiomyoma in the broad ligament reported due to its rarity, and the diagnostic and management dilemma it poses.

ISP-9-4 What is efficient marker determining necessity of surgical hemostasis for postoperative bleeding after laparoscopic surgery? Abdominal drainage volume or vital sign change?

Juntendo University
Keisuke Murakami, Jun Kumakiri, Yuko Ikemoto, Rie Ozaki, Yuki Ujihira, Makoto Jinushi, Keiji Kuroda, Mari Kitade, Satoru Takeda

[Objective] Postoperative bleeding is major complication from laparoscopic surgery. Abdominal drains is useful, however, routine use is controversial and there is no consensus criterion determining necessity of surgical hemostasis. We aimed to review value of drains for postoperative management. [Methods] Drainage volume and vital sign in cases with re-operation for hemostasis after laparoscopic surgery were reviewed (n=8, 2009-2015). As a comparative data, relatively large drainage volume cases (total drainage volume at 12 hours>200ml) without re-operation were used (n=84, 2013-2015). [Results] In cases with re-operation, drainage flow at 1, 3 hours were 80 (40-190), 93 (50-160), shock index were 0.7 (0.5-0.9), 0.8 (0.5-1.1). In contrast, drainage flow at 1, 3, 6, 12 hours were 30 (0-110), 20 (0-85), 12 (0-67), 9 (0-45), shock index were 0.6 (0.4-1.1), 0.7 (0.4-0.9), 0.7 (0.4-0.9), 0.7 (0.4-1.0) in cases without re-operation. ROC analysis showed drainage flow at 3 hours were the most efficient indicator for surgical hemostasis (AUC 0.977). All cases with drainage flow>100ml/h at 3 hours underwent re-operation whereas none of cases with drainage flow<50ml/h had re-operation. [Conclusion] Drainage flow volume was the most efficient marker for re-operation. In cases with continuous excessive drainage, surgical hemostasis should be undergone immediately to avoid critical complications.

ISP-9-5 Evaluation of a new modified abdominal wall suspension system for gasless laparoscopic operation

Huhhot First Hospital, Hohhot Mongolia, China
Yinfeng Li, Lili Gao, Meiying Fen, Xiaoyun Gao

[Objectives] Gasless laparoscopy using subcutaneous wire suspension has been reported. In the conventional system the subcutaneous wire is connected to an elevator arm which is fixed to the operating table. Instead of using elevator arm, I developed a modified system with the subcutaneous wire connected to a suspended chain from the roof of the operating room. [Method] Laparoscopic myomectomy was performed in 90 women. They were randomly divided into conventional group (n=46) and modified group (n=44) depending on utilizing traditional or modified instruments to assist abdominal wall-lift during the laparoscopic surgery. [Results] The operating time and bleeding amount were both significantly decreased in the group using modified instrument ($p<0.05$, respectively). [Conclusion] Because the elevator arm is not used, the operating field above the abdomen is less obstructed, so that the operation can be performed more smoothly and quickly. As a result I consider the modified abdominal suspension system to be an effective and safe method assisting the laparoscopic operations.

ISP-9-6 Introducing Curved Needles through the Homemade Glove Port in Laparoscopic Surgery

Taiwan Adventist Hospital, Taiwan
Li-Yun Chou, Wen-Chun Chang, Bor-Ching Sheu

[Ojectives] To evaluate the clinical outcomes of introducing curved needles through the homemade glove port in laparoscopic surgery. [Methods] Thirty women with benign ovarian cysts underwent two-port laparoscopic cystectomy between September 2014 and March 2015. Ovarian hemostasis was achieved with sutures after the excision of the ovarian cysts without bipolar electrocoagulation. The needle was gently penetrated through the glove port to prevent tearing of the glove and then pass through the 1.5-cm umbilical wound into the abdominal cavity to complete the sutures. For retrieving the needle out, the needle was held close to the trocar and gently penetrated out from the glove port. [Results] The mean age was 30.9 years. Most of the patients (67%) had endometriotic cysts, followed by mature cystic teratoma (30%). About one third of the patients (30%) had bilateral cysts, and about half (40%) had more than one cyst. The mean size of the cysts was 8.6 cm, the mean operative time was 69.9 minutes, and the mean blood loss was 51.3 mL. It took less than 10 minutes to complete the suture procedure, and the mean postoperative hospital stay was 1 day. The postoperative wound pain was evaluated with a 10-cm visual analog scale at postoperative day 1, and the mean pain scale score was 1.9. There were no operative complications, conversions to laparotomy, or additional trocar insertions. [Conclusions] Introducing a curved needle through the homemade glove port prevents the need of applying another 12-mm trocar for the needle pass, thus minimizing collisions when using a large-sized trocar at the glove port. This method could be used easily in the glove port laparoscopic system for one- or two-port gynecologic or general surgery.

ISP-9-7 Development of the model for prediction of treatment response of uterine myoma after Uterine artery embolization

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[Objective] Uterine artery embolization (UAE) is one of the uterus-preserving treatment option of uterine myoma, and is increasing recently. However, studies about factors predicting the therapeutic effect after UAE are limited. The aim of this study is to develop the model for prediction of treatment response of uterine myoma after UAE. [Methods] Between December 2008 and August 2014, 104 patients underwent UAE for managing uterine myoma in Seoul St. Mary's Hospital. We randomly decided 70% of the patients as a model group and 30% as a model validation group. Model group was divided into a high-response group and low-response group according to the reduction rate of both uterine volume and largest myoma after UAE. If the reduction rate was over median of the group, it was defined as a high-reponse group. And if the reduction rate was under median of the group, it was defined as a low-response group. We analysed about patient's age, body mass index, marriage, and parity. We measured uterine volume, largest myoma volume, diameters of myomas, location of myoma, T1 and T2 signal intensity of myoma, contrast enhancement, b 1000 and ADC in pelvic magnetic resonance imaging (MRI) before and after uterine artery embolization. t-test and Chi-squared test were used to analyse variables. After univariate analysis, we decided significant variables which used in development of the model using logistic regression analysis. And then, we verified the validity of the model using the ROC curve and box plot. [Results] In high-response group, the proportion of submucosal myoma was higher and the number of myomas and sum of diameters of myomas were less than low-response group ($P<0.05$). And T2 signal intensity of myoma and fibroid-to-muscle ratio was higher in high-response group. Location of myoma and T2 signal intensity of myoma was selected as significant variables through logistic regression analysis, and we developed the model using these two variable. The area-under-curve in ROC was 0.833 in the model and 0.791 in model validation group. [Conclusions] We developed the model for prediction of treatment response of uterine myoma after UAE using location of myoma and T2 signal intensity of myoma. This model's performance was satisfactory for estimating treatment response after UAE. This model will be useful to predict the response of UAE and to manage myoma patients in clinic.

ISP-9-8 Evaluation risk factors of uterine rupture after laparoscopic myomectomy using MRI findings

Showa University
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[Objective] We aimed to evaluate risk factors of uterine rupture after laparoscopic myomectomy (LM) using MRI findings. [Methods] Subjects were women who were taken LM in our hospital between January 2013 and September 2015. We defined the thinning myometrium to be the thickness less than 50% of normal one. We evaluated whether there were differences about the thickness of their myometrium after LM among all cases, uterine-ruptured cases, and thinning myometrium cases. This study was conducted based on the approval of the ethics committee in our hospital. [Results] Result1 ; The target cases were 126 patients, the uterine-ruptured cases were 3 samples. The former's median was 8.91mm (3.57-16.1), the latter's median was 4.72mm (4.24-4.99). As compared to the control group, the group of the uterine rupture was significantly thinner ($p<0.01$). Result2 ; The thinning myometrium cases were 30 samples and their median was 6.15 mm (3.57-9.22). There was no difference between the thinning myometrium group and the uterine-ruptured group ($p>0.05$). [Conclusion] We demonstrated that theier condition of thinning myometrium after LM have a risk of uterine rupture during pregnancy from result1. However, result2 indicates that the cause of the uterine rupture is not only thinning myometrium but also other factors. In the future, we believe that we will proceed with the consideration for other factors.

ISP-9-9 Gynecological examination for women with severe motor and intellectual disabilities

Sakai City Support Center for Severely Handicapped Children & Persons, Verde Sakai
Hiroyuki Hashimoto

[Objective] To estimate success in pelvic examination, pathology results of the cervical cytology and identify the physical risk factors for the failure of pelvic examination in women with severe motor and intellectual disabilities. [Methods] A retrospective review of charts for 33 women with severe motor and intellectual disabilities for data on the success in pelvic examination, pathology results of the cervical cytology and physical functions of the lower extremities such as the presence of high tone in hip adductor muscles, hip dislocation, hip contracture and knee contracture. Institutional ethical committee approved this study. [Results] Of the 33 women, 20 and 14 had physical function of high tone in hip adductor muscles and hip dislocation. Of these, only 11 pelvic examinations could be completed successfully. Of the 32 available cervical smears, 13 contained endocervical cells and no cytological abnormalities were present. The endocervical cells with success in pelvic examination were 72.7% and were 23.8% without success ($p=0.007$). High tone in hip adductor muscles with success was 27.2% and was 77.3% without success ($p=0.006$). Hip dislocation with success was 27.3% and was 50% without success ($p=0.21$). [Conclusion] For the success of pelvic examination, support for the relaxation of adductor muscles must be considered.

ISP-9-10 Need of the surgical treatment in endometriotic cyst based on preoperative image views

Showa University
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[Objective] Operative treatment in endometriosis is not useful in some cases, and conservative treatment may be chosen from the viewpoint of ovarian functional preservation. In addition, it is known that the endometriotic cysts sometimes result in explosion and abscess, leading to a long term hospitalization and surgical management. In the present study, we evaluated MRI images to identify the critical findings to indicate the operation. [Methods] Women who had endometriotic cyst and underwent laparoscopic surgery in our hospital from 2012 through 2013 were subjected. MRI findings in patients who needed urgent hospital admission (case, n=8) were compared to patients underwent scheduled operation (control, n =153). [Results] The frequencies of MRI findings such as bilateral (p=0.004), shading (p=0.003), fluid-fluid level (p=0.001), and wall thickening (p=0.004) in cases were significantly higher than control. Tumor diameter, ascites, multilocular, irregularity, enhancement part, and hydrosalpinx were not different in both groups. [Conclusion] It is indicated the MRI findings of shading, a wall thickening, fluid-fluid level are associated with urgent hospital admission. It is suggested that surgical operation may be better management in patients with these MRI findings.

ISP-10-1 Three cases of gynecological malignant tumor that resulted in thrombocytopenia during an anticoagulant therapy

University of Toyama
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[Background] Heparin-induced thrombocytopenia (HIT) is critical complication in anticoagulant therapy. It is difficult to diagnose HIT because malignant patients have variable situation causing thrombocytopenia. We report 3 gynecological malignancy cases resulted in thrombocytopenia during heparin therapy. [Case presentation] (1) 54 y.o. woman with recurrence of cervical cancer treated by CDDP/CPT11 was diagnosed as DVT and PE. Heparin was started, but platelet had been decreased to 3.9 (10^4/μl). After heparin was stopped, platelet had improvement. HIT antibody was positive. She was diagnosed HIT, and the use of argatroban made it possible to continue chemotherapy. (2) 54 y.o. woman was suspected Trousseau syndrome and DIC, caused by serous adenocarcinoma without detectable primary lesion. Heparin was started, but platelet had been decreased to 5.9. Thrombocytopenia and DIC was controlled by PTX/CBDCA for carcinoma. (3) 66 y.o. woman with cerebral infarction was suspected Trousseau syndrome caused by uterine sarcoma. After pazopanib was stared while using heparin, platelet had been decreased to 11.5. Stopping pazopanib and heparin made platelet-level better. HIT antibody was negative. It was concluded that pazopanib caused thrombocytopenia. [Conclusion] It is important to distinguish HIT or other reason for thrombocytopenia during the use of heparin, especially malignant patients.

ISP-10-2 Advanced microvasive staging surgery in vaginal melanoma：A rare case report and literature review

Chen Chi-wen, Taiwan
Ngo Yeh-Giin

[Objective] Vaginal melanoma are rare. FIGO stage was not correlated with outcome. This is a first report treated by advanced robotic microinvasive staging surgery in vaginal melanoma. [Case presentations] This is a 60-year-old woman, G3P3, diagnosed with vaginal melanoma, who had vaginal bloody discharge with itching sensation for 2 months. Colposcopy showed an indurated lesion with 2cm in size and contact bleeding on the right middle anterior vaginal wall. Urethral orifice, cervix and anus were not invaded. Biopsy reported malignant melanoma. MRI showed no parametrial invasion and no lymph node enlargement. ViKY-Robotic laparoscopic radical vaginectomy, total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node sampling were performed. Final pathology was malignant melanoma, nodular type, pT4bN0, stage IIC (AJCC 7th edition (2010) cutaneous melanoma staging). No B-RAF gene mutation was detected. IHC resulted S-100 and HMB-45 positive. After operation and oncologic tumor board discussion, she has received adjuvant immunotherapy with peginterferon alfa-2b and Imatinib. Unfortunately 5 months later, abdominal CT showed recurrence with bilateral pelvic lymph nodes and lung metastasis. Recently, she is under concurrent chemo-radiation with 3-weekly Dacarbazine and local pelvic radiotherapy. [Results and Conclusion] An updated cohort was presented at the Annual Society of Gynecologic Oncology meeting in March 2013 that included 75 vulvar and 43 vaginal melanomas over a 17-year period. The median survival were 22, 9, 23, and 6 months for patients with FIGO stage I, II, III and IV respectively. In locally advanced cases, an exenterative procedure is potentially required；however, radiation with or without concurrent immunotherapy is another choice. The role of adjuvant therapy remains unclear. Salvage surgery or radiation can be considered in recurrent disease. Systemic chemotherapy can only achieve limited response. Novel immunotherapeutic and targeted agents have been reported to improve survival and able to be used in vulvovaginal melanoma. We presented a case underwent aggressive laparoscopic surgery and immunotherapy；however, she still experienced recurrent disease, unfortunately.

ISP-10-3 Clinicopathologic characteristics of primary peritoneal carcinoma—A retrospective analysis of single institute experience

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[Objective] Primary peritoneal carcinoma is a rare malignancy. The aim of this study was to evaluate clinicopathologic characteristics in Japanese patients with primary peritoneal carcinoma. [Methods] We retrospectively analyzed patients with primary peritoneal carcinoma treated at our institute from October 2002 to May 2012. [Results] We identified a total of 9 Japanese patients with median age 61.4 (range：54–67) years. All patients were histopathologically diagnosed as serous adenocarcinoma. One patient was classified as FIGO stage 3b and 8 patients were stage 3c. One patient had a family history of breast cancer. All patients demonstrated abnormal elevation of CA125 levels and mean value was 3186 (range：21–15088) IU/ml. Although all patients were underwent primary surgery, only one patient achieved optimal cytoreduction. All patients received postoperative chemotherapy and 2 (22.2%) patients attained disease-free alive during median follow-up period 49 months. Median survival period was 12.7 months. [Conclusion] Although primary peritoneal carcinoma was diagnosed as advanced stage, optimal cytoreductive surgery combined with postoperative taxan/platinum chemotherapy would be improved patient's prognosis.

ISP-10-4 MRI and FDG-PET/CT in the clinical evaluation of patients undergoing secondary debulking (cytoreduction) surgery for gynecologic malignancy

Kobe University
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[Objective] To compare the use of MRI with FDG-PET/CT in the evaluation of patients with gynecologic malignancy for secondary debulking (cytoreduction) surgery. [Methods] Eighteen patients with recurrent gynecologic carcinoma (4 cervical；6 uterine；8 ovarian) underwent secondary debulking surgery. All patients had MRI and PET/CT during 90 days before surgery. The median treatment-free interval was 7 months. [Results] Following surgical debulking 78% of patients (14/18) had negative surgical resection margins；in 22% (4/18), positive surgical resection margins were confirmed histologically. Surgical resection of adjacent organs was required in 33% (6/18). The median tumor diameter in cases that required adjacent organ resection was greater than that in cases that did not (8.2 cm vs. 3.9 cm；p=0.05). In 89% (24/27) of post-operative tumor nodules showing FDG uptake, recurrent cancer was found histologically. Using MRI, the sensitivity and specificity of detecting adjacent organ invasion were 100% and 80%, respectively；the sensitivity and specificity of detecting pelvic wall invasion were 25% and 83%, respectively. [Conclusion] In patients undergoing secondary debulking surgery for gynecologic malignancy, PET/CT was of clinical value in the diagnosis of recurrent tumor nodules. MRI was a more sensitive method of detecting tumor invasion of adjacent organs but not pelvic wall invasion.

ISP-10-5 End of life care at a general gynecology unit

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[Objective] To assess treatment patterns of end of life care in a gynecology unit. [Methods] A retrospective study of patients who received palliative care at a single institution and died during 2013 and 2014 was performed. Approval for the data acquisition was obtained from the institutional review board. [Results] We identified 19 patients. The median survival time after the last chemotherapy was 3 months during 2013 and 2 months during 2014. During 2013, all patients received intervention by a palliative care team, of which 63% for treatment with opioids. During 2014, 75% of patients received intervention, of which 25% for treatment with opioids. There was not a significant difference concerning selection of opioids, corticosteroids between patients who were referred to a palliative care team and patients who were not. Frequency of neuropathic pain and delirium treatments were higher in the group which were referred to a palliative care team. [Conclusion] There was improvement in treatment with opioids before receiving intervention by a palliative care team during 2014. There was not a significant difference concerning symptom relief between patients who were referred to a palliative care team and patients who were not. The factors contributing to this may be continual education of the gynecology staff on palliative care and appropriate consultation to the palliative care team.

ISP-10-6 The retrospective study on the usefulness of re-evacuation after molar pregnancy removal surgery

Kyushu University
Eisuke Kaneki

[Objective] In Japan, after molar pregnancies removal surgery, re-evacuation has been performed in a number of facilities. However, some studies have reported that re-evacuation is unnecessary. Thus, we retrospectively analyzed the usefulness of re-evacuation after molar pregnancy removal surgery. [Methods] Our subjects were 63 patients who had molar pregnancy removal at our department since 2003. The diagnosis of complete mole (CM) or partial mole (PM) was based on JSOG classification 2011. We analyzed association between the presence or absence of re-evacuation and postmolar gestational trophoblastic disease (PGTD). The clinical course of each case was collected from medical records. [Results] From the 63 cases, 57 cases had CMs and 7 cases had PMs. PGTD developed in 15 cases. PGTD were observed in 26% of the CMs, whereas it was not observed in PMs. Among the 35 of CMs with re-evacuation, PGTDs were observed in 6 patients (17%). Among the 22 CMs without re-evacuation, 9 patients (41%) developed PGTD. In the CM cases which had molar pregnancy removal in less than 14 weeks, incidence of PGTD was a significantly lower in the re-evacuation group ($p=0.03$). [Conclusion] In the case of CMs, the incidence of PGTD was lower in the re-evacuation group, especially in the cases with less than 14 weeks of pregnancy. From these findings, the usefulness of re-evacuation can be seen.

ISP-10-7 Renal protective effect of magnesium sulfate in gynecologic cancer patients during cisplatin-containing chemotherapy

Kyushu University
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[Objective] Nephrotoxicity is diagnosed in 28-42% of patients applied cisplatin. Mg^{2+} is involved in active transport of cisplatin in proximal tubule cells, therefore, we retrospectively examined whether Mg^{2+} supplementation prevent nephrotoxicity during cisplatin-containing chemotherapy. All patients provided written informed consent before treatment. [Methods] Forty four patients of gynecologic cancer treated in our hospital from Oct 2014 to Sep 2015 (study group) were analyzed. They were supplied magnesium sulfate containing 8mEq of Mg^{2+} just before cisplatin administration. Serum creatinine level (Cr : mg/dL) and glomerular filtration rate (GFR : mL/min) were examined before and after treatment. These laboratory data were compared with those of 74 patients treated previously without Mg^{2+} supplementation (control group). [Results] Statistically significant Cr elevation ($+0.11 \pm 0.17$ vs -0.03 ± 0.10) and GFR decrease (-13.0 ± 22.2 vs $+2.2 \pm 17.6$) were found in control group compared with study group ($p < 0.001$). Discontinuation of chemotherapy occurred in 8 cases in control group due to renal dysfunction. However, all patients in study group could receive scheduled treatment. [Conclusion] Magnesium sulfate supplementation might be effective for renal protection during cisplatin-containing chemotherapy.

ISP-10-8 Short hairpin RNA library-based functional screening of genes associated with hormone therapy resistance in breast cancer

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Toshiyuki Okumura[1], Satoru Takeda[2]

[Objective] Hormone therapy using anti-estrogen tamoxifen or aromatase inhibitors is used to treat breast cancer. Many patients, however, often acquire resistance to hormone therapy. In the present study, we explored genes involved in acquired resistance to tamoxifen in breast cancer cells using short hairpin RNA (shRNA)-based functional screening. [Methods] Breast cancer MCF7 cells infected with a lentiviral shRNA library were cultured with tamoxifen or vehicle for one month and shRNAs integrated in the genome were quantified by microarray analysis. Gene expression and survival analysis in breast cancer patients were performed using public databases. Quantitative PCR and cell proliferation assay were performed in MCF7 cells and tamoxifen-resistant (OHTR) cells. [Results] Microarray analysis of shRNA library-infected and tamoxifen-treated MCF-7 cells determined decreased shRNAs compared to control cells. We focused on such shRNAs, targeting genes associated with oxidative phosphorylation, DNA repair, and proteasome. Several candidate genes associated with tamoxifen resistance were upregulated in OHTR cells compared to the parental MCF-7 cells. The proliferation of OHTR was suppressed by siRNAs specific for the candidate genes. [Conclusion] shRNA-based functional screening is useful to identify the genes involved in acquired resistance to tamoxifen in breast cancer.

ISP-11-1 The evaluation of Surgical Management for the recurrent gynecological cancer patients

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[Objective] To investigate the efficacy and the safety of surgical management for recurrent gynecological cancer patients in our department. [Methods] This study has been approved by research ethics committee in our university. Eighty patients who underwent surgical management for recurrent gynecological cancer patients from first January 2001 to 31th December 2012 were analyzed retrospectively. We divided the patients to the two groups : first is patients of radical surgery and second is patients of palliative surgery. [Results] The origin of tumor were uterine cervix (n=19), uterine body (n=27), ovary (n=36), vulva (n=8) and vagina (n=1). The amount of bleeding during surgery was largest among the patients for cervical cancer and that is why the patients underwent irradiation. Surgery for the recurrent uterine body cancer was safest considering of the volume of bleeding and adverse event due to surgery. 5 year overall survival was 40% for cervical cancer, 45% for ovarian cancer and 50% for uterine body cancer. Surgery for the palliative care was due to the vowel obstruction and the all patients who underwent colostomy became able to eat something and that is quite important for improvement of QOL. [Conclusion] Surgical management for the recurrent gynecological cancer patients is almost acceptable and important option even if the patients need radical cure or palliative care.

ISP-11-2 The effectiveness of the preventive education for lymphedema in the early postoperative period for gynecological cancer patients

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[Objective] The aim of this study was to examine the effect of early preventive patient education for lymphedema after lymphadenectomy in patients with gynecological cancer. [Methods] 524 gynecological cancer patients who received lymphadenectomy after 1995 were enrolled in this study. Each patient was evaluated for three main risk factors (suprafemoral node dissection, radiation therapy and lack of patient education), the year of surgery and presence of lymphedema in each patient were checked. Surgery years were divided into three periods (A : before 2005, B : from 2006 to March, 2008, C : from April, 2008 to the present). Patient education for lymphedema has been provided to all patients in our gynecological ward since 2006. Since April 2008, the norm has been for early postoperative cancer patients to learn about self-care management for lymphedema. [Results] 1) There was a significant relationship between the each risk factor and the onset frequency of lymphedema ($p<0.05$).2) The overall lymphedema onset was 21.2% and lymphedema onset by surgery year was as follows : A 23.9%, B 18.4%, C 11.0%, showing a significant decrease ($p<0.05$) in proportion to routine patient education. [Conclusion] Patient education in the early period after gynecological surgery is suggested to be effective for early detection and prevention of lymphedema.

ISP-11-3 Toxicity profile alteration by UGT1A1 genotyping in gynecologic cancers treated with of low-dose irinotecan plus platinum : a historical-controlled study

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[Objective] To determine whether UGT1A1 genotyping altered toxicity profiles in gynecologic cancer patients treated with of low-dose irinotecan plus platinum. [Methods] After approval by the IRB of our hospital, a historical-controlled study to investigate gynecologic cancer patients treated with low-dose irinotecan plus platinum between 2003 and 2012 in our hospital was conducted. Before 2007, dose reduction of irinotecan was based on physical status or previous myelosuppression (Non-UGT group). Since 2007, irinotecan doses were mainly modified according to UGT1A1*28/*6 genotype (UGT-group). [Results] 217 cases were treated with irinotecan-based therapy : 59 with cervix, 30 with uterine corpus, and 128 with mullerian cancers. 109 patients received UGT1A1 genotyping : 66 with wild-type, 38 with hetero-type, and 5 with homo-type/double hetero-type. UGT-group patients had relatively lower Grade4 hematologic toxicities (11% vs. 9%, $p=0.08$), and significantly lower Grade4 non-hematologic toxicities (0% vs. 5%, $p=0.02$). [Conclusion] Tailor-made chemotherapy according to UGT1A1 genotyping enabled us to reduce severe toxicities in gynecologic patients treated with low-dose irinotecan plus platinum. Further investigations including response evaluation at reduced doses are needed to facilitate UGT1A1 genotyping.

ISP-11-4 Mental mood of gynecologic cancer patients assessed by distress and impact thermometer (DIT) and hospital anxiety and depression scale (HADS). KCOG-G1103 study

Nara Prefecture General Medical Center[1], Nagoya City University, Graduate School of Medicine[2], Hyogo College of Medicine[3], Kansai Rosai Hospital[4], Meiwa General Hospital[5], Okayama Ohfuku Clinic[6], Nagoya City East Medical Center[7]
Yoshio Itani[1], Atsushi Arakawa[2], Hiroshi Tsubamoto[3], Kimihiko Ito[4], Ryutaro Nishikawa[7], Shizuka Shichido[4], Yasunari Miyagi[6], Naoto Furukawa[5], Kayo Inoue[3]

[Objective] Thirty percent of cancer patients are reported to suffer from psychological distress but that is often underestimated in clinical settings. HADS is not used widely because it is cumbersome to score. DIT is a 2-item (distress and impact) self-report questionnaire, but is not well verified. [Methods] One hundred and seventeen patients were enrolled between 2011.5.1 and 2012.3.31 and 95 were eligible. Median age was 54 years (range 31-77). The numbers of completed questionnaires (HADS & DIT) at (a) pretreatment, (b) 3 months, and (c) 6 months were 95, 80, and 70, respectively. This trial was received ethical approval from the review boards of the KCOG and each institution. (UMIN000005727) [Results] 1) Areas under the curve of receiver operating characteristic curves for Distress and Impact with respect to HADS positivity were 0.855 and 0.875 respectively. 2) In each patient, the mean scales of (b) were significantly reduced in HADS (mean 3.2 ; $p<0.0002$) and in Distress (mean 1.7 ; $p<0.0001$). Those of (c) were significantly reduced in HADS (mean 4.5 ; $p<0.0001$), in Distress (mean 2.3 ; $p<0.0001$), and in Impact (mean 1.09 ; $p=0.031$) compared with (a) (Student's paired t-test). [Conclusion] 1) DIT is a reliable tool for ruling out clinical psychiatric distress. 2) For the first 6 months of treatment, mental mood would have a tendency to be improved, but not completely.

ISP-11-5 Oncogenic BRAF promotes global DNA hypomethylation via upregulation of DNA demethylase TET3 level

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[Objective] A hallmark of human cancer genomes is global DNA hypomethylation accompanied by focal DNA hypermethylation, however, the basis of DNA hypomethylation remains to be determined. We herein tried to uncover the mechanisms and the biological significance of DNA hypomethylation in carcinogenesis. [Methods] Mouse embryonic fibroblasts from oncogenic BRAFV600E knock-in mice were used to analyze expression levels of TET family proteins, and DNA methylation levels. Human colorectal adenoma samples were immunohistochemically evaluated for the expression of these molecules. [Results] Expression of BRAFV600E was sufficient to promote global DNA hypomethylation, which was mediated by TET3. TET3 was maintained at low levels resulting from ubiquitination and degradation by SCF^{FBXW7}. BRAFV600E increased TET3 levels via inhibition of GSK3β, an initiator of TET3 phosphorylation that is required for SCF^{FBXW7}-mediated ubiquitination. Consistent with these results, we found that increased levels of TET3 and 5-hydroxymethylcytosine in patient-derived human colorectal adenomas containing BRAFV600E. Conversely, we showed that knockdown of Tet3 resulted in decreased BRAFV600E-induced tumorigenesis. [Conclusion] Our results elucidate a mechanism of global DNA hypomethylation promoted by oncogenic BRAF and establish an essential role for TET3 at an early stage of oncogenesis.

ISP-11-6 EZH2 stimulates Twist expression by epigenetic silencing of its suppressor miR-361 through an YY1-dependent mechanism

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[Objective] Although substantial data indicates that EZH2 epigenetically silences genes with tumor suppressor functions, its impact on the activation of oncogenes via the suppression of microRNA (miRNA) is poorly understood. [Methods] By using the microarray-based integrating approach, we aimed to identify novel miRNAs that are suppressed by EZH2 in endometrial cancer (EC) cells, and further investigated the functional roles of miR-361 and the interaction between miR-361 and *Twist* mRNA in EC cells. [Results] We identified miR-361 as an EZH2-suppressed miRNA that exhibits tumor suppressive effects to attenuate cancer cell proliferation and invasiveness, and abrogated cancer stem cell-like properties. EZH2 acts through YY1 to epigenetically suppress miR-361, leading to enhanced expression of Twist, a direct target of miR-361. Treatment of EC cells with specific EZH2 inhibitor GSK343 induced miR-361 expression, decreased Twist levels and inhibited EC cell proliferation and invasiveness *in vitro*. An inverse correlation between EZH2/Twist and miR-361 expression was observed in human EC tissues. [Conclusion] Our findings suggest that EZH2 upregulates Twist by epigenetic repression of its negative regulator miR-361 via an YY1-dependent mechanism.

ISP-11-7 SOCS-1 enhances T cell-mediated anti-tumor immunity by negative regulation of PD-L1 and inhibits cancer proliferation

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[Objective] Suppressor of cytokine signaling (SOCS)-1, showed stronger anti-tumor effect in vivo than expected by the results from in vitro. We aimed to clarify the mechanisms of anti-tumor immunity regulated by SOCS-1. [Methods] Five human ovarian cancer (OC) cell lines and 4 murine cancer cell lines were assessed. SOCS-1 or LacZ were overexpressed by adenoviral vector. Anti-proliferative effect was assessed by WST-8 assay. Female BALB/c mice were injected with CT26 for subcutaneous xenograft. AdSOCS-1 or AdLacZ was administered intra-tumorally every other day. PD-L1 expression in tumor cells and activation levels of tumor infiltrated T cells were analyzed by flow cytometry. [Results] Overexpression of SOCS-1 inhibited proliferation of all cancer cell lines. Three of 5 OC and all 4 murine cell lines constitutively expressed PD-L1. Expression levels of PD-L1 in OVCAR-3 and CT26 cells were down-regulated at 30% by overexpressed SOCS-1 in vitro. In CT26 allografted model, SOCS-1 significantly inhibited tumor growth ($62.2 \pm 5.2\%$, $P < 0.01$) and suppressed PD-L1 expression ($65.2 \pm 8.4\%$, $P < 0.05$). GranzymeB and CD107a expression of infiltrated T cells were increased more than 50% ($P < 0.05$) in the AdSOCS-1 injected group. [Conclusion] SOCS-1 potently inhibited tumor growth preventing the interaction of PD-1/PD-L1 and resulted in the enhancement of T cell mediated anti-tumor immunity in vivo.

ISP-12-1 CX3CL1-CX3CR1 system enhances ovarian cancer progression via recruitment CX3CR1 positive tumor associated macrophages (TAMs)

Wakayama Medical University
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[Objective] The interactions between tumor and stromal cells via cytokine and chemokine systems are essential for tumor progression. We explored the pathophysiological roles of CX3CL1 (fractalkine) and its receptor, CX3CR1, in ovarian cancer. [Methods] The mRNA and protein expressions of CX3CL1 and CX3CR1 were examined in human ovarian tumor samples that were obtained under informed consent. In the next study, mouse ovarian carcinoma, ID8 cells were inoculated intraperitoneally into C57Bl/6 (WT) and *Cx3cr1*$^{-/-}$ (KO) mice and the tumor growth and the survival were compared. [Results] CX3CR1 and CX3CL1 were detected in human serous ovarian cancer. Upon ID8 cells inoculation, the KO mice survived significantly longer than WT ones. Supportively, the tumor number in the abdominal cavity was significantly reduced in KO mice, compared with WT ones. Immunohistochemically, intratumorous macrophage recruitment was significantly suppressed in KO mice, compared with WT mice. Intratumorous MMP-2 and TGF-β expression was attenuated at mRNA and protein levels in KO mice, compared with WT mice, and they were colocalized at macrophages (TAMs). [Conclusion] CX3CR1 positive TAMs that are recruited under the guidance of CX3CL1-CX3CR1 systems have detrimental roles in ovarian cancer progression.

ISP-12-2 ZEB1 regulates chemo-resistance and metastasis in epithelial ovarian cancer

Nagoya University
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[Objective] Among EMT-inducing genes, ZEB1 is considered to play a crucial role in cancer progression. In this study, we investigated the role of ZEB1 simultaneous influence over metastasis and paclitaxel (PTX)-resistance in epithelial ovarian carcinoma (EOC). [Methods] Expression levels of ZEB1 in various EOC cell lines were evaluated using Western blot. We performed in vitro experiments whether silencing ZEB1 led to reverse PTX-resistance and metastatic potential in EOC cell lines including ES2, SKOV3, NOS3, NOS3TR (PTX-resistant human EOC cell line). In addition, to validate whether ZEB1 promotes PTX-resistance and metastasis, we performed in vivo experiments. Furthermore, expression of ZEB1 in EOC tissues and its association of oncologic outcome was investigated. [Results] ZEB1 is expressed in several EOC cell lines and controls cell migration, invasion, adhesion to mesothelial cells and PTX sensitivity. Subsequently, we treated tumor-bearing animals grafted with either sh-ZEB1 or sh-control cells with PTX concentrations. This resulted in a significantly decreased tumor size and metastasis of shZEB1 animals. Moreover, ZEB1 expression in EOC patients is predictive of shorter survival (OS : P=0.04, PFS : P=0.01). [Conclusion] These results show that target of this molecule may contribute to reverse these malignant potential as well as foresee oncologic outcome for EOC patients.

ISP-12-3 Transferrin is involved in the carcinogenesis of high-grade serous ovarian cancer by facilitating the DNA double-strand breaks via transferrin receptor 1 in fallopian tube

Tohoku University
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[Objective] Fallopian tube epithelium (FTE) is a candidate for the origin of high-grade serous ovarian cancer (HGSOC). Although accumulation of DNA double-strand breaks (DNA-DSBs) in FTE is involved in the carcinogenesis, the mechanism underlying the formation of DNA-DSBs has not been clarified. Hydroxyl radicals, the reactive oxygen species (ROS) promoting DNA-DSBs, is produced in a Fenton reaction catalyzed by iron ion. As follicular fluid contains transferrin that serves as an iron ion transporter, we investigated the involvement of transferrin in DNA-DSBs formation. [Methods] Human FTE cells and A2780 ovarian cancer cells were treated with transferrin. Phospho-histone 2AX (γH2AX) was employed as a marker for DNA-DSBs. Murine adnexes were prepared for ex vivo study. Human follicular fluid was analyzed based on the approval of the ethic board. [Results] Transferrin incorporated into the cells via transferrin receptor 1 promoted ROS formation and increased γH2AX expression. Transferrin treatment also introduced DNA-DSBs to murine FTE ex vivo. Follicular fluid contained adequate amount of transferrin, and part of the follicular fluid introduced DNA-DSBs to the cells. [Conclusion] We found the novel aspect of transferrin as a molecule facilitating DNA damage and genomic instability. It is plausible that transferrin is involved in the carcinogenesis of HGSOC.

ISP-12-4 Establishment of ovarian cancer patient-derived-xenograft

Kyoto Uiversity
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[Objective] Patient-derived-xenograft (PDX) is created by transplanting surgically resected patient tumors into immunocompromised mice to maintain cytogenetics and tumor heterogeneity of donor tumors, thus providing resource of translational analyses. We report clinical factors that influence the establishment of PDX from ovarian cancer. [Methods] Ovarian tumor tissue fragments from patients undergoing surgery between March 2014 and March 2015 at our hospital were transplanted subcutaneously into NOD-SCID mice. After 2-6 months, tumors grown on mice were excised and serially transplanted into additional mice for propagation. We analyzed clinical information according to whether or not PDX tumors were established. Histological analysis was performed for PDX and their original tumors. [Results] PDX was successfully established with the ratio of 31.3% (10/32) ; 2 high grade serous, 4 clear cell, 2 undifferentiated and 2 non-gynecological adenocarcinomas. The ovarian cancer patients whose tumors established PDX had more advanced stage, higher grade and worse survival rate than not established ($p<0.05$, respectively). The established PDX tumors were histologically similar to the corresponding patients' tumor. [Conclusion] In ovarian cancer, PDX can be established exclusively from poor prognostic and aggressive tumors. PDX may be useful in searching effective treatments for these tumors.

ISP-12-6 IGFBP5-derived peptide as a novel angiogenesis inhibitor for treatment of ovarian cancer

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[Objective] Insulin-like growth factor-binding protein 5 (IGFBP5) plays a role in cell growth, differentiation, and apoptosis. We found that IGFBP5 was markedly downregulated in ovarian cancer tissue, and that its overexpression in cancer cells induced cell death. In this study, we undertook to evaluate the functional significance of each region of IGFBP5 as a tumor suppressor of ovarian cancer. [Methods] We found that the C-terminal region of IGFBP5 inhibited tumor growth in a 2774 cell xenograft mouse model, and that expression of VEGF, IL-6, and TNF-α were inhibited in 2774 cells stably expressing the C-terminus of IGFBP5. In order to evaluate its effects on tumor suppression, a peptide derived from the C-terminus of IGFBP5 (BP5-C) was synthesized. As a control, a peptide mutated in the IGF-binding site of BP5-C (BP 5-Cmut), as well as peptides derived from the IGFBP2 C-terminus and heparin-binding site were also synthesized. [Results] Of these peptides, BP5-C and BP5-Cmut inhibited VEGF expression and NF-kB activity. Furthermore, BP5-C inhibited angiogenesis in an in vitro and an ex vivo system, consisting of HUVEC tube formation and rat aortic ring blood vessel sprouting, respectively. The in vivo effect of BP5-C on tumor growth was studied using i.p. injection of ovarian cancer 2774 cells into mice, as well as with a patient-derived xenograft mouse model. BP5-C peptide significantly inhibited tumor growth, angiogenesis, and VEGF expression in both xenograft models. [Conclusion] These results suggest that the C-terminus of IGFBP5 exerts an anti-cancer activity by inhibiting angiogenesis via downregulation of VEGF in an IGF-independent manner, and may be considered as a novel angiogenesis inhibitor for the treatment of ovarian cancer.

ISP-12-7 Ethanolic and aqueous extract from Medemia argun fruits' ebryo kill ovarian cancer cells by inducing mitochondrial-dependent apoptosis and DNA damage

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[Objective] The objective of this study is to evaluate the toxicity of both the ethanolic and the aqueous extract from Medmia argum (M. argun) on the different ovarian cancer cells and to map out the mechanism of action. [Materials and Methods] Ovarian cancer cells, KF, KFr13 and SKOV-3 cells were used in this study. The cytotoxicity of each extract was evaluated by viability and clonogenic assays. DNA content was used to study the effect of extracts on the cell cycle. Apoptotic signals were detected by Annexin staining and Western analysis. DNA relaxation assay and comet assay and H2AX staining proved DNA damage. [Results] Both extracts reduced colony forming ability and showed significant toxicity on all ovarian cancer cells used with LC50 at ng scale. Both extracts' treatment significantly inhibited the proliferating factor ERK. Extracts accumulated cells in the S phase followed by cell death. The cyclin D1 and CdK4 increased by extracts treatment. Significant Bcl2 down-regulation and Bax up-regulation indicated mitochondria-dependent apoptosis while DNA relaxation by extracts proposed possible topoisomerse (TOPO) inhibiting ability of the extracts. Moreover, comet assay and H2AX staining confirmed the DNA damage induced by extracts treatment. [Conclusion] Extracts of M. argun fruits' embryo significantly inhibit proliferation and kill ovarian cancer cells by S phase arrest followed by mitochondrial apoptosis and DNA damage with possible TOPO inhibiting ability.

ISP-12-8 BRCAness status of ovarian cancer with somatic large genomic rearrangements

Keio University
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[Objective] BRCAness tumors are defined as sporadic cancers that share characteristics with BRCA1 or BRCA2 (BRCA1/2) mutant tumors. Because BRCAness cancersproven to be sensitive for Poly-ADP ribose polymerase (PARP) inhibitors, profiling of ovarian cancer (OC) cells with BRCAness status will be essential. [Methods] DNAs was extracted from frozen tissues of 248 OCs (76 serous, 31 mucinous, 53 endometrioid, and 88 clear cell). Multiplex ligation-dependent probe amplification (MLPA) was applied to detect large genomic rearrangement that classified to BRCAness, and non-BRCAness. This study was conducted with approval from the institutional ethical committee and we took written informed consent before getting sample. [Results] Seventy of 248 (28.2%) of cases were identified as BRCA1-like tumors. BRCA1-like tumors were significantly more frequently found in serous OC (41/76, 53.9%) than non-serous OC (29/172, 16.9%) ($p < 0.001$). [Conclusion] Our result revealed the frequency of BRCAness OC with large genomic rearrangement that have theoretically benefit from PARP inhibitors.

ISP-12-9 TAS-117, a novel allosteric AKT inhibitor, shows potent antitumor activity on ovarian clear cell adenocarcinoma cells from fresh surgical samples in 3-dimentional culture

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[Objective] Activation of PI3K/AKT pathway is thought to be one of the possible mechanisms of intrinsic or acquired chemoresistance of ovarian clear cell carcinoma (OCCC). We have previously reported TAS-117 showed potent activities on ovarian serous carcinoma cells from ascites in an AKT2 -dependent manner. We have examined AKT2 in OCCC and evaluated growth inhibitory effects of TAS-117 alone and combined with paclitaxel and carboplatin (TC) on OCCC under 3-dimentional culture condition for the first time. [Methods] With the approval of the institutional review board, 70 paraffin-embedded and 4 fresh surgical samples were applied. AKT isoforms (AKTs) were measured by qRT-PCR. Cancer cells were isolated from fresh samples and cultured in collagen gel with TAS-117, GDC-0068 (ATP-competitive AKT inhibitor) and TC. [Results] In OCCC, AKT2 expression was higher than other AKTs and this expression pattern of AKTs was different from the other histological subtypes. TAS-117 showed high effects with mean growth inhibition rate of 59% (47-70%) at 0.1 μM, clinically achievable concentration, while that of TC was only 32% (16-48%). TAS-117 combined with TC showed higher effects than TC or TAS-117 alone in 3 of 4 cases. Further, the effects of TAS-117 were higher than GDC-0068 in 2 cases. [Conclusion] TAS-117, especially when treating in combination with TC, may be suitable treatment for OCCC.

ISP-12-10 Identification through a functional genomics screen of factors whose down-regulation enhances the cancer stem cell population in ovarian cancer

Kyoto University
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[Objective] Cancer stem cells (CSC) are regarded as the cause of tumor recurrence. We aimed to identify genes whose downregulation increase CSC phenotype of serous ovarian cancer through a functional genomics screening. [Methods] Using a library of 81,000 shRNA lentiviral plasmids (Cellecta) targeting 15,000 genes and two serous ovarian cancer cell lines, CH1 and SKOV3, which harbor minimal side population (SP) fractions (less than 0.1%), we detected genes whose downregulation markedly increased SP. In addition, we examined the functions of SP, such as sphere formation ability, single cell clonogenicity and in vivo tumorigenicity. [Results] Suppression of *GeneA, GeneB and GeneC* markedly increased the SP in CH1 cells (control ; 0.08% vs *GeneA* ; 1.1%, *GeneB* ; 1.0%, *GeneC* ; 2.0%). Suppression of *GeneD, GeneE and GeneF* markedly increased the SP of SKOV3 cells (control ; 0.07% vs *GeneD* ; 1.4%, *GeneE* ; 1.1%, *GeneF* ; 1.0%). All generatad SP cells had significantly high ability of sphere formation, single cell clonogensity and in vivo tumorgenesity compared to major population cells ($p<0.05$, respectively). Overexpression of all six genes markedly decreased the SP in A2780 and IGROV 1 cells ($p<0.0001$). [Conclusion] We identified six genes whose downregulation increased the CSC phenotype of serous ovarian cancer. Our findings may be important to reveal molecular mechanisms of tumor recurrence.

ISP-13-1 The usefulness of ultrasonographic evaluation of malignant ovarian tumors by IOTA (International Ovarian Tumor Analysis) study

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[Objective] To clarify the usefulness of ultrasonographic evaluation by using IOTA study for malignant ovarian tumors. [Methods] We compared the rate of proper diagnosis of ovarian tumors by using both ultrasonography and MRI scans from Feb. 2014 to May 2015 with approval of IRB. We used IOTA criteria as the tool for ultrasonographic evaluation. On the basis of the previous research, we set 0.1 of the probability of malignancy (POM) as the cutoff value. Then, we diagnosed malignant ovarian tumors when the POM was over 0.1. When it was under 0.1, we considered benign tumor. [Results] Out of 165 ovarian tumor surgeries, 142 were benign, 19 were malignant and 4 were borderline malignancy by pathological study. The median percentage of POM in benign and malignant ovarian tumors were 0.017 and 0.78, respectively. We set 0.78 as the cutoff value. There were 27 cases which were over 0.1 of the POM. 23 cases were malignant, and 4 cases were benign. The ovarian tumors which were under 0.1 of the POM were all benign. We pre-diagnosed that 30 ovarian tumors might be malignant using MRI scans before surgery. After surgery, 22 were malignant and 8 were benign. [Conclusion] When diagnosing ovarian tumors, ultrasonography is easy and useful. It is concluded that ultrasonography is not inferior to MRI scans when diagnosing ovarian tumors.

ISP-13-2 Attempt of preoperative risk estimation of ovarian malignancy by ultrasound : Using 3D ultrasound and IOTA study

Nagasaki University
Tsuneo Inoue, Hideaki Masuzaki

[Objective] To examine whether preoperative evaluations of benign or malignant ovarian masses by IOTA (International Ovarian Tumor Analysis) methods and 3DUS are possible or not. [Methods] 45 cases underwent surgery for ovarian masses since January 2013 enrolled. 2DUS, 3DUS and MRI have been performed before surgery. Preoperative 2DUS (IOTA LR2, ADNEX model), 3DUS and MRI findings are compared with the histological diagnosis. We retrospectively evaluated which method is useful for the differential diagnosis of benign or malignant ovarian masses. [Results] By 3DUS and MRI, 7 of 12 cases of borderline (BL) malignancy and malignancy had been correctly estimated. By IOTA methods, only two cases were failed. As compared with 3DUS and MRI, the findings by IOTA methods had a false positive rate tended to be higher. For the diagnosis of BL malignant and malignant tumors by 3DUS and MRI, specificity, negative predictive value (NPV) and accuracy rate were higher. On the other hand by IOTA methods, sensitivity and NPV was higher, but positive predictive value was low. [Conclusion] 3DUS evaluation showed a similar trend as MRI against the accuracy of the risk estimation of ovarian malignancy, but the evaluation by IOTA methods showed the different tendency with 3DUS and MRI. The combination analysis of 3DUS and IOTA methods may provide discrimination between benign and malignant ovarian masses.

ISP-13-3 A comparative analysis of diagnostic performance to detect ovarian malignancy among three assessment indices

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[Objective] This study was aimed to examine the clinical usefullness of three different methods, the International Ovarian Tumor Analysis (IOTA) logistic regression models (LR2 and simple rules), and echo pattern classification of the Japan Society of Ultrasonics in Medicine (JSUM), and risk of malignancy index (RMI) in preoperative assessment of ovarian malignancy. [Methods] This study was conducted under approval of the ethics committee in our institution. 100 patients with ovarian tumors who underwent surgery from 2012 to 2015 at our hospital were randomly chosen and included in this study. IOTA models, JSUM classification, RMI were applied retrospectively among all patients included. Sensitivity and specificity of each diagnostic model were determined based on pathological diagnosis of surgical specimen. [Results] Among 109 ovarian tumors, prevalence of malignancy was 32% (26 primary invasive epithelial ovarian cancers, 8 borderline tumors, 1 malignant sex-cord stromal tumor). Sensitivity and specificity of IOTA LR2 were 97% and 68%, those of IOTA simple rules were 97% and 78%, those of JSUM were 97% and 71% and those of RMI were 51% and 89%, respectively. [Conclusion] IOTA models and JSUM classification displayed higher sensitivity as compared with RMI, suggesting the advantage of IOTA models and JSUM classification over RMI to rule out ovarian malignancy as a screening tool.

ISP-13-4 Prognostic significance of the Recurrence pattern and Risk factors for survival in ovarian cancer patients with No gross residual disease after Primary Debulking Surgery

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[Objectives] The aim of this study was to analyze the patterns of recurrence and their association with clinical outcomes in recurrent ovarian cancer patients with no gross residual disease after primary debulking surgery. [Methods] This study was conducted on 303 ovarian cancer patients with no residual disease after primary cytoreduction in Samsung Medical Center since January 2002 to December 2012. For each relapse, information on date of clinical/pathological recurrence, and pattern of disease presentation were retrieved. [Results] Within a median follow-up of 53 months (range 3~156), 88 recurrences (29.0%) and 28 cancer-associated deaths (9.2%) were recorded. By analyzing the pattern of relapse, most of the recurrences were distant (n=65, 73.9%), discrete (n=57, 64.8%) and transcoelomic (n=41, 46.6%). Of 88 recurrences, 79 cases (89.8%) recurred within 36 months. Percentage of distant recurrence of stage III, IV was comparably higher than stage I, II (83.3% vs. 53.6%, p=0.005). Percentage of platinum resistant was higher in mucinous and clear cell group than endometrioid and serous group (39.1% vs. 4.6%, $p<0.001$). In multivariate analysis for overall survival, independently significant indicators related to recurrence were location, recurrence type and spread pattern. Also, histology type and platinum sensitivity were significantly associated with overall survival. [Conclusions] In recurrent ovarian cancer patients with no gross residual disease after primary debulking surgery, patients with distant, diffuse recurrence, mixed spread pattern, mucinous and clear cell histology, and less than 6 months of platinum free interval are likely to have higher risk in overall survival.

ISP-13-5 Accuracy of ROMA (Risk of Ovarian Malignancy Algorithm) in Predicting Malignancy of Ovarian Tumours for Pre-menopausal Women

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Win Win Mya, Kyu Kyu Hlaing

[Objective] To evaluate diagnostic accuracy of ROMA (Risk of Ovarian Malignancy Algorithm) in predicting malignancy of ovarian tumour of pre-menopausal women. [Methods] This is a cross-sectional study of sixty-eight premenopausal women with ovarian tumours. Preoperative serum levels of HE-4 (Human Epididymis protein 4) and CA 125 (Carcinogenic Antigen) were measured using the ECL assay (ECLIA - Electrochemilumininescence) and Elecsys HE 4 was analysed by Coba 411. These data were calculated to get ROMA value. Histological diagnosis of ovarian tumour was done by Haematoxylin-Eosin stain. Predictive accuracy of ROMA was analysed by using SPSS version 16. [Results] Mean level of ROMA for malignant ovarian tumour (42.5%) was significantly higher than benign tumour (8.4%) ($P<0.0001$). At the optimal cut-off point of 16.4% ROMA value was sensitivity of 86.4%, specificity of 89.1%, positive predictive value (PPV) of 76%, negative predictive value (NPV) of 95.3% and accuracy of 88.2%. Moreover mean level of ROMA malignant epithelial tumour (49.2%) was significantly higher than that of benign epithelial tumour (9.3%) ($P<0.0001$). The sensitivity, specificity, PPV, NPV and accuracy were 100%, 86.4%, 85.7%, 100% and 92.5% respectively. [Conclusion] The ROMA assessment is useful in predicting malignancy in premenopausal women during pre-operative counseling and planning the management of ovarian tumour.

ISP-13-6 Incidence and risk factors of lower extremity lymphedema after gynecological surgery in ovarian cancer

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[Objective] There is no standard method to establish an early diagnosis of lower extremity lymphedema (LEL). LEL can be diagnosed by physical examination and laboratory tests when patients complain of typical clinical symptoms. The objective of this study was to investigate the incidence and risk factors of LEL in patients with ovarian cancer. [Methods] The medical records were reviewed retrospectively in patients with ovarian cancer treated at Seoul St. Mary's Hospital from January 1990 to July 2014. [Results] A total of 479 patients with ovarian cancer were analyzed. Forty-nine patients (10.3%) developed LEL, and 65.4% of these patients had LEL within 1 year after surgery. The mean number of resected lymph node (LN) S was larger in patients with LEL (42.8 ± 16.7, range 12 to 88) than in those without (30.9 ± 20.0, range 0 to 99) (P < 0.0001). The number of resected LNs was significantly associated with the occurrence of LEL (odds ratio (OR) 1.026, 95% CI 1.006–1.045, P=0.009). [Conclusion] A significant proportion of patients with ovarian cancer could develop LEL after surgery. This study suggests that the occurence of LEL is associated with the number of resected LNs.

ISP-13-7 Clinical study of immature teratoma

Nippon Medical School
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[Objective] An ovarian immature teratoma is a rare disease with limited reports on treatment and prognosis. In this study, we examined the prognosis of cases we experienced. [Methods] We conducted a retrospective study regarding the treatment and prognosis, in patients who underwent initial treatment at our hospital between January 2004 and September 2015 and were diagnosed with ovarian immature teratomas. [Results] Of 240 patients who had any ovarian malignancies during the study period, 7 (2.9%) had immature teratomas with the mean age of 18.7 (6–29) years. All patients had bulky tumors reaching upper abdomen with the mean maximum tumor length of 19.6 (10–25) cm. Of the 7 patients, 5 were diagnosed with immature teratomas and 2 with mature teratomas before surgery. Fertility-sparing surgery including unilateral salpingo-oophorectomy was performed in all patients. The FIGO stage was IA in 5 patients, IC (b) in 1 patient, and IIB in 1 patient. The grade was G1 in 3 patients, G2 in 4 patients. BEP (bleomycin, etoposide, cisplatin) therapy was given additionally in the 4 G2 patients. All patients had a favorable outcome without recurrence. [Conclusion] In this study, no recurrence was noted despite the fertility-sparing treatment in all patients, a stage II patient included, and G2 in 57% of patients. These results are suggesting that sufficient treatment was given.

ISP-13-8 Chemotherapeutic Retroconversion of Immature Teratoma of the Left Ovary with Subsequent Occurrence of Mature Teratoma in the Uterus : A Case Report

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Carlomer Tan Camanong

Teratomas are the most common germ cell. Extragonadal teratomas are rare. A 27-year-old woman diagnosed with Immature Teratoma was given chemotherapy after surgical management. At 2nd look laparotomy, multiple abdominal implants were found & biopsy was mature teratoma. After the surgery, she had vaginal spotting ; ultrasound was suggestive of endometrial polyp. She underwent transcervical resection of polyp & endometrial curettage. Histopathology report was mature teratoma. Chemotherapeutic retroconversion incidence was reported as low as 2-8%. Gliomatosis peritonei (GP), also found in the patient, is a rare phenomenon associated with teratomas. The pathogenesis is still not well understood. There was no mention of specific statistics as to how rare uterine teratomas are but Iwanaga mentioned that the uterine teratoma they have discussed was the 14th case recorded in world literature. The two probable etiology of the uterine mature teratoma is also discussed : parthenogenetic theory and blastomere theory. Before considering tumor recurrence after surgical management and chemotherapy in cases of immature teratoma, chemotherapeutic retroconversion is part of the differentials. Although a rare occurrence, uterine teratomas should be considered as part of the consideration of patients presenting with any uterine mass, even in the absence of typical sonologic features.

ISP-13-9 Ovarian Serous borderline tumor：Clinicopathologic analysis of 103 cases

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[Objective] The aim of this study was to clarify clinicopathologic features associated with malignant potential in ovarian serous borderline tumor (SBT). [Methods] 103 cases with SBT, underwent primary surgery from 2000 to 2014, were enrolled. The clinicopathologic features including pathologic risk factors and KRAS/BRAF expressions were examined. The study was approved by our IRB. [Results] Eighty cases presented with FIGO stage I and 23 cases with stage II–IV. Bilateral involvement was found in 26 cases and exophytic growth in 25 cases. SBT with micropapillary pattern, stromal invasion, extraovarian implant, and lymph node involvement were observed in 13, 29, 17 and 6 cases, respectively. Either bilateral involvement or exophytic growth was significantly correlated with extraovarian implant. Of 42 cases, KRAS overexpression was found in 7 cases and BRAF in 14 cases. There was significant correlation between micropapillary pattern and KRAS and/or BRAF overexpressions. [Conclusion] Since SBT with either bilateral occurrence or exophytic growth tends to have extraovarian implant, these growth pattern may be important as prognostic factors in SBT. The activation of KRAS/BRAF protein kinase pathway in SBT with micropapillary pattern could be one possible mechanism for SBT to progress toward low-grade serous carcinoma.

ISP-13-10 Malignant transformation of mucinous borderline tumor long after primary laparoscopic surgery

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[Objective] We report a case of recurrent borderline ovarian tumor (BOT) with invasive recurrence and multiple metastases after 12-years of primary treatment. [Case report] A 55-year old woman with lower abdominal pain was pointed out right multi-cystic ovarian tumor, with normal serum tumor markers. She underwent laparoscopic right-salpingo-oophorectomy, and the postoperative pathology was endocervical like mucinous borderline tumor, surgical stage IC1 due to surgical spill. Since additional treatment was not agreed, the patient was checked by serum tumor markers and image examination regularly. At the three-year follow-up, splenic simple cyst was newly detected, but FDG uptake was not observed in PET/CT. Subsequently, splenic cyst was gradually increasing, and became multi-cystic at the ten-year follow-up with slight elevation of CA19-9 (126 U/ml). Restudy of PET/CT was negative. However, at the twelve-year follow-up, the level of CA19-9 extremely elevated (2,754 U/ml), and PET/CT revealed arising solid part in splenic cyst and FDG uptakes in spleen and liver. Liver-biopsy was performed and resulted metastasis of ovarian adenocarcinoma with stromal invasion. In purpose of QOL maintenance, she declined chemotherapy, and received palliative treatment. [Conclusion] The possibility of recurrence and malignant transformation should be re-recognized in the follow-up of BOT.

ISP-14-1 Pulmonary type of small cell carcinoma of the ovary：a case report

Osaka City University
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Small cell carcinoma of the ovary is a very rare and aggressive tumor with a poor prognosis, and it is classified into pulmonary type and hypercalcemic type. There is no standard treatment for patients with this disease. We reported the case of a 55-year-old woman with small cell carcinoma of the ovary of pulmonary type. A 55-year-old woman came to the doctor because of abnormal genital bleeding. MRI confirmed the presence of large adnexal mass of solid appearance with the diameter of 15 cm. Then the tumor was suspected to be a malignant ovarian tumor, and she was referred to our hospital. Explorative laparotomy with hysterectomy, bilateral salpingo-oophorectomy, dissection of lymph nodes and partial omentectomy were conducted. Postoperative pathological examination gave a diagnosis of the pulmonary type of ovarian small cell carcinoma, FIGO IC1 stage. After surgery, irinotecan hydrochloride and cisplatin were administered to her as front line chemotherapy by reference to the treatment of pulmonary small cell carcinoma. At present, six months have passed since her first operation was performed and there has been no evidence of recurrence on imaging. Small cell carcinoma of the ovary is a very rare disease. But when we find a solid tumor of ovary, it is necessary to keep in mind a small cell carcinoma of the ovary as the differential diagnosis.

ISP-14-2 Mitotically active cellular fibroma of the ovary：a case report and literature review

Osaka Medical College
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[Introduction] The ovarian cellular fibrous tumor with mitotic figure more than 4 per 10 high power field without moderate to severe atypia is defined as mitotically active cellular fibroma (MACF) according to the 2014 WHO classification. [Case] A 36-year-old, G3P3, woman had a 10-year history of right 6-cm ovarian tumor. The serum levels of tumor markers were negative for CEA, CA125, CA19-9, SCC, HCG and AFP. MRI showed a 61-mm solid tumor, benign tumor (fibroma/fibrothecoma) or malignant tumor (germ cell tumor, lymphoma, GIST) was suspected. Laparoscopic surgery was performed. The tumor was noted in the Douglas pouch, protruded from right ovary without adhesion. Laparoscopic right salpingo-oophorectomy was performed. The tumor, cut into small pieces in the bag, was pulled out from the umbilicus. The sectioned surface was solid and light-yellow. In immunohistochemical findings, inhibin-α, vimentin, PgR, CD10, CD56 and WT1 were positive, and AE1/AE3, ER, calretinin and EMA were negative. Final histological diagnosis was MACF. To date, only 5 cases of MACF have been reported. Our patient is the first case of MACF of the ovary treated with laparoscopic surgery. [Conclusion] MCAF of the ovary is a newly defined category and few cases have been reported, while prognostic factors have also not yet been fully characterized. Long-term clinical follow-up is necessary.

ISP-14-3 Primary Papillary Serous Cystadenocarcinoma of the ovary complicated by Neoplastic pericardial effusion：A case report

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Pericardial involvement in patients with ovarian cancer is a very rare event. The development of pericardial effusion in primary serous papillary carcinoma (PSPC) of the ovary is not a common complication and little information is published about it. We described a 47 year old patient with advanced stage of primary serous papillary cystadenocarcinoma of the ovary who presented with pericardial effusion post operatively.

ISP-14-4 Chemotherapy in patients with recurrent or persistent clear cell carcinomas

Dokkyo Medical University
Kayoko Takahashi, Kiyoshi Hasegawa, Takanori Sakamoto, Nobuaki Kosaka, Ichio Fukasawa

[Objective] This study was conducted to retrospectively evaluate the effectiveness of salvage chemotherapy in patients with recurrent or persistent clear cell carcinomas (CCC).(approved by IRB) [Methods] Fifteen patients who received chemotherapy for recurrent or persistent CCC were enrolled. Primary outcomes were response rate (RR；CR+PR), and disease control rate (DCR；CR+PR+SD). Clinical response was evaluated every two or three cycles using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. [Results] The median age was 59 (range, 48 to 76) years. The median time to recurrence was 10 (range, 1 to 36) months. Eight regimens were used more than two cycles as salvage chemotherapy. The median number of chemotherapy regimens after recurrence were 3 (range, 0-6), and the median cycles of each regimen was 6 (0~23). The RR and DCR in eight regimens were as follows；CPT-11+CDDP, 0% and 16.7% (1 SD and 5 PD)；PTX+CBDCA, 20% and 40% (1 PR, 1 SD and 1 PD)；gemcitabine, 20% and 60% (1 CR, 2 SD and 2 PD)；PLD, 0% and 25% (1 SD and 4 PD)；CPT-11+DTX, 0% and 25% (1 SD and 3 PD)；PTX, 0% and 50% (2 SD and 2 PD)；DTX, 3 PD；topotecan, 3 PD. [Conclusion] The treatment effects was more favorable in the patients treated with gemcitabine. The combination treatment with gemcitabine and molecular target therapy, such as bevacizumab is required to clarify the efficacy in the future.

ISP-14-5 Survival analysis of revised 2014 FIGO staging classification of epithelial ovarian cancer and comparison with previous FIGO staging classification

Kobe University
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[Objective] To analyze the prognostic role of revised version of International FIGO stage 2014 in epithelial ovarian cancer and compare with previous version staging classification. [Methods] Ninety-nine patients with epithelial ovarian patients from 2010 to 2015 were enrolled. We reclassified the patients based on the revised FIGO staging classification. Prognosis was evaluated by PFS and OS as an endpoint. [Results] Previous stage IC (n=23) was subdivided into IC1 (n=14), IC2 (n=4), and IC3 (n=5). Previous stage IIIC (n=20) was subdivided into IIIA1 (i) (n=2), IIIA1 (ii) (n=1), IIIB (n=4) and IIIC (n=13). In addition, previous stage IV (n=16) was categorized into IVA (n=3) and IVB (n=13) in new staging classification. Stage IIC (n=4) has been eliminated and integrated into IIA (n=1) and IIB (n=3) in revised classification. Stage was changed on 52 cases (52.5%) after revising. The median follow-up time for all patients was 24 months (range 1-67). In the patients with revised FIGO stage III, there was no significant difference on PFS or PS among sub-stages. OS of stage IVB was tended to be poor than that of stage IVA. [Conclusion] Revision of FIGO surgical staging in 2014 for ovarian cancer is not clear to improve risk stratification. Further validation should be needed in large population based study.

ISP-14-6 Recurrence pattern in 80 cases of stage III/IV ovarian carcinomas with complete intraperitoneal cytoreduction

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[Objective] The prognosis of stage III/IV ovarian cancer is poor even after the complete cytoreduction. The aim is to investigate recurrence pattern in stage III/IV ovarian cancer by focusing on the timing of complete intraperitoneal cytoreduction. [Methods] We reviewed the records of 80 stage III/IV ovarian cancer patients with recurrence after complete intraperitoneal cytoreduction from 1996 to 2015 under approval of our ethical committee. Complete cytoreduction after primary debulking surgery was classified as PDS group (n=35), whereas that after interval debulking surgery was classified as IDS group (n=45). Clinicopathological characteristics, progression free interval (PFI) and recurrence pattern in each group were analyzed. [Results] Among all patients, 93% of pT1/2 patients belonged to PDS group, whereas 68% of pT3 patients were in IDS group ($p<0.0001$). Lymph node status, histological types and PFI were not statistically different in the two groups. However recurrence with peritoneal dissemination was more frequent in IDS group (78%) compared with PDS group (51%, $p=0.016$). Inversely, lymph node metastasis was more common in PDS group (43%) compared with IDS group (20%, $p=0.031$). [Conclusion] These findings suggest that recurrence pattern is associated with the timing of cytoreductive surgery and that peritoneal dissemination frequently occurs in the IDS group patients.

ISP-14-7 Outcomes of laparoscopic fertility-sparing surgery in presumed early-stage epithelial ovarian cancer

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[Objective] Fertility-sparing surgery (FSS) is becoming an important technique in the surgical management of young women with early-stage epithelial ovarian cancer (EOC). We retrospectively evaluated the outcome of laparoscopic FSS in presumed early-stage EOC. [Methods] We retrospectively searched databases of patients who received laparoscopic FSS for EOC between January 1999 and December 2012 at Samsung Medical Center. Women aged $\leq$ 40 years were included. The perioperative, oncological, and obstetric outcomes of these patients were evaluated. [Results] A total of 18 patients was evaluated. The median age of the patients was 33.5 years (range : 14-40) years. The number of patients with FIGO stage IA, IC, or IIIA1 was 5 (27.8%), 11 (61.1%), and 2 (11.1%), respectively. There were 7 (38.9%), 5 (27.8%), 3 (16.7%), and 3 (16.7%) patients with mucinous, endometrioid, clear cell, and serous tumor types, respectively. Complete surgical staging to preserve the uterus and one ovary with adnexa was performed in 4 (22.2%) patients. During the median follow up of 47.3 (11.5-195.3) months, there were no perioperative or long term surgical complications. Four (22.2%) women conceived after their respective ovarian cancer treatments. Three (16.7%) of them completed full term delivery and one is expecting a baby. One patient had disease recurrence. No patient died of the disease. [Conclusion] Laparoscopic FSS in patients with presumed early-stage EOC can be a feasible option for selected patients who desire fertility preservation.

ISP-14-8 Comparison of two groups diagnosed recurrence by different initial diagnostic method in recurrent epithelial ovarian cancer patients with secondary cytoreductive surgery

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[Objectives] The aim of this study was to compare two groups of recurrent epithelial ovarian cancer (EOC) patients who had secondary cytoreductive surgery (SCS) with initially diagnosed recurrence by CA-125 elevation or imaging study. [Methods] This study was conducted on 99 recurrent EOC patients who had SCS in Samsung Medical Center since January 2002 to December 2013. Patients with optimal debulking in primary cytoreduction, more than 6 months of platinum-free interval (PFI), without ascites and extensive dissemination at recurrence diagnosis for SCS were included in this study. By reviewing electric medical records, we investigated patient baseline characteristics, surgical characteristics, recurrence pattern and survival outcomes. Survival probabilities were compared by the log rank test. [Results] Within a median follow-up of 67 months (range 21~189), 19 cancer-associated deaths (%) were recorded. Most of the patients were stage III (n=71, 71.7%) and serous type (n=70, 70.7%). First recurrence was initially noticed by either CA-125 elevation (n=40, 40.4%) or imaging study (n=59, 59.6%). High percentage of extra-pelvic recurrence (50.0% vs 17.2%, p=0.003), multiple recurrence (46.4% vs.20.5%, p<0.001) and no residual after SCS (66.7% vs. 15.7%) were shown in group diagnosed recurrence by CA-125 elevation compared to group diagnosed by imaging study. Differences in median PFI were also shown (19.5 (6~83) vs. 26 (7~151), p=0.008). In survival analysis, group diagnosed with imaging study showed better result for overall survival (p=0.004), post SCS overall survival (p=0.023), progression free survival from initial treatment (p=0.003) and progression-free survival from SCS (p<0.001). [Conclusions] In recurrent EOC patients who had SCS, patients diagnosed for recurrence by CA-125 elevation are associated with multiple, extra-pelvic recurrence and they are expected to have poor survival than patients diagnosed recurrence by imaging study without CA-125 elevation.

ISP-15-1 Expression of VEGF in ovarian cancer suppresses tumor immunity via recruitment of myeloid derived suppressor cells (MDSC)

Kyoto University
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[Objective] High expression of VEGF in ovarian cancer is a known poor prognostic factor. In this study, the impact of VEGF on ovarian cancer immunity, including MDSC, was explored. [Methods] Under the approval of institutional ethical committee, ovarian cancer clinical samples were analyzed by gene expression microarray and immunohistochemistry. Mouse HM-1 sh-Vegfa cells were generated and inoculated into B6C3F1 mice subcutaneously. The frequencies of MDSC and lymphocytes in tumors were analyzed. The direct effects of Vegfa on functions of MDSC were examined. [Results] Microarray analysis of 32 cases revealed that, in VEGF-high expressing cases, several inducers of myeloid cells were up-regulated. In immunohistochemical analysis of 56 cases, the number of CD33+MDSC positively correlated with the VEGF expression (r=0.43, p<.05). Patients with high infiltration of MDSC in peritoneal metastasis exhibited shorter overall survival (p<.05). In the mouse model, silencing Vegfa resulted in diminished infiltration of MDSC and increased infiltration of CD8 + lymphocytes (p<.05). The treatment with anti Gr-1 antibody reduced HM-1 tumor burden, however did not affect HM-1 sh-Vegfa tumor. Both ex vivo generation and migration of MDSC were regulated by VEGF signaling (p<.05). [Conclusion] VEGF inhibits ovarian cancer tumor immunity via recruitment of MDSC and contributes to poor prognosis.

ISP-15-2 SIRT1 increases proliferation, chemo-resistance and invasiveness of ovarian carcinoma cells

Shinshu University
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[Objective] Sirtuin 1 (SIRT1), initially identified as a longevity gene, is considered to protect cells against age-related diseases including cancer. In contrast, several previous studies suggested oncogenic roles of SIRT1. We previously reported that the overexpression of SIRT1 was an independent poor prognostic factor for ovarian carcinoma (OvCa). The present study aimed to clarify the functional roles of SIRT1 in OvCa. [Methods] The OvCa cell lines (ES2, TOV21G and RMG1) were used to examine the functions of SIRT1 on cell proliferation and chemo-sensitivity (WST-1 assay), apoptosis (Annexin V assay), migration and invasion (invasion assay). The effect of SIRT1 on tumor growth was examined using OvCa xenograft in nude mice. [Results] Knock-down of SIRT1 by siRNA/shRNA decreases cell proliferation (TOV21G and RMG1, P<0.05), cisplatin-resistance (ES2, P<0.05). Overexpression of SIRT1 by cDNA facilitated the chemo-resistance against cisplatin (P<0.05) and paclitaxel (P<0.05), invasion (P<0.05), and reduced apoptosis (P<0.05) in ES2 cells. These effects in ES 2 cells were canceled out by the addition of selective SIRT1 inhibitor, EX527. SIRT1 over-expression resulted in increased tumorigenicity in vivo. [Conclusion] SIRT1 may be involved in the acquisition of aggressiveness and chemo-resistance in OvCa, hence indicating a novel candidate of therapeutic target.

ISP-15-3 Cancer cell and oncogene alter subset populations of T and dendritic cells in the tumor microenvironment of disseminated ovarian cancer model

The University of Tokyo
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[Objective] Tumor microenvironment (TME) is modulated by cancer. Little is known about how oncogenes affect adaptive immunity in the TME. We here demonstrate how immune cells in the TME are modulated by cancer dissemination and K-ras. [Methods] Murine ovarian cancer cell line, ID8, or Kras-transduced ID8 (ID8-Kras) was injected into the peritoneal cavity and ascites production was monitored. Subset populations of T cells and dendritic cells (DC) in spleen or ascites from both mice were examined for CD8/CD4, CD11c/mPDCA, regulatory T cell (Treg)/CD4 using flow cytometry. [Results] Ascites production was accelerated in ID8-Kras mice compared with ID8. CD8/CD4 ratio in ascites was increased in either ID8 or ID8-Kras mice compared with control, however there was no difference in the ratio between ID8 and ID8-Kras mice. $CD11c^{high}mPDCA^{-}$ DC subset (conventional DC) was increased in ascites of ID8 mice. However, increase of the DC subset was cancelled in the ID8-Kras mice. Neither ID8 nor ID8-Kras injection altered Treg proportion in ascites. There was no difference in population of T cells and DCs in the splenocytes. [Conclusion] $CD11c^{high}mPDCA^{-}$ DC subset in the TME was increased with ID8 cancer dissemination, followed by the increased CD8-dominant immune response. K-ras-positive cancer cell may inhibit conventional DC migration followed by adaptive immune response to tumor.

ISP-15-4 LATS1 phosphorylation at serine 909 by $G\alpha_{13}$ is involved in YAP activation in ovarian cancer cells

Kyushu University
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[Objective] G protein-coupled receptors (GPCRs) and their ligands have been implicated in the progression of human cancers. In the previous study, we demonstrated that the activation of heterotrimeric G protein, $G\alpha_{12/13}$, promotes cell proliferation through YAP activation in ovarian cancer cells. We herein evaluated the underlying mechanisms by which $G\alpha_{12/13}$ activate YAP. [Methods] To examine the signaling pathway exclusively regulated by $G\alpha_{13}$, we employed a synthetic biology approach using a GPCR activated solely by artificial ligands (RASSLs). The activation of LATS1 and YAP regulated by $G\alpha_{13}$ was evaluated by Western blot. The expression of LATS1 and two YAP-targeted genes, CTGF and CYR61, was examined by real time PCR. [Results] $G\alpha_{13}$ induced YAP dephosphorylation and augmented the gene expression of CTGF and CYR61 in ovarian cancer cells. LATS1 phosphorylation at threonine 1079 decreased, conversely, serine 909 phosphorylation significantly increased. Interestingly enough, LATS1 protein level decreased markedly, though LATS1 mRNA level did not changed. In the presence of proteasome inhibitor, MG132, $G\alpha_{13}$-mediated LATS1 protein degradation was suppressed. [Conclusion] Proteasome-dependent LATS1 degradation after serine 909 phosphorylation induced by $G\alpha_{13}$ might contribute to YAP activation in ovarian cancer cells.

ISP-15-5 Global cancer-related microRNA expression analysis in epithelial ovarian cancer

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[Objective] This study aimed to clarify whether cancer-related microRNA (miRNA) expression profile could have clinical and biological associations with ovarian cancer. [Methods] We analyzed 85 cancer-related miRNAs expression in 12 serous carcinoma (SC) and 15 clear cell carcinoma (CCC) by real-time RT-PCR analysis with informed consent. Hierarchical clustering analysis was performed, and differentially expressed miRNAs between SC and CCC were identified by class comparison analysis. We further evaluated biological significance of *miR-9* overexpression in CCC. [Results] Unsupervised clustering analysis identified two distinct clusters, and the association between the clusters and clinicopathological features showed significant difference in histotype. When we compare miRNA expression among SC vs. CCC, 5 miRNAs including *miR-9* had statistically higher expression in CCC. *miR-9* inhibition in CCC reduced cell invasion ability. We further showed that *miR-9* could directly bind E-cadherin using luciferase reporter assay. [Conclusion] Global cancer-related miRNA expression analysis identified unique expression profiles in ovarian cancer, which could discriminate the histotype. *miR-9* overexpression may be involved in CCC pathogenesis by inducing epithelial-mesenchymal transition through E-cadherin, suggesting that *miR-9* could be served as a potential therapeutic target for CCC.

ISP-15-6 Can gynecologic oncologist counsel effectively BRCA genetic test and counseling among advanced ovarian carcinoma

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[Objectives] It is recommended for ovarian carcinoma patients to offer BRCA mutation test and information for another cancer prevention and target treatment. It is not easy to offer and persuade genetic counseling because of disease severity. We undertook this study to investigate clinical significance between advanced staging and acceptance rate of BRCA testing and genetic counseling by gynecologic oncologist. [Methods] Two groups were divided between early (I–II) and advanced (III–IV) ovary carcinoma patients regarding BRCA mutation and genetic counseling acceptance. Total 34 patients were evenly divided between them. After complete surgical staging and pathology result, same gynecologic oncologist offered genetic counseling. [Results] Early stage group was younger than advanced stage, median age of 52.53 (20–73) vs 57.77 (45–75). Among 34 patients, only 2 patients refused. In early stage group, BRCA testing time after the operation (126.38 (6–981 days) vs 50.69 (6–315 days) ($p>0.05$)) was not statistically significant longer than advanced stage group.Time to acceptance from operation became shorter with accumulation of counseling experience, First 11 patients took 236days (9–981) and later it were 10.8 (7–30) and 11.3 (6–30). BRCA1 was found by three patients in advanced stage group while BRCA2 was found by one patient in early stage group. [Conclusions]It is feasible for gynecologic oncologist to offer early genetic counseling even at advanced stage of ovary cancer. Therefore, advanced staging patient may not be an obstacle for early counseling by surgeon about BRCA mutation.at advanced stage of ovary cancer.

ISP-15-7 Anti–LSR monoclonal antibody inhibits ovarian cancer growth via inhibition of lipid metabolism

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[Objective] Developing new treatment for ovarian cancer is urgently required. We aimed to identify a new ovarian cancer antigen and to develop a novel monoclonal antibody (mAb). We evaluated its preclinical anti–tumor efficacy against ovarian cancer and performed fuctional analysis of a new antigen protein in ovarian cancer. [Methods] We identified a new ovarian cancer antigen ; lipolysis–stimulated lipoprotein receptor (LSR) by quantitative proteomics. Novel mAb against LSR was developed and its preclinical anti–tumor efficacy was investigated in vivo and in vitro. We also investigated LSR function in ovarian cancer. [Results] LSR expression in normal tissues were lower than cancers in RT–PCR. High LSR expression was poor prognostic factor in ovarian cancer patients ($p<0.05$). Our newly developed anti–LSR mAb showed significant in vitro inhibition of cell proliferation ($p<0.05$), and in vivo inhibition of tumor growth in xenografted model in ADCC independent manner ($p<0.01$). Anti–LSR mAb also inhibited tumor growth in patient–derived tumor xenografted model ($p<0.05$). LSR cDNA transfected cell line (L45) significantly reserved lipid metabolite ($p<0.01$). L45 cells showed increased uptake of VLDL ($p<0.05$), and anti–LSR mAb inhibited its uptake ($p<0.05$). [Conclusion] Our preclinical data showed that LSR is a promising target for ovarian cancer treatment via manipulating lipid metabolism.

ISP-15-8 CDX2 regulates Multidrug Resistance 1 expression in ovarian mucinous adenocarcinoma

Hiroshima University
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[Objective] Resistance against chemotherapeutic agents often develops in ovarian cancer patients. The Multidrug Resistance 1 *(MDR1)* gene encodes P–glycoprotein, which affects the pharmacokinetic properties of anticancer agents. CDX2 is a factor that influences cancer cell differentiation, malignancy, and cancer progression. We hypothesized that profiling of CDX2 and MDR1 expression could be an effective strategy for predicting anticancer drug resistance. [Methods] We studied the expression of these factors in clinical samples, and examined about MDR1–regulation and drug resistance by CDX2 in ovarian mucinous adenocarcinoma cell lines. [Results] We found that endogenous *MDR1* expression was positively associated with CDX2 expression in ovarian mucinous adenocarcinoma. Using ovarian mucinous adenocarcinoma cell lines, we also observed decreased *MDR1* expression following inhibition of CDX2 by RNA interference. In addition, CDX2 overexpression in MN–1 cells, which display low endogenous CDX2, resulted in upregulation of *MDR1* expression. CDX2 induced MDR1–dependent resistance to paclitaxel. [Conclusion] Our findings show that CDX2 promotes upregulation of *MDR1* expression leading to drug resistance in ovarian mucinous adenocarcinoma. Therefore, our study suggests the potential of novel chemotherapy regimens based on CDX2 status and MDR1 expression in ovarian mucinous adenocarcinoma.

ISP-15-9 Interleukin-6 Expression and its Relationship with Clinicopathological Features including ARID1A Expression in Stage I Clear Cell Carcinoma of the Ovary

The Jikei University
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[Objective] In clear cell carcinoma of the ovary (CCC), the critical molecular events include mutations in *ARID1A* and upregulation of IL-6 signal. It was reported coexistent *ARID1A-PIK3CA* mutations could promote carcinogenesis through sustained IL-6 overproduction in a CCC mouse model. We aimed to identify the IL-6/ARID1A expression signature associated with patient characteristics in stage I CCC. [Methods] Immunohistochemical analyses for IL-6/ARID1A were performed in 138 stage I CCC cases.(approved by IRB). IL-6 expression was categorized as Low or High (0-50%, low ; 60-100%, high). We investigated the correlation between IL-6/ARID1A expression and either age, CA125, CRP, ascites cytology, rupture, stage, endometriosis or prognosis. [Results] High IL-6 expression was found in 31% and correlated with poor prognosis (OS, p=0.034 ; PFS, p=0.043). However, there was no significant association between IL-6 expression and any of these clinicopathological parameters. Although ARID1A loss was found in 54% and correlated with stage (IA+IC1 vs. IC2+IC3 ; p=0.02) and ascites cytology (p=0.05), there was no relationship between ARID1A loss and prognosis. There was no correlation between high IL-6 and ARID1A loss. [Conclusion] IL-6 expression may be useful prognostic marker in stage I CCC. There was no evidence that ARID1A loss could be possible reason for IL-6 overexpression.

ISP-15-10 Elevated level of circulating microRNA-99a correlates with serous epithelial ovarian cancer and can be used as a potential biomarker

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[Objective] There is a critical need for improved diagnostic markers for ovarian high grade serous cancer (HGSC). micro RNAs (miRNAs) stably exist in circulating blood, reflecting tissue or organ conditions and present in circulating microvesicles such as exosomes. The purpose of this study was to identify which miRNAs are highly produced from HGSCs and analyze whether circulating miRNA can discriminate patients with HGSC from healthy volunteers. [Methods]Secreted exosomes from serous ovarian cancer cell lines were collected and exosomal miRNAs were extracted. miRNA microarray (Affymetrix GeneChip) was performed and several elevated miRNAs specific to ovarian cancer cells were picked-up. Among these, we focused on miR-99a in this study. Sera were collected from 9 patients with HGSC and 5 healthy volunteers. Expression level of miR-99a was determined by miRNA RT-qPCR. [Results] In patients, serum miR-99a levels were significantly increased (7.2 fold) compared with healthy controls. ROC analysis showed that at the cut-off of 2.1 times compared with control, the sensitivity and specificity of this marker were 77.8% and 100% respectively for detecting HGSC (AUC=0.84). [Conclusion] Exosomal miRNAs can be detected in sera of patients with HGSC and have the potential to predict ovarian cancer.

ISP-15-11 PAI-1 (plasmin activator inhibitor 1) as a therapeutic target for ovarian cancer

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[Objective] PAI-1 is known to be associated with poor prognosis in several cancers. The aim of this study is to analyze whether PAI-1 expression affects the prognoses of ovarian cancer and assess the therapeutic potential using a selective PAI-1 inhibitor. [Methods] PAI-1 expression was evaluated in 154 patients with ovarian cancer. Using ovarian cancer cell lines, the effect of PAI-1 inhibitor (IMD-4482) was assessed on cell viability, cell cycle, and invasion. [Results] 66% (101/154) of ovarian cancer showed strong PAI-1 expression, and its strong expression was significantly related to poor prognoses (PFS ; 19 vs. 27 months, P=0.0041). Especially, among Stage II-IV patients with serous adenocarcinomas, PAI-1 expression was an independent prognostic factor. PAI-1 expressions were observed in 3 out of 6 serous ovarian cancer cell lines (HeyA-8, SKOV3ip1, CaOV3). The treatment of 10μM IMD-4482 suppressed proliferation and induced G1 arrest, which led to apoptosis of PAI-1 positive ovarian cancer cells, accompanied by the inhibition of the phosphorylation of ERK and FAK. In *in vitro* invasion analysis, IMD-4482 significantly inhibited ovarian cancer invasion. [Conclusion] PAI-1 expression is a novel prognostic factor in ovarian cancer patients. Its functional inhibition significantly inhibited ovarian cancer progression. PAI-1 might be a potential therapeutic target for ovarian cancer.

ISP-16-1 Prediction of taxane and platinum chemosensitivity in ovarian cancer based on gene expression profiles

Kyoto University[1], Kinki University[2]
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[Objective] It remains unclear which cases exhibit a benefit from taxane or platinum in ovarian cancer. We aimed to predict drug sensitivity using gene expression profiles. [Methods] We identified differentially expressed genes in responsive and resistant cases from an ovarian cancer dataset (GSE15622), which contains expression data of biopsy specimens and responses to paclitaxel or carboplatin monotherapy. Then, we generated a scoring system for prediction of taxane or platinum response (T-score and C-score) and applied it for external datasets. [Results] High C-score levels were significant in responders compared to non-responders in breast cancer cases treated with cisplatin monotherapy (GSE18864, p=0.042). In cases with high T-scores, taxane-containing regimens exhibited better survival than non-taxane regimens in two ovarian cancer datasets (GSE9891 : p=0.0007 ; GSE3149 : p=0.048), whereas in cases with low T-scores, addition of taxane did not result in improved survival. T-scores and C-scores negatively correlated with each other in the ovarian cancer datasets (p <0.0001, respectively), suggesting the complimentary roles of taxane and platinum. [Conclusion] Our scoring system successfully predicted platinum or taxane response. This finding could be useful to develop individualized treatments of ovarian cancer.

ISP-16-2 Three-combined treatment, a HDAC inhibitor OBP-801/YM753, paclitaxel and 5-fluorouracil induces G2-phase arrest in human ovarian cancer cells

Kyoto Prefectural University
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[Objective] Herein we examined the efficacy and molecular mechanisms of the three-combined treatment, a HDAC inhibitor OBP-801/YM753, paclitaxel (PTX) and 5-fluorouracil (5-FU), in human ovarian cancer SKOV-3 and OVCAR-3 cells. [Methods] The effects of this three-combined treatment on the growth of ovarian cancer cells were examined using WST-8 assays. The distribution of the cell cycle was analyzed by flow cytometry. The expression of cell cycle-related protein was investigated by western blotting. [Results] Three-combined treatment significantly inhibited the cell growth on comparison with both each single agent alone and two-combined treatment, and induced G2-phase arrest with the phosphorylation of p38 (Thr180/Tyr182) in both ovarian cancer cells. Moreover, the p38 inhibitor SB203580 inhibited the G2-phase arrest induced by the three-combined treatment. [Conclusion] This three-combined treatment can induce G2-phase arrest through activation of the p38 signaling pathway in ovarian cancer cells. We therefore believe that this combination is promising for a novel therapeutic strategy against ovarian cancer.

ISP-16-3 Number of somatic mutations by whole-exome sequencing is associated with both surgical outcome and chemosensitivity in high-grade ovarian serous carcinoma

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[Objective] Residual tumor and chemo-sensitivity are important prognostic factors in ovarian high-grade serous carcinoma (HG-SC). We aimed to clarify relationship between mutation profile and clinical outcome in HG-SC. [Methods] We performed whole exome sequencing in 78 clinical samples of stage II-IV HG-SC under informed consent and approval of our ethics committee. All the patients received primary surgery (PDS) and platinum-based chemotherapy. Correlation between mean number of non-synonymous somatic mutations (No. of mut) and residual tumor or chemo-sensitivity was analyzed by likelihood ratio test. [Results] The number of patients with treatment free interval (TFI) <12m was 37 (classified as low-responder), while the number of those with TFI>12m or no recurrence was 41 (high-responder). No. of mut was significantly higher in high-responder group (n=137.0 ± 238.9), compared with that in low-responder group (n=76.5 ± 36.7) (p=0.0041). In addition, No. of mut in the group with no residual tumors after PDS (n=241.9 ± 109.7) was significantly higher than that (n=83.1 ± 5.9) in the other group (p=0.0030). Progression free survival of the high mutator group (No. of mut>100) was significantly better than the other group (p=0.0131 by log-rank test). [Conclusion] The number of mutations was associated with both tumor resectability and response to platinum-based chemotherapy in HG-SC.

ISP-16-4 Doxorubicin hydrochloride and Bevacizumab for the patients with Platinum-taxane resistant ovarian cancer

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[Objective] Whether pegylated liposomal doxorubicin (PLD) and bevacizumab are of any value for carboplatin/paclitaxel (TC)-refractory ovarian cancer than PLD alone. [Methods] Subjects were 79 patients who received second-line PLD or PLD plus bevacizumab with patient's agreement. 61 were treated with PLD and 18 with PLD plus bevacizumab after TC failure. Efficacy and safety of the chemotherapies were compared between two groups. [Results] The average number of the courses administered of PLD and PLD plus bevacizumab were 5.6 and 5.5, respectively. Response to the chemotherapy was 21.6% and 28.6%, and clinical benefit was 40.0% in PLD and 78.6% in PLD plus bevacizumab. Median time to disease progression was 8.2 months and 9.2 months, respectively (P=0.34), and median survival time was 16.4 months and 13.2 months, respectively (P=0.56). Grade 3-4 hematologic and non-hematologic toxicities were no difference between 2 groups. Next, patients were divided 2 groups : those refractory to TC chemotherapy (n=45, Group A) and those who were TC-sensitive (n=34, Group B). In Group A, Median time to disease progression in PLD and PLD plus bevacizumab was 5.4 months and 11.9 months, respectively (P=0.13). [Conclusion] Bevacizumab provided no additional benefit for the patients treated with PLD. In the patients refractory to initial chemotherapy have more tendencies to response to bevacizumab.

ISP-16-5 Bevacizumab in ovarian cancer : its safety and effectiveness

Osaka University
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[Objective] Bevacizumab (BEV) was approved for ovarian cancer in Japan in November 2013. After the approval, we have used BEV for some patients suffering from ovarian cancer. We report our experiences of BEV. [Methods] We use BEV in the primary treatment of advanced epithelial ovarian cancer or in the treatment of recurrent epithelial ovarian cancer. We review the effectiveness and the safety of BEV from medical records. [Results] We used BEV in 10 cases together with other chemotherapy regimens ; 8 cases were as the primary treatment, and 2 were for recurrent cancer. In the primary treatment, 7 cases were with TC and the other with CPT-11, in which the patient had an allergy to TC. In 4 cases the patients had undergone intestinal resection in the preceding surgery ; no one developed severe adverse events such as intestinal perforations. The recurrence of the cancer during maintenance treatment with BEV alone was observed in 2 cases. For the patients with recurrent cancer, we used BEV with TC or liposomal Doxorubicin ; the patients ended up with SD or PD. [Conclusion] BEV is considered to be safe because no severe adverse events were observed. But both patients with recurrent cancer did not improve ; it seems to be necessary to study which is the most effective regimen to be combined with BEV.

ISP-16-6 Withdraw

ISP-16-7 Our experience of bevacizumab in the chemotherapy of ovarian cancer

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[Objective] To evaluate the efficacy of Bevacizumab combination chemotherapy for ovarian cancer in our hospital. [Methods] For pertinent clinical data, we reviewed the hospital records of 46 patients treated by Bevacizumab combination chemotherapy between March 2014 and September 2015. All the patients had recurrent ovarian cancer (n=32) or untreated advanced (FIGO stage III to IV) ovarian cancer (n=14). We investigated the treatment results and Bevacizumab related adverse events. [Results] Median age was 62.0 years (range 30–84). The number of prior chemotherapy regimens 0/1/2/3– was 31.8/38.6/11.4/18.2%, respectively. Median duration of bevacizumab therapy was 9.3 months (range 0.4–18.7 with pauses). In initial therapy (n=14), response rate (RR) was 78%. In recurrence–therapy (n=32), platinum sensitive and sensitive patients were 12 and 20 cases, respectively. RR was 52.3% and 9.1%. Bevacizumab related grade 3–4 adverse event was included GI perforation (2.2%), GI hemorrhage (2.2%), wound–healing complications (4.5%), hypertension (4.5%), and cerebrovascular disease (2.2%). The rare adverse event included grade 2–acute subdural hematoma (2.2%). [Conclusion] In our experience, Bevacizumab combination chemotherapy for initial/recurrent therapy was shown effectiveness with acceptable tolerability in ovarian cancer patients.

ISP-16-8 A study on the efficacy of bevacizumab (BEV) for advanced and recurrent ovarian cancer

Kyushu University
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[Objective]BEV is mainly used for initial treatment of advanced ovarian cancer patients in Japan. We herein studied the efficacy of BEV for advanced and recurrent ovarian cancer. [Methods] Medical records of ovarian and peritoneal cancer patients who received chemotherapy with BEV from May 2014 to June 2015 were retrospectively reviewed. All patients provided written informed consent before treatment. [Results] Twenty nine patients (primary treatment, n=8 ; recurrent treatment, n=21) were included in this study. The median age and PS were 64 years old (35–79) and 0 (0–1), respectively. Paclitaxel+carboplatin (TC)+BEV therapy was performed for 8 primary (stage I, n=0 ; stage II, n=1 ; stage III, n=3 ; stage IV, n=4) and 12 sensitive relapse cases. Nine refractory relapse cases received nogitecan (NGT)+BEV treatment. Treatment response was CR, n=3 ; PR, n=7 ; and SD, n=10 (response rate (RR) : 50%) in primary and sensitive relapse cases ; PR, n=3 ; SD, n=4 ; PD, n=2 (RR : 33%) in refractory relapse cases. Adverse effects were detected as follows : intestinal perforation, 1 case (3%) ; high blood pressure, 6 cases (21%) ; leukopenia, 10 cases (34%) ; neutropenia, 19 cases (66%) ; anemia, 2 cases (6.8%) ; thrombocytopenia, 4 cases (14%). [Conclusion] BEV could be effectively used with TC or NGT for advanced and recurrent ovarian cancer.

ISP-16-9 The experience of the treatment of the epithelial ovarian cancer with bevacizumab

Osaka City University
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[Objective] Bevacizumab was approved to be applicable to insurance for the epithelial ovarian cancer (EOC) in November 2013 in Japan. We reported our experience of the treatment of EOC with bevacizumab. [Methods]We reviewed the patients with EOC who are treated with bevacizumab from April 2014 to August 2015. In our hospital, bevacizumab is administered to the patients with EOC, peritoneal cancer and tubal cancer stage III/IV. [Results] Eight patients (24.2%) of 33 patients who are candidates of bevacizumab administration were treated with bevacizumab. The reason of nonuse of bevacizumab were no wish of patients (7 cases, 28%), bad condition of intestine (8 cases, 32%), bad general condition (5 cases, 20%), embolism (4 cases, 16%), advanced age (1 case, 4%). Grade III and IV adverse effects were identified as one grade IV ileal perforation, one grade III urinary fistula, one grade III neutropenia, four grade IV neutropenia, one grade III thrombocytopenia and one grade III stomatitis. These events did not differ significantly from those observed in the cases treated with only carboplatin plus paclitaxel. Besides those adverse effects, two grade II hypertension and four grade I proteinuria were identified. [Conclusion] Bevacizumab should be administered to the strictly selected patients and after administration the careful observation of patients condition should be needed.

ISP-17-1 Clinical features of obstetrical antiphospholipid syndrome in the Japanese population—A multicenter study

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[Objective] This study aimed to assess the clinical features of obstetrical antiphospholipid syndrome (APS) to evaluate the risk factors for adverse pregnancy outcomes. [Methods] The institutional ethics boards approved this study, and 74 APS women who meet Sydney criterion were registered. Clinical characteristics, serologic data, and pregnancy outcomes were evaluated. [Results] Of 85 pregnancies from the 74 APS women, 58 were treated with low-dose aspirin (LDA)+heparin (H); 12 with LDA+H+immunoglobulins (IVIg); 11 with LDA or H alone; 4 with others. Live-birth rates of LDA+H, LDA+H+IVIg, LDA/H alone, and others were 91.4%, 75%, 72.7%, and 0%, respectively (n.s.). However, gestational age at delivery (median 36wks) in LDA+H±IVIg was less than that (38wks) in LDA/H alone ($p<0.05$). Among 62 pregnancies treated with LDA+H±IVIg (n=70) and ended in live-birth, a positive test for dRVVT-LA, aβ2GP-I, multi-aPL and a history of stillbirth ($p<0.05$) were risk factors for premature delivery. By multivariate regression analyses, positive test for aβ2GP-I, (OR 121, 95% CI: 1.6-9380) was independent predictive for delivery before 34wks. [Conclusion] LDA+H therapy had been commonly used for obstetrical APS in Japan. Even when LDA+H therapy was used, women with a positive test for aβ2GP-I was at a high risk for adverse pregnancy outcomes.

ISP-17-2 Retrospective analysis of the perinatal outcomes of 191 cases who were treated with the combination therapy of low dose aspirin and heparin

The Jikei University
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[Objective] Although patients with recurrent pregnancy loss were treated with combination of low dose aspirin and heparin (LDA+Hep), the indication for this therapy has not been established. We aimed to reveal the perinatal outcome of the patients who were treated with LDA+Hep. [Methods] We examined 191 cases who were treated with LDA+Hep in five years. We classified them into following three groups; antiphospholipid syndrome group (APS), APS like syndrome (APLS) group and coagulation dysfunction (CD) group. Abortions before 12 weeks and cases could not be classified into three groups were excluded. We retrospectively analyzed delivery week, birth weight and the other characteristics of perinatal outcomes. IC was obtained before treatment. [Results] The mean delivery week was 38.3, and there was no significant difference among three groups. The incidence of birth weight<2,500g was 18.8% in APS group, 14.5% in APLS group and 34.6% in CD group and the incidence of preterm birth was 12.9%, 13.6% and 20.0%, respectively. There was no significant difference among three groups for the incidence of fetal growth restriction, the other characteristics or perinatal outcomes. No severe adverse effect was observed. [Conclusion] Although the incidence of preterm birth and low birth weight were higher than general population, LDA+Hep provided favorable perinatal outcomes.

ISP-17-3 Th1/Th2 immune polarity induced by invariant NK cell stimulation determines the incidence of mouse miscarriage

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[Objective] Invariant NKT (iNKT) cells play a central role in the determination of Th1/Th2 T cell polarity. It is previously reported that iNKT-specific stimulation can cause miscarriage in mice, although its immunological mechanism is not fully elucidated. This study aimed to clarify the involvement of iNKT in the etiology of miscarriage focusing on Th1/Th2 polarity. [Methods] α-GalCer (AGC) stimulates Th1 polarity of iNKT cells, whereas OCH Th2 polarity. AGC and OCH were injected to pregnant C57BL/6 mice intraperitoneally at 9.5 d pc. The incidence of miscarriage was evaluated at 72 hr after the administrations. Additionally, the effect on Th1/Th2 polarity shift was examined by measuring IL4/IFN-γ mRNA expression ratio in the splenocytes. [Results] The rate of in-utero fetal absorption was significantly lower in OCH administration (8.2%) than that in AGC administration (59.2%). AGC stimulation up-regulated IFN-γ and OCH stimulation preferentially induced IL-4 expression rather than IFN-γ in the splenocytes, whereas the IL-4 induction after AGC stimulation was weak. [Conclusion] Th2 polarity but not Th1 induced by iNKT stimulation is protective against the miscarriage. Our findings imply the involvement of iNKT-dependent Th1/Th2 polarity in the pathophysiology of miscarriage.

ISP-17-4 How do the women feel after having NIPT? A year later survey among 3000 women

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[Objective] To explore women's mood and attitude regarding NIPT among women who have given birth after underwent NIPT. [Methods] A mail-in survey concerning women's feedback on NIPT and genetic counseling was performed as a clinical study by the Japan NIPT consortium. Women who received NIPT and have got negative result were subjected. This study was obtained approval from ethics committees. [Results] Responses from 2923 women were analyzed. It revealed that the women had high satisfaction rating even after a year. It denotes most of the same tendency between of the result of first reaction for NIPT and a year later reaction. The necessity of genetic counseling was high rated (90%). They well understood that the feature and the limitation of NIPT and perceived the need of special care for women who had positive result. In the result of first reaction for NIPT, 96.5% of the women with negative test results indicated that they would choose NIPT in their next pregnancy, but the rating of choosing NIPT decreased to 75% in a year later. [Conclusion] We confirmed that the manner of the genetic counseling we conducted created an opportunity for pregnant women to sufficiently consider prenatal testing. In the clinical application of NIPT, an appropriate genetic counseling is essential. A more careful approach was considered to be necessary for women who received positive test results.

ISP-17-5 Noninvasive Prenatal Screening and its Relevance to Clinical Practice：Update on Clinical Outcome Metrics on Over 85,000 Cases

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[Objective] The verifi® noninvasive prenatal test (NIPT) has been available through Illumina's accredited clinical lab since February 2012. In follow-up to Illumina's first published clinical experience paper (Futch et al., 2013), this study highlights continued efforts to provide clinically relevant metrics for chromosomes 21, 18, and 13. [Method] Outcome information (karyotype/birth outcome) was requested from providers for singleton samples reported as aneuploidy detected (AD) or aneuploidy suspected (AS) for chromosomes 21, 18, or 13. Voluntary outcome reporting was encouraged for all discordant outcomes. [Results] Of 86,658 cases, 85,298 (98.4%) met inclusion criteria for NIPT result reporting, 101 (0.1%) were cancelled for technical reasons and 1,259 (1.5%) for administrative reasons. Average turnaround time was 3.3 business days. Of 85,298 reported cases, there were 2,142 (2.5%) positive results：1,858 AD (2.2%) and 284 AS (0.3%). Informative clinical outcomes were available for 851 (39.7%) positive cases. Of 85,298 reported samples, 108 (0.13%) AD cases were reported as putative false positives；15 (0.02%) false negatives were reported. The observed overall positive predictive value was 94.2% for AD samples and 88.9% for AD/AS samples combined. The overall observed negative predictive value was＞99.9%. [Conclusion] Since 2012, there have been improvements in turnaround time and cancellation rates, as well as a significant decrease in the aneuploidy suspected results. Information about clinical performance of NIPT aids in appropriate pre- and post-test counseling.

ISP-17-6 Uniparental disomy analysis in trios using genome-wide SNP array and whole-genome sequencing data imply the segmental uniparental isodisomy in general populations

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[Aim] It is known that a whole chromosomal and segmental uniparental disomy (UPD) is one of the causes of imprinting disorder and other recessive disorders. The aim of this study was to investigate a whole chromosomal and segmental UPD in general population. [Materials and Methods] All samples were obtained after receiving written informed consent and the study protocol was approved by the IRB. Here, we present results of a whole chromosome and segmental UPD analysis using single nucleotide polymorphism (SNP) microarray data of 173 mother-father-child trios (519 individuals) from six populations (including 170 HapMap trios). [Results] We identified obvious one segmental paternal uniparental isodisomy (iUPD) (8.2 mega bases (Mb)) in one HapMap sample from 173 trios using Genome-Wide Human SNP Array 6.0 (SNP6.0 array) data. On the other hand, we could not find the shorter segmental iUPD in two trios using whole-genome sequencing data. Finally, we estimated the rate of segmental UPD to be one per 173 births (0.578%) based on the UPD screening for 173 trios in general populations. Based on investigated autosomal chromosome pairs, we estimate the rate of segmental UPD to be one per 3806 chromosome pairs (0.026%). [Conclusion] These data will imply the possibility of hidden segmental UPD in normal individuals.

ISP-17-7 Monitoring of intrinsic optical signals relating to cerebral hemodynamics and cellular morphology in a rat hypoxic ischemic encephalopathy model

The University of Tokyo
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[Objective] For hypoxic ischemic encephalopathy (HIE) during labor, no valid diagnosis is established. In this study, we aimed to identify intrinsic optical signals to detect tissue deterioration prior to the occurrence of HIE during labor using a rat model. [Methods] Seven days old rats were underwent left carotid artery ligation, and 120 minutes later the rats were exposed to 8% oxygen for 135 minutes. Time courses of diffuse reflectance intensities were measured to monitor total hemoglobin, deoxy-Hb concentration and light scattering signal associated with cellular morphology. Staining for mitochondria by triphenyltetrazolium chloride (TTC) was conducted to evaluate brain tissue deterioration caused by HIE. [Results] During hypoxia, the diffuse reflectance intensities corresponding to total hemoglobin and deoxy-Hb concentration indicated the reduction in cerebral blood flow and deoxygenation of blood in the ligation hemisphere were more remarkable in the ligation hemisphere than in the non-ligation hemisphere. Light scattering signal was reduced in the ligation hemisphere, which may indicate edema formation. In agreement with the data of optical signals, TTC staining showed avascular necrosis only in the ligation hemisphere. [Conclusion] The optical signals measured in this study are promising parameters to monitor brain tissue deterioration triggered by hypoxia during labor.

ISP-17-8 Prenatal diagnosis of urorectal septum malformation sequence with the description of new variant. Insight into the embryogenesis

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[Objectives] Urorectal septum malformation (URSM) sequence is a spectrum of anomalies that includes the absence of urethral and vaginal, external genital defects and anorectal abnormalities. We reviewed 4 cases in a single center, Taiwan University Hospital, over a period of 20 years (1995-2015) to evaluate possible embryogenesis and histology of URSM. [Methods] Four cases diagnosed with URSM prenatally were included in this study. We collected the data of clinical presentations, prenatal ultrasonography figures, and final autopsy results and reviewed the current literatures. [Results] All of our cases had the similar clinical features, such as ambiguous genitalia, imperforate anus, invisible perineal opening or urethral opening. Pelvic cysts, oligohydramnios, urinary bladder agenesis, and renal dysplasia were noted during the prenatal examination in three cases. A new variant as intermediate form of URSM was noticed in case1 ; because that we were unable to locate it in this full continuum of spectrum due to the URS has formed but there is no perineal opening. Therefore, a preferable name such as "URS (representing urorectal septum)- CM (representing cloaca membrane) malformation sequence" might be more appropriate to describe the pathogenesis and manifestation of this whole disease spectrum. [Conclusion] Faulty development of URS apparently cannot explain the whole spectrum of the disease. We strongly recommended using URS-CM malformation to describe the original spectrum of URSM. More clinical cases and animal studies should be collected to verify this notion.

ISP-17-9 Omphalopagus—A Rare Case Report

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[Objectives] To find out the incidents of congenital anomalies in Bangladesh & also to know the relationship between consanguineous marriage & congenital anomalies. [Methods] It is a single case report. [Results] A 20 year old primigravida, hailing from a Muslim lower middle class family was diagnosed as a case of 40 weeks twin pregnancy with breech presentation of both fetuses, referred from a district hospital to a tertiary center. It was a consanguineous marriage with her 1st degree cousin. The patient underwent elective caesarean section & was found to be a case of conjoined twins. During the process of caesarean section the delivery of the twins was done by breech extraction with considerable difficulties. The fetuses were attached below the xiphisternum up to lower abdomen with single umbilicus & single umbilical cord. Both were female fetuses weighing about 6.2 kg together & had good Apgar score. Initially the babies were managed by a neonatologist just after birth & was referred to the dept. of pediatrics, Rajshahi Medical Collage Hospital, Rajshahi, Bangladesh. Because of their dissatisfaction with the conjoined twins the patient's party took them to their home with no treatment. After 2 days, they decided to shift the babies to Dhaka Child Hospital, Dhaka, Bangladesh. The USG of the fetuses revealed that the babies had single heart. During the process of conservative treatment the twins died after 2 days. The post-operative condition of the mother was good, except psychological trauma. [Conclusion] Early diagnosis of the conjoined twins by proper modern imaging as well as the decision to terminate the pregnancy is crucial for parents & obstetricians, for it can reduce the mental burden of both the family & doctors who are concerned.

ISP-17-10 Conditioned medium from human amniotic fluid stem cell ameliorated glutamate-induced apoptosis

Keio University
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[Objective] Glutamate-induced apoptosis (G-apoptosis) plays a central role in the pathogenesis of perinatal brain injury. In this study, mesenchymal stem cells derived from human amniotic fluid (hAF-MSC) were established and the effect of conditioned medium (CM) from hAF-MSC on G-apoptosis was determined. [Methods] The study was approved by the institutional review board of our university and informed consent was obtained from all patients. hAF samples were obtained by amniocentesis. $CD117^+$cells selected by microbeads were characterized by flow cytometry for surface markers of mesenchymal (CD29, CD73, and CD90) and hematopoietic (CD14, CD34, and HLA-DR) stem cells. $CD117^+$cells were analyzed to confirm their differentiation into osteogenic, adipogenic, and chondrogenic lineages. SH-SY5Y human neuroblastoma cells were treated with excess glutamate in the presence and absence of CM. After 24 hours of treatment, apoptotic cells were quantified using annexin-V immunostaining. [Results] $CD117^+$cells were positive for mesenchymal markers, but negative for hematopoietic markers. The differentiation of $CD117^+$cells into three lineages was confirmed by Alizarin Red S, Oil Red O and Alcian Blue staining. The number of apoptotic cells increased after glutamate treatment ; however, CM treatment alleviated this effect. [Conclusion] We established hAF-MSC and CM from hAF-MSC alleviated G-apoptosis.

ISP-17-11 Does the oxytocin during induced labor directly increase the risk of autism?

Juntendo University
Takashi Hirayama, Satoru Takeda

[Objective]Some data about the relationship between Oxytocin(OXT)-induced labor and autism have been reported. However, those studies were restricted only in epidemiological analysis, and the molecular mechanism is unclear. In this study, we investigated the relationship between OXT-induced labor and autism using new animal model. [Methods] To establish the animal model for induced labor, OXT was administered to gestational day18.5 mice using osmotic pump. Male offspring were used for autism related behavioral analysis. We then evaluated the number of Oxytocinergic neurons and Oxytocin receptor mRNA expression. We assessed the ischemia by c-Fos expression and cell death.(approved by IRB) [Results] The duration of labor was shortened and pup viability was not affected in 0.6 and 6 μgOXT/day. While no behavioral and expression differences were observed, cell death was exacerbate in specific brain regions related to some mental disorders. [Conclusion] We found no direct relationship between OXT itself and autism-like behaviors using an animal model, even excessive cell death was observed in the brain regions related to some mental disorders. Our results suggest that OXT-induced labor is not a risk of autism if it is in appropriate dosage. However this study is also edifying us an importance of keeping appropriate dosage and paying attention to the hypercontraction during induced labor.

ISP-18-1 Changes of time-interval in the ventricular inflow patterns in fetal growth restriction

Osaka City University
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[Objective] The aim of this study is to investigate, in growth-restricted fetuses (FGR), whether prenatal Doppler parameters are correlated with neonatal circulatory change. [Methods] This cross-sectional study included 310 normal fetuses aged 16 to 38 gestational weeks and 15 FGR fetuses aged 25 to 32 gestational weeks. FGR was defined as an estimated fetal weight below -2.0SD with an elevated umbilical artery pulsatility index above the 95th percentile. The time-interval between the peak of early ventricular filling wave and the peak of atrial contraction wave (EA-interval) in the ventricular inflow pattern was measured by Doppler methods. The EA-intervals were measured through tricuspid valve (TV-EA) and mitral valve (MV-EA). The data were obtained within one week before delivery in FGR group. Statistical analysis was performed using Z-score. [Results] In normal fetuses, positive correlation with gestational age was shown in MV-EA whereas there was no correlation in TV-EA (TV-EA : $r=0.139$, MV-EA : $r=0.365$). Compared with the normal controls, significant increases were observed in both EA intervals in FGR fetus (TV-EA : $p=0.007$, MV-EA : $p=0.003$). [Conclusion] Physiological changes of EA-interval with advance of gestational age were shown in normal fetuses. Moreover, striking differences were shown in EA-intervals in FGR complicated with placental dysfunction.

ISP-18-2 Myocardial diastolic function with early diastolic intraventricular pressure difference in fetuses

Juntendo University
Yuka Yamamoto, Yo Takemoto, Atsuo Itakura, Satoru Takeda

[Objective] Early diastolic intraventricular pressure difference (IVPD), which is a diastolic suction, has been known to be a useful marker to evaluate myocardial function in adult and children. There have been no studies on fetal IVPD. The purpose of this study was to determine the existence of IVPD during fetal stage and to validate the usefulness of the fetal IVPD. [Methods] This study was approved by ethics committees from the university. The study was collected from ninety-six healthy pregnant women at 17 to 36 weeks of gestation. We collected the data such as E/A ratio, myocardial performance index (MPI), velocity time integral (VTI) and valve diameters to get fetal cardiac output (CO). Color M-mode was used to calculate IVPD with MATLAB. [Results] The IVPD in the right (RV) and left (LV) ventricle significantly increased toward term (RV, LV : $r=0.63, 0.71$, $p<0.001$, respectively). Indeed the apical IVPD, but not basal IVPD, increased toward term. Both VTIs were well correlated with the IVPD ($p<0.001$), which induced a linear correlation between the CO and the IVPD ($p<0.001$). Combined CO ($p<0.001$) and E/A ratio ($p<0.05$), but not left MPI, demonstrated a good correlation with the IVPD. [Conclusion] Increased apical IVPD with gestation might imply the acquired diastolic suction with myocardial maturation. IVPD might be a novel index reflecting fetal myocardial function.

ISP-18-3 HDlive silhouette mode in diagnosis of fetal jejunal atresia

Kagawa University
Masato Mashima, Mohamed Aboellail, Megumi Ito, Nobuhiro Mori, Uiko Hanaoka, Hirokazu Tanaka, Toshiyuki Hata

[Objective] We present our first experience of using HDlive silhouette mode to construct images of two cases of jejunal atresia diagnosed in the third trimester of pregnancy. [Case series] In the first case, two-dimensional (2D) sonography revealed cystic dilatations in the upper region of fetal abdomen. HDlive silhouette mode clearly depicted panoramic ventral view of fetal gastrointestinal tract (GIT) showing the dilated stomach, different part of the dilated duodenum in addition to the atretic jejunum. Active peristalsis of the duodenum was evident. Diagnosis of jejunal atresia was ascertained after birth. In the second case, 2D sonography showed double bubble appearance of dilated stomach and duodenum. HDlive silhouette mode detected the small atretic jejunum. Moreover, spatial relationships between fetal GIT, and surrounding anatomical landmarks as spine and umbilical vein were demonstrated. Diagnosis of jejunal stenosis was confirmed postnatally. Every sonographic examination in this study was performed based on the consent of the patient. [Conclusion] HDlive silhouette mode provides more comprehensive, detailed view of different parts of fetal GIT that might be beneficial in diagnosing and differentiating cases of intestinal atresia.

ISP-18-4 Perinatal diagnosis and outcome of fetal skeletal dysplasia : a report of 8 cases

Kyoto Prefectural University
Mari Kawamata, Miyoko Waratani, Tadahiro Yasuo, Hidetoshi Fujisawa, Koichi Iwasa, Kazuhiro Iwasaku, Jo Kitawaki

[Introduction] The incidence of fetal skeletal dysplasia (SD) is 2/10,000 delivery and about 50% of them display adverse outcomes. We reported here diagnosis and perinatal outcome of cases with SD. [Materials and Methods] We experienced 8 cases of SD between 2012 and 2014 and all cases were diagnosed by ultrasonography and three-dimensional computed tomography. We investigated delivery methods, fetal and neonatal outcomes in these cases. [Results] A remarkable short femural length was found in six cases between 15 weeks and 36 weeks. One previously suspected case with fetal heart disease was later confirmed with SD. One case was identified as Desbquosis syndrome. Imaging modalities revealed 3 cases with osteogenesis imperfect (OI), 2 cases with thanatophoric dysplasia (TD), one case each of achondroplasia (ACH) and campomelic dysplasia (CD). Five cases survived after hospital discharge and 3 cases (OI type 2A and 2 of TD) died soon after birth. Caesarian section was performed in 6 cases, and two cases had vaginal delivery. One case with prenatal diagnosis of OI later conformed as CD after birth. One case of ACH was complicated with trisomy 21. [Conclusion] A variable perinatal outcome was observed in our cases with fetal skeletal dysplasia. An accurate imaging diagnosis of SD is necessary for making delivery decision and careful perinatal management in clinical practice.

ISP-18-5 Sirenomelia associated with an abdominal cyst and a single umbilical artery

Ryukyu University
Yui Kinjo, Tadatugu Kinjyo, Hayase Nitta, Yukiko Chinen, Hitosi Masamoto, Yoichi Aoki

[Introduction] Sirenomeila is a rare congenital anomalies characterized by fusion of the lower limbs. Two main pathogenic hypothesis are proposed, the defective blastogenesis hypothesis and vascular steal theory. [Case report] A 40-year-old woman, para0, An sonography revealed an abdominal mass in fetus at GA13weeks. At GA14weeks oligohydramnios was seen and a single blood vessel flow alongside the abdominal mass coursing into the umbilical artery. At GA17weeks abdominal mass was enlarged to 46*16mm. Close observation of the limbs were limited by the oligohydramnios. Infant prognosis was considered poor due to the sever oligohydramnios, patient chose a termination. An infant weighing 226g was delivered vaginally at GA19weeks. Infant showed bulging abdomen, fusion of lower limbs, anorectal atresia, absent external genitalia, and diagnosed as Sirenomelia. Prenatal diagnosis was missed. On autopsy, there was a pulmonary hypoplasia, duodenal atresia, absence of right kidney, abdominal cyst that revealed by sonography proved to be saccular cloaca ; cranial part was intestinal epithelial tissue and caudal part was bladder. [Conclusion] Detection of the lower limbs by sonography and an assessment of the aberrant abdominal vascular of the fetus using color and power Doppler could be useful for diagnosis. Prenatal diagnosis of Sirenomelia is beneficial for family to predict prognosis of infant.

ISP-18-6 The survey of thrombocytopenia in newborn baby

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[Objective] It is well known that maternal ITP can cause thrombocytopenia in the newborn baby. Recently, neonatal alloimmune thrombocytopenia (NAIT) has been noticed as another cause of thrombocytopenia. Because the complete blood count (CBC) is not routinely tested for newborn baby, the frequency of NAIT has not been known. In this study, we analyzed the CBC data of the newborn babies hospitalized in NICU. [Methods] This is a retrospective study. Since 2012 to 2014, the 218 newborn babies hospitalized in NICU in our hospital. The 207 babies' platelet count was analyzed. We did not apply this study to the ethics committee because this is a retrospective study of the medical records. [Results] Thirty three babies (15.9%) showed the platelet count under 150,000/μ L. Nine babies had a chromosomal abnormality, eight babies were born from mothers suffered from PIH or HELLP syndrome. The other 16 babies' causes of low platelet count were unclear. The babies of NAIT might be included in these 16 babies (7.7%). There were no cases who presented symptoms of low platelet such as subcutaneous bleeding. [Conclusion] About one sixth of newborn babies were found to show a low platelet count, and 7.7% babies could be NAIT. This is a pilot study and the additional study is needed to unveil the actual frequencies of NAIT among the newborn babies.

ISP-18-7 Prenatal demonstration of distal right coronary artery in normal and growth-restricted fetuses

Dokkyo Medical University
Susumu Miyashita, Kazumi Tada, Anriko Kanamori, Mariko Watanabe, Tatsuko Nagai, Kaori Kiuchi, Emi Motegi, Tatsuya Kuno, Hiroshi Watanabe, Ichio Fukasawa

[Objective] We aim to investigate clinical efficacy of demonstrated distal right coronary artery (dRCA) by ultrasonography in normal and growth-restricted fetuses. [Methods] Forty-four fetuses of normal growth and 37 of growth-restricted cases were enrolled with approval from the IRB. We employed color or power Doppler to visualize dRCA at the one-third of the apex side of the right ventricular free wall. Pulsed Doppler examination was added to prove characteristic flow patterns in coronary arteries. We investigated the demonstration rate, relations to fetal biometry, cardiothoracic area ratio (CTAR), ventricular wall thickening, amniotic fluid index, Doppler examinations in umbilical/middle cerebral artery and perinatal outcomes. [Results] Distal RCA was demonstrated frequently in FGR cases (normal 5% (2/44), FGR 51% (19/37), $P<0.001$). Amniotic fluid index was smaller in dRCA demonstrated (dRCA (+)) cases (dRCA (−) 12.3cm (7.5, 19.5), dRCA (+) 9.7 cm (2.6, 16.7), $P=0.021$) (median (max, min)) and CTAR was larger (dRCA (−) 32.4% (30.4, 42.1), dRCA (+) 40.9% (30.2, 52.8), $P=0.00088$) among FGR cases. We could not prove significant differences in Doppler indicies and adverse perinatal outcomes. [Conclusion] Demonstrated dRCA would indicate deterioration of heart function and could be a direct and feasible sign of heart-sparing effect, which was independent of brain-sparing in FGR.

ISP-18-8 *In utero* stem cell therapy for Osteogenesis Imperfecta：a clinical case report

Osaka University
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Osteogenesis Imperfecta（OI）can be a lethal disorder that can be diagnosed prenatally. Recently, several reports demonstrated clinical benefit of prenatal human fetal mesenchymal stem cell（hfMSCs）transplantation on OI patient. We present *in utero* hfMSCs transplantation for OI type IV in our in stitution.［Case］ Our patient was a male fetus identified at 27 weeks of gestation in a 32-year-old woman. The first daughter of this woman was affected with OI type IV with *COL1A2* gene mutation. The fetal short long bones were identified with ultrasound. OI was suspected due to the clinical findings and his family history. The mother decided to join an international clinical trial of *in utero* transplantation of hfMSCs for OI at 32 weeks of gestation. The fetus was transplanted hfMSCs intravenously. After the transplantation, the fetus developed no bone fractures prenataly. The child was delivered at 37 weeks of gestation by elective cesarean section. A full-body skeletal survey at birth confirmed the presence of bilateral femur fractures. This neonate developed two new femur fractures during the first month after birth. Genotyping of the neonate revealed the same mutation in *COL1A2* gene with his sister.［Summary］This is the first Japanese case report of fetal stem cell transplantation for OI. However, it is still a highly experimental therapy, and further studies are needed.

ISP-18-9 A case of X-linked VACTERL-H association with FANCB mutation

Yamagata University
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［Introduction］VACTERL-H association is a rare disorder characterized as：Vertebral defects（V）, anal atresia（A）, cardiac malformation（C）, tracheoesophageal fistula（T）, esophageal atresia（E）, radial or renal dysplasia（R）, limb abnormalities（L）, hydrocephalus（H）. We diagnosed a male fetus as VACTERL-H association. We report his clinical course and counseling for his family.［Case］ 24-years-old woman with male fetus with hydrocephalus at 23 weeks' gestation were reffered. The fetus was suspected multiple congenital malformation including hydrocephalus, cardiac malformation, duodenal atresia, radial dysplasia, and renal dysplasia. Her two brothers died in the neonatal period with multiple malformations like the fetus, X-linked VACTERL-H association was suspected. During pregnancy, we maintained a counseling with the family. The neonate was born at 37 weeks' gestation. He had hydrocephalus, esophageal atresia, tetralogy of Fallot, duodenal atresia, radial dysplasia, unilateral renal dysplasia, fused vertebra, and anal atresia. Regardless of treatments, he died because of renal failure at the age of 3 months. By exome sequencing, we identified deletion of exon3 of FANCB, which maps to Xp22.2. This study was approved by IRB of our university.［Discussion］ A case of X-linked VACTERL-H association have been reported. According to these literature, FANCB mutation may cause the phenotype.

ISP-18-10 HDliveFlow with HDlive silhouette/glass-body rendering mode of the fetal heart

Kagawa University
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［Objective］ We present our experience with normal fetal heart and congenital heart diseases（CHD）reconstructed using HDliveFlow with HDlive silhouette/glass-body rendering mode.［Methods］ Seven normal fetuses and seven with CHD（1 case each of truncus arteriosus（TA）, tricuspid regurgitation（TR）, ventricular septal defect（VSD）, right aortic arch（RAA）, hypoplastic left heart syndrome（HLHS）, and double-outlet right ventricle（DORV）at 12-35 weeks were included.［Results］ In normal fetuses, origins of pulmonary artery（PA）from right ventricle（RV）and aorta（Ao）from left ventricles（LV）with their crisscross arrangements were seen. Spatial three-vessel view demonstrated their relation to superior vena cava, and spine, and allowing size comparison between them. In TA, single arterial trunk straddling both ventricles, giving rise to PA and Ao was identified at 12w6d. In RAA, vascular ring around trachea with clear visualization of diverticulum of Kommerell and aberrant left subclavian artery was at 34w. In HLHS at 16w4d, diminutive LV, significant TR with shunt flow across large VSD were seen. In DORV, large Ao and small PA leaving RV in parallel were shown at 30w4d and at 31w5d.［Conclusion］ This technique may assist in evaluation of fetal heart, its great vessels, their spatial relationship with both ventricles, and differences in sizes of great vessels and cardiac chambers.

ISP-19-1 Prevention of Preterm Labor by ω3 Polyunsaturated Fatty Acids (PUFAs)

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[Objective] Metabolites of ω3PUFAs have anti-inflammatory property, opposing inflammatory actions by ω6 derived eicosanoids. This study aimed to investigate the possible role of ω3PUFAs in the regulation of intrauterine inflammation. We evaluated the relevance of ω3PUFAs and its metabolite, 18HEPE and RevE3 to the pathology of preterm birth using a mouse model. [Methods] Preterm birth was induced by administering LPS transcervically at day 15pc. RevE3, 18HEPE, or etOH was injected. Incidence of preterm birth was evaluated. The mRNA expression levels for inflammatory cytokines in the placenta and the uterus were determined by rtPCR. This study was conducted under the approval of ethics committee. [Results] Preterm birth occurred in 88% in control, 56% with RevE3, and 0% with 18HEPE ($P<0.05$). The rate of the fetuses which escaped preterm birth after LPS injection was 35% in control and 65% with RevE3, and 100% with 18HEPE ($P<0.01$). The uterine mRNA levels for TNFα, IL1β, and MIP2 with RevE3 were lower than those of control ($P<0.01$). Placental mRNA levels of TNFα, IL6, MIP2, and KC mRNA levels with RevE3 were lower than those of control ($P<0.01$). [Conclusion] We found that ω3PUFAs suppress preterm birth induced by LPS by reducing the production of inflammatory cytokines. Anti-inflammatory metabolites derived from ω3PUFAs can be promising candidates for a new therapeutic medicine for preterm birth.

ISP-19-2 Iron supplementation is ineffective for anemia triggered by ritodrine hydrochloride administration in women with threatened preterm labor

The University of Tokyo[1], The University of Tokyo Hospital[2]
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[Objective] Ritodrine hydrochloride (RH) is a beta-adrenergic agonist which is commonly used as a tocolytic agent in women with threatened preterm labor (TPL). Beta-stimulants develop hemodilutional anemia through activation of renin angiotensin system and water retention. This study aimed to assess clinical effect of iron supplementation (IS) for RH-induced anemia. [Methods] Medical records of the women who received RH infusion therapy for TPL in our hospital from 2010 to 2015 (n=123) were reviewed retrospectively under approval of our ethics committee. The association of iron supplementation with the shift of peripheral hemoglobin (Hg) concentration during RH administration were analyzed. [Results] Hg reduction from 11.2 ± 0.91 g/dl (mean ± SD) to 9.9 ± 0.78 g/dl was observed peaking a few days after initiation of RH administration. The Hg reduction was comparable between group IS (1.11 ± 0.48 g/dl) and group non-IS (1.05 ± 0.53 g/dl). Elevated Hg values from the bottom were 0.20 ± 0.30 g/dl in group IS and 0.35 ± 0.45 g/dl in group non-IS at two weeks after the starting RH, showing no significant difference between the two groups. [Conclusion] Although RH administration causes temporary Hg reduction, iron supplementation is not effective for RH-induced anemia and partial self-recovery can be expected in a couple of weeks.

ISP-19-3 Appropriate antibiotic therapy for preterm labor with or without intra-amniotic microbes evaluated by rapid and false positive-negative PCR system could prolong gestational period

University of Toyama
Satoshi Yoneda, Arihiro Shiozaki, Noriko Yoneda, Mika Ito, Tomoko Shima, Shigeru Saito

[Objective] To examine the efficacy of antibiotics for preterm labor with intact membranes by detecting the intra-amniotic microbes using rapid and false positive-negative PCR system. [Methods] 104 preterm labor cases (<32 weeks) were recruited. Until May 2012, the antibiotics were empirically prescribed based on the clinical severity. The result of intra-amniotic microbes in stock samples was evaluated later by our PCR system, and we examined the effect of antibiotics. The appropriate antibiotic therapy was defined as beta-lactam antibiotics therapy against the bacteria, macrolide antibiotics therapy against Mycoplasma or Ureaplasma or no therapy against no microbes. [Results] In the case of positive microbes (n=37) in amniotic fluid, the appropriate antibiotic therapy was significantly associated with prolonged gestational days (45 vs. 12 days ; $p<0.0001$) without adverse neonatal complication, while in negative (n=67), the antibiotics made the gestational period significantly shorter (35 vs. 57 days ; $p<0.0001$). The prolonged gestational days in appropriate antibiotic therapy group were significantly longer than that in not appropriate antibiotic therapy group (56 vs. 27 days, $p<0.0001$). [Conclusion] We should not use antibiotics in infection-free preterm labor cases. Antibiotic therapy to microbes positive cases could prolong the gestational period without neonatal complications.

ISP-19-4 The effects for administration of preterm labor with protocol alteration in tocolytic agents

Showa University
Masamitsu Nakamura, Tomohiro Oba, Tatsuya Arakaki, Hiroko Takita, Ryu Matsuoka, Junichi Hasegawa, Akihiko Sekizawa

[Objective] To evaluate the effect of long-term (LT) use of tocolytic agents (TA) to prevent the preterm delivery (PD) and to improve the perinatal outcomes. [Methods] A historical cohort study was performed. We revised the protocol for preterm labor (PPL) from (LT) to short-term tocolysis. The revised PPL was as follows : 1. Up to 48 hours or their uterine contractions (UC) controlled, TA were administered to pregnant women who had both regular UC and internal cervical os opened>1cm. 2. When TA started, corticosteroid would administer to reduce neonatal complications. Perinatal outcomes and given dose of TA before and after PPL revision were compared. [Results] 1444 deliveries after protocol PPL revision were compared to 1548 deliveries before that. Frequencies and total ampules (A) of ritodrine were 4.1% and 4654 A in previous PPL and 1.0% and 514 A in new one. Those of magnesium sulfate were 1.0% and 1574 vials (V) in previous protocol PPL and 0.4% and 193 V in new one ($p<0.01$). The PD before 36 and 28 weeks' gestation were 11.8% and 1.3% in previous PPL, and 10.6% and 1.2% in new one (ns). [Conclusion] There was no significant change in the PD before and after the protocol PPL revision. Because decrease in tocolytic agents TA didn't lead to the increase of PD. LT tocolysis wasn't effective to prevent the PD, and LT tocolysis for preterm labor should be reconsidered.

ISP-19-5 Effect of progesterone on human cervical fibroblast—from basic research to clinical significance

Nippon Medical School
Yoshimitsu Kuwabara, Saori Kanbe, Mirei Yonezawa, Nozomi Ouchi, Ryuhei Kurashina, Rintaro Sawa, Akihito Nakai, Toshiyuki Takeshita

[Objective] Recently, vaginal progesterone (P4) supplementation has been shown to significantly reduce the risk of preterm birth. This study was undertaken to assess the effect of progesterone on uterine cervix under different levels of inflammation and/or the timing of progesterone treatment. [Methods] Human uterine cervical fibroblast cultures were established and incubated for 12 h with 2.0 μg/mL LPS (high-LPS) or 0.2 μg/ml LPS (low-LPS) in the presence or absence of 1.0 μM P4 treated simultaneously (simultaneous P4 treatment) or 1 h prior to LPS stimulation (prior P4 treatment). Cellular mRNA was extracted and subjected to real-time RT-PCR analyses to assess the gene expression pattern of IL6, IL8, IL-1beta, PTGS, MMP1 and HAS2. [Results] The expression of IL8 and IL6 stimulated with high-LPS was not suppressed by simultaneous P4 treatment, but IL6 expression was significantly suppressed by prior P4 treatment. The expression of IL8 and IL6 stimulated with low-LPS was significantly suppressed by simultaneous and prior P4 treatment, and the suppression was more pronounced in prior P4 treatment. Other molecules showed similar expression patterns with the exception of HAS2 which was not suppressed by P4 in any condition. [Conclusion] Early or prophylactic administration of P4 is considered important to achieve effective P4 action to reduce the risk of preterm birth.

ISP-19-6 Laparoscopic Cervicoisthmic Cerclage to Prevent Preterm Birth in Second Trimester

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Ya-Min Cheng

A 36-year-old female, gravida 1, para 0 with a history of cervical cancer stage Ia1 status post knife conization 3 years ago, came to our hospital for prenatal care at 10th weeks of gestation on March 6, 2013. At her prenatal follow-up visit, short cervical length (1.5cm) measured via transvaginal ultrasound at the 13th weeks gestational. Conventional McDonald's cervical cerclage failed due to extremely short cervix. She was a candidate for a trans-abdominal cervicoisthmic cerclage due to her short cervix. Then she received a successful laparoscopic cervicoisthmic cerclage surgery at the 18th week of gestational age. Surgical procedure was described as follows : Under general endotracheal anesthesia, she was placed in the dorsal lithotomy position with Foley catheter insertion and no uterine manipulator used. The laparoscopy was performed through one 11mm umbilical port and three 5mm ancillary ports. One ring forceps covered with the gauze was put into the anterior cervical fornix and lower segment of uterus was compressed with retractor to reveal bladder reflection. Then the vesicouterine fold was incised and the bladder was dissected downward. The vesicouterine peritoneum was dissected and pushed the bladder downward gradually to prevent the injury to ureter, exposing the bilateral uterine vessels anteriorly. Otherwise, severe pelvic adhesions with uterus, left adnexa, sigmoid colon and cul-de sac were noted. After doing adhesiolysis, windows in the broad ligament medial to the uterine vessels at the level of the internal cervical os bilaterally were created, the posterior lip of broad ligament was push downward during the procedure to make sure that the ureter will go away from the cervicoisthmic region. The 5-mm Mersilene tape without needles was pulled through the windows and surrounded the cervix. The tape was then tied tightly anteriorly with five knots using an intracorporeal knot tying and the vesicouterine peritoneum was left without re-approximation. After the surgery, fetal cardiac activity was confirmed and the cervix length with 2.6cm trans-abdominal ultrasound examination. Post-operation follow up course was smooth. During her prenatal follow-up visit, there was no vaginal bleeding, vaginal watery discharge nor preterm uterine contraction. Scheduled Cesarean sections performed at 38th week of gestation and found filmy scar tissue covering the cerclage knot. The Mersilene tape was left in situ after surgery. Transabdominal cervicoisthmic cerclage was first described by Benson and Durfee in 1965 as an alternative obstetrical procedure in patients who have either failed two or more previous transvaginal cerclages or in whom a transvaginal cerclage is technically impossible to perform due to extreme shortening, or scarring of the cervix. Scibetta and colleagues first reported the use of laparoscopy cervicoisthmic cerclage since 1998 with the benefit of fast recovery and less postoperative pain. It is a safe and effective alternative to laparotomy for the placement of abdominal cervicoisthmic cerclage and may be used before and during a pregnancy. It is reported to have the complication of massive bleeding, suture migration, infection and preterm labor via transabdominal cervical cerclage procedures. To date there is no randomized controlled trial about the comparison between the laparoscopic approach and open technique, the evidence on the outcomes is still wanted. We present a pregnant case with a history of microinvasive cervical cancer who received knife conization complicated with an extremely short cervix and failed transvaginal cervical cerclage. She had a successful pregnancy after laparoscopic cervicoisthmic cerclage. This procedure is a minimally invasive, extremely safe and effective procedure in properly selected patients. The benefit of laparoscopic cervicoisthmic cerclages were confirmed from literature review. We believed that this is the first case who received laparoscopic cervicoisthmic cerclage during second trimester in Taiwan.

ISP-19-7 Comparison Between Nitroglycerin Dermal Patch And Nifedipine For Treatment Of Preterm Labor, a randomized clinical trial

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[Objective] The purpose of this study was to compare the effect of nifedipine and nitroglycerin (NG) dermal patch for taking control of preterm labor. [Method] The study was performed as a randomized clinical trial on women who had been admitted in the hospital diagnosed with preterm labor. In one group, nitroglycerin (NG) dermal patch and in the other group, nifedipine was prescribed. Then the women of the 2 groups were followed up to delivery and were 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 in order to have enough time for prescribing corticosteroids. [Results] The women of the 2 groups did not have any significant difference according to age, BMI, primary Bishop Score, gestational age at the time of tocolytic therapy, history of abortion, vaginal or cesarean 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 also, for 7 days [47 (78.3%) VS 37 (61.7%), p=0.046], than the women in nifedipine group. 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 statistically 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 and negligible in both groups. [Conclusion] NG patch is a more effective method for preterm labor control than nifedipine with regards to minimal side effects.

ISP-19-8 The effect of prophylactic cervical cerclage in triplet pregnancies

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[Objective] to evaluate the effect of prophylactic cervical cerclage in triplet pregnancies. [Methods] This is a retrospective study of 29 triplet pregnancies from 2002 to 2014. There were five pregnancies with prophylactic cerclage and 24 pregnancies without prophylactic cerclage. We compared the perinatal outcome in two groups. [Results] The criteria of our management of triplet pregnancies is 1) hospitalization at 24th week of gestation, 2) not to perform prophylactic cerclage. Prophylactic cerclage were performed 5 cases(17%). In four cases, cerclage were performed outside our hospital and before patient were referred. Two of those were suspected of cervical infection and the cerclage were removed. In non-prophylactic cerclage group, rescue cerclage were performed in three cases. There is no significant difference in the mean gestational age at delivery, 35w5d in prophylactic cerclage group and 34w0d in non- prophylactic cerclage group. There are five(5.7%) perinatal morbidity. One was associated with multiple anomalies, other four cases were delivered between 24th and 28th week of gestation. [Conclusion] The prophylactic cerclage in triplet pregnancy may increase the risk of preterm delivery. The importance of the prevention of the preterm delivery in triplet pregnancy is realized again regarding to perinatal outcome with or without the cerclage.

ISP-19-9 Cervical SLPI expression during pregnancy is regulated by progesterone in mouse

The University of Tokyo
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[Objective] Secretory Leukocyte Protease Inhibitor (SLPI) is a multifunctional secretory protein with anti-protease, anti-microbial and anti-inflammatory properties. We previously reported that cervical SLPI production increases during the progression of pregnancy. This study aimed to clarify the impact of progesterone on the regulatory mechanism of cervical SLPI expression. [Methods] Cervical SLPI expression was examined in a mouse model of preterm birth induced by a progesterone antagonist, RU486, in comparison with normal pregnancy. Additionally, the effect of the pharmacological blockade of steroid 5 alpha reductase type 1 (SRD5A1), a key enzyme of progesterone degradation, on cervical SLPI expression was analyzed. This study was conducted under the approval of ethics committee. [Results] In both normal pregnancy and the preterm birth model, cervical SLPI expression was significantly decreased at 24 h before delivery, whereas cervical SRD5A1 expression was elevated. SRD5A1 blockade maintained the expression of cervical SLPI and postponed the parturition possibly due to the impaired cervical ripening. [Conclusion] Our findings demonstrated SLPI expression at the cervix was influenced by progesterone metabolism. The reduction of cervical SLPI resulting from progesterone degradation by SRD5A1 might be a crucial step in cervical ripening prior to delivery.

ISP-20-1 Management of severe hypertension by nicardipine IV drip in pregnancyinduced hypertension after cesarean section

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[Objective] In pregnancy-induced hypertension (PIH) patients, the hypotensive treatment is switched to IV drip such as nicardipine in postpartum after cesarean section (C/S). [Methods] Fifty one PIH patients, including 27 preeclampsia (PE) and 24 gestational hypertension (GH) were enrolled. They were divided into two of level I (160 -179 mmHg) and level II (>79 mmHg in systolic BP (SBP)). There was 23 PE and 14 GH in levelI. After C/S, 1 to 6 mg/h of nicardipine was given by IV drip at 140-159mmHg for almost 2 days. The effective dose of nicardipine were evaluated. The changes on SBP were investigated focused on reascension. It was determined by transient increase in SBP>160mmHg or daily average SBP>160 mmHg. This study was accepted by ethical committee. [Results] The stable dose was greater in PE (1.9±0.8 mg/h) than that (1.5±0.6 mg/h) in GH, even though most PE patients belonged to level I. 2. Transient SBP reascension was seen in 39% PE and 36% GH in level I, while it was in 60% of GH in level II in spite of most patients (76%) taking oral administration. However, reascension of daily average SBP was seen in 13% of PE and 7% of GH in level I, while it was in 30% of GH in level II. In 2 of PE, IV drip was resumed. [Conclusion] In retrospective study, transient reascension was seen in about 40% of the patients, although reascension in SBP average was reduced.

ISP-20-2 Acute Pulmonary Edema in Preeclampsia and Gestational Hypertension : a Single-center Retrospective Study

Metropolitan Bokutoh Hospital
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[Objective] Acute pulmonary edema (APE) is one of the life-threatening events in preeclampsia and gestational hypertension, but the underlying mechanism is still unknown. To determine the risk factors of APE, characteristics in preeclampsia or gestational hypertension women, with or without APE, were assessed retrospectively. [Methods] Cases which diagnosed with preeclampsia or gestational hypertension at single tertial center from January, 2014 to August, 2015 were recruited for the study with patient's IC. Past history, urine protein, blood pressure and total infusion volume during the hospitalization were investigated in the medical records. [Results] During the study period, 89 cases were diagnosed with preeclampsia or gestational hypertension. Four cases were excluded because of twin pregnancy and one was because data were missed. Twelve APE cases were identified and they had higher blood pressure, more urine protein, and larger infusion volume. The cutoff value of the systolic blood pressure was 180mmHg, diastolic blood pressure 110mmHg, urine protein 2 g/day, and infusion volume 6550ml, respectively. [Conclusion] Higher blood pressure, severe urine protein, and excessive infusion volume were related to APE.

ISP-20-3 Magnesium sulfate may ameliorate oxidative stress and inflammation in preeclampsia

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[Objective] Oxidative stress and inflammation are involved in pathophysiology of preeclampsia (PE). The aim of this study was to evaluate antioxidant and anti-inflammatory activities of Magnesium sulfate ($MgSO_4$) in cases of PE and trophoblast cells. [Methods] Urine 8-isoprotein (oxidative stress marker) was measured before and after $MgSO_4$ therapy for early-onset severe PE. This research was approved by the ethics committee. Human trophoblast cells (TCL1) were treated with $MgSO_4$ (4-8mM, 24hr), and mRNA glutathione cysteine ligase modulatory subunit (GCLM) and glutathione cysteine ligase catalystic subunit (GCLC) were measured by quantitative RT-PCR. In order to investigate the effect of $MgSO_4$, following experiments were performed using $MgSO_4$-pretreatd cells. TCL1 cells were treated with H_2O_2 (100uM, 1hr) and reactive oxygen species (ROS) was examined by flow cytometry. TCL1 cells were treated with LPS (100ng/ml, 30min) and nuclear factor-κB (NF-κB) was verified by western blot analysis. [Results] Urine 8-isoprotein was decreased by $MgSO_4$ in three of four cases. In TCL1 cells, *GCLM* and *GCLC* were increased by $MgSO_4$. ROS was decreased by $MgSO_4$ (n=3, p=0.0112). Western blot analysis showed that nuclear NF-κB was inhibited by $MgSO_4$ (n=3, p=0.0233). [Conclusion] These results suggested that $MgSO_4$ may be effective for PE through inhibiting oxidative stress and inflammation on placenta.

ISP-20-4 Serial findings of cerebral imaging together with changes in blood pressure and biological marker in eclampsia

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[Objective] Cerebral imaging could diagnose eclampsia by detection of vasogenic edema. It is caused by broken autoregulation in cerebral blood flow due to possibly elevated systemic blood pressure (BP). Endothelial cell dysfunction might aggravate it. We retrospectively investigated serial findings of cerebral imaging and BP. [Methods] Eleven eclamptic women, 4 of antepurtum, 3 of intrapartum and 4 of postpartum onset were enrolled. Magnetic resonance imaging (MRI) and angiography (MRA) were taken two time. The serum concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) were measured. This study obtained the approval of the Ethical Review Board. [Results] Findings of posterior reversible encephalopathy syndrome (PRES) were seen after the onset immediately and disappeared one month after the onset. They were located on temporal, parietal and occipital lobe and basal nuclei. Vasospasm appeared from onset three days later and disappeared within one month later. BP had been increasing just before the onset and stabilized within a day. Serum concentrations of sFlt-1 were more increasing in eclampsia without proteinuria than it with proteinuria. [Conclusion] PRES appeared just after the onset together with elevated BP, while in some patients, vasospasms was present. The concentrations of sFlt-1 were not increasing in patients without preeclampsia.

ISP-20-5 A case of subarachnoid hemorrhage under the optimal blood pressure control after eclampsia without pregnancy induced hypertension

Chugoku Rosai Hospital
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We report a case of subarachnoid hemorrhage after postpartum eclampsia and reversible posterior leukoencephalopathy syndrome (RPLS) without pregnancy induced hypertension (PIH). Patient was 40 years old, primipara. On 40 weeks of gestation, an emergency cesarean section was performed due to arrest of labor. During the pregnancy and perioperative period, proteinuria and hypertension were not shown. On 4 postoperative days, eclampsia suddenly occurred with neck convulsion and increased deep tendon reflexes. Intravenous infusion of diazepam and $MgSO_4$ were immediately administered to prevent further convulsion. Her blood pressure increased to 160/90mmHg, and nicardipine was administered. Magnetic resonance imaging (MRI) revealed RPLS. Computed tomography (CT) did not show brain hemorrhage. Magnetic resonance angiography (MRA) did not show cerebral vascular anomaly, neither. We continued to control the blood pressure level, but the next day a sudden intense headache occurred. Brain CT revealed subarachnoid hemorrhage around cerebral falx, and mild paresis on her right side occurred. Cerebral vascular spasm did not occur after the hemorrhage. Her paresis gradually improved with rehabilitation, and she discharged after 25 postoperative days. A brain hemorrhage after eclampsia and RPLS can occur by under normotension, it is very important to undergo brain CT and MRI after eclampsia.

ISP-20-6 A case of hepatic infarction as a result of HELLP syndrome

Yokohama City University Hospital
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[Background] Hepatic infarction is a rare complications during pregnancy. [Case] A 35 year-old woman presented to our institute with high blood pressure of 160/90 mmHg and proteinuria at 27 weeks of gestation. Two days later, the patient complained sudden epigastric pain with high blood pressure (180/100 mmHg) and the blood test revealed elevated liver enzymes. She was performed an emergency cesarean section at 28 weeks 1 day of gestation, and an 800 g female was delivered. After delivery, the laboratory finding demonstrated extremely high liver enzymes (AST 6154U/L, ALT 6795U/L), which indicated severe liver injury. A computed tomography (CT) showed infarction of right hepatic lobe. The continuous hemodiafiltrations and plasma exchanges were undertaken. Laboratory findings were normalized 1 week after the initiation of the treatment. The patient was discharged 5 weeks after delivery. The hepatic infarction ameliorated by CT-scan 2 months after delivery. [Conclusion] Hepatic infarction is one of the crucial maternal complications. CT can be useful for diagnosis and should be considered when liver enzymes are exceedingly high. Introduction of intensive care is important to cure the disease.

ISP-20-7 ER stress regulates PlGF transcription and potential therapeutic strategy for pre-eclampsia

Sapporo Medical University
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[Objective] Placental endoplasmic reticulum (ER) stress is identified to be elevated in early-onset pre-eclampsia (PE) but is only very subtle in late-onset PE. ER stress-mediated placental protein synthesis inhibition, reduction in cell growth and proliferation, and activation of apoptotic cascade plays crucial role in pathophysiology of these pregnancy complications. In this study, we identified a novel mechanism for ER stress modulates angiogenesis via regulation of PlGF gene expression and its potential role in the low circulating PlGF levels found in PE. [Methods] We used placentas of term control and PE placentas with patient's Ic and also the human choriocarcinoma cell line, BeWo for analysing the effect of ER stress in PE. Several candidates for therapeutic reagents such as aspirin and statin tested under ER stress condition. [Results] Transcripts analysis in PE placentas showed that a decrease of PlGF mRNA and an increase ER stress markers, ATF4, ATF6a and ATF6b mRNA only in the early-onset PE placenta compared to term control placentas. In vitro study also showed siATF6 β+siATF4 double knockdown lead a synergistic effect in up-regulation of PlGF mRNA. Low dose aspirin up regulated the PlGF mRNA level in BeWo under ER stress. [Conclusion] These results further support that targeting of placental ER stress could provide a new therapeutic intervention for preeclampsia.

ISP-20-8 Circulating levels of C19MC-cluster microRNAs in pregnant women with severe preeclampsia

Nagasaki University
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[Objective] The aim of this study was to clarify the association between circulating C19MC microRNAs in maternal plasma and severe preeclampsia. [Methods] All samples were obtained after receiving written IC and the study protocol was approved by the IRB. Maternal blood samples (7ml) at 27-34 weeks of gestation were obtained from 20 pregnant women with severe preeclampsia (sPE group) and 20 uncomplicated pregnant women (NP group). The sPE group were classified into 14 cases of late-onset (sPELO group) and 6 cases of early-onset (sPEEO group). The plasma concentrations of C19MC microRNAs (miR-518b, -1323, -516b, -516a-5p, -525-5p, -515-5p, -520h, -520a-5p, -519d and -526b) were measured by quantitative real-time RT-PCR. [Results] The circulating levels of all 10 C19MC microRNAs in maternal plasma were significantly increased in the sPE group compared with the NP group. Plasma concentrations of all 10 microRNAs tested were significantly increased in the sPEEO group compared with the NP group, while plasma concentrations of 9 miRNAs were significantly increased in the sPELO group compared with the NP group. 8 miRNAs were significantly increased in the sPEEO group compared with the sPELO group. [Conclusion] This study demonstrated for the first time that the up-regulation of C19MC miRNAs occurred as a consequence of, not in advance of, the onset of preeclampsia.

ISP-20-9 Novel inflammatory markers of adipose tissue in the normal pregnancy and preeclampsia : New strategy into understanding of pathophysiology of the disease

Nara Medical University
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[Objective] Recently, the pathophysiology of preeclampsia (PE) is characterized by systemic exaggerated inflammatory response after the abnormal placentation. We investigated the inflammation in adipose tissue in the course of normal pregnancy and preeclampsia. [Methods] Under the informed consent, serums samples (n=10 each) were taken from normal pregnant women (in every trimester) and early onset severe PE patients. Free Fatty Acid (FFA, an inflammatory molecule in adipose tissue), chemokine MCP-1, Malondialdehyde (MDA, a marker of oxidative stress on lipid) and CIDEC (Fat Specific Protein 27, a marker of pathologic fat storage) were measured. [Results] FFA was increased in the course of normal pregnancy, and increased in PE. MCP-1 was also increased in PE, but decreased in normal pregnancy. MDA was increased in later pregnancy, and showed significant increase in PE. CIDEC showed no significant difference within pregnancy, or in PE than normal pregnancy. But interestingly, the basic concentrations of CIDEC showed 10 times difference between the subjects, unrelated to normal pregnancy or PE. [Conclusion] Our results in PE reflected inflammation in adipose tissue. However, decrease of MCP-1 in normal pregnancy showed a maternal safe guard against physiological insulin resistance. Preliminary finding in CIDEC telling us a need of research into the function of adipose tissue itself.

ISP-20-10 Effects of omega-3 fatty acids on Nod-like receptor 3 (NLRP3) inflammasome in decidual macrophages

The University of Tokyo
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[Objective] Omega-3 fatty acids (ω-3FAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are known to prevent preeclampsia (PE), a maternal systemic inflammatory disease. However, the mechanism is unknown. Nod-like receptor 3 inflammasome (NLRP3) has been shown to contribute to the pathogenesis of PE. The aim of this study was to test the effects of ω-3FAs on NLRP3 in decidual macrophages (DM). [Methods] Under informed consents and the IRB approval, amniotic membrane was collected at Cesarean section. DM were isolated and treated with either ATP or nigericine in the presence of lipopolysaccharide (LPS) in order to activate NLRP3. These cells were cultured in the presence or absence of EPA or DHA. Concentration of IL-1β and IL-18, and activation of caspase-1 in supernatants were measured by ELISA. [Results] EPA and DHA significantly reduced NLRP3-induced IL-1β ($72.5 \pm 5.8\%$, $p < 0.05$, $73.8 \pm 5.8\%$, $p < 0.05$, respectively) and IL-18 ($19.8\% \pm 7.3\%$, $p < 0.05$, $12.1 \pm 8.6\%$, $p < 0.05$) secretions, and caspase-1 activation ($46.8 \pm 6.5\%$, $p < 0.05$, $64.6 \pm 6.3\%$, $p < 0.05$) in DM. [Conclusion] ω-3FA control NLRP3 related inflammation in DM, explaining the clinical advantage of ω-3 FA in preventing PE.

ISP-21-1 Breast-feeding in complex disaster：results from the Fukushima Health Management Survey

Fukushima Medical University
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[Objective] The Great East Japan Earthquake and Tsunami caused catastrophic damage and the Fukushima Daiichi Nuclear Power Plant accident. The aim of this study was to examine feeding methods in this complex disaster. [Methods] We used the Fukushima Health Management Survey results. For comparison, Soso district was defined as an affected area and Aizu district was defined as a less affected area. To assess changes in the rates of three feeding methods (exclusive breastfeeding, exclusive formula feeding, or mixed breastfeeding) over time, the dates of birth were divided into four periods. The feeding methods of the newborns of each period were compared between the two areas. We also examined the area differences in the trends of feeding methods. [Results] There were no significant differences between the two areas regarding the feeding methods during the first and second periods. However, the methods differed significantly between the areas during the third and fourth periods. When each method was compared, we observed no significant change in the rate of exclusive breastfeeding across the time periods in the both areas. Regarding the trends in the rates of exclusive formula feeding, a significant increase was found in the affected area. [Conclusion] In this study, we found no differences between the two areas in term of the breast feeding rates.

ISP-21-2 Emergency preparedness on Maternal and Child health System with ALSO/BLSO—Lessons learned in the Great East Japan Earthquake Affected Areas

National Institute of Public Health[1], Keiju Medical Center[2], Yamanashi Red Cross Hospital[3], Nippon Medical School Tama-Nagayama Hospital[4], Osaki Citizen Hospital[5], Tohoku Medical Megabank Organization[6], Kameda Medical Center[7], Japan Association for Development of Community Medicine[8], Yamanashi University[9]
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[Objective] The Great East Japan Earthquake and Tsunami revealed health care issues that Japan already had. The birth outcomes of this catastrophic area tell us the importance of the pre-hospital OB care team in disaster response for mothers and babies. Now we are developing maternal and child shelter, safety confirmation system for mothers and babies, obstetrics training and network system in some governments. [Methods] Advanced disaster response planning includes adequate representation for special populations, addressing issues ahead of time, education, training, preparation. The Basic Life Support in Obstetrics (BLSO) has been assessed to prepare participants to manage labor and obstetrical emergencies in disaster. [Results] Pre-hospital resuscitation, communication in transition to hospital care can be improved when pre-hospital and hospital providers share a conceptual framework. BLSO is one of the effective tools for disaster preparedness and we should enlarge the emergency training for all of the medical team and try to have a standardized database for special populations and special tasks. [Conclusion] Empowering the OB providers in the community and organizing roundtable meetings with the midwife, disaster relief teams and the local government could vocalize community needs and develop disaster preparedness and response team in obstetrics to save the next generation.

ISP-21-3 The Optimal Period for the Deliveries of Diamniotic Dichorionic Twin Pregnancies with Selective Fetal Growth Restriction

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[Objective] To determine the optimum delivery timing for dichorionic diamniotic (DD) twin pregnancies with fetal growth restriction. [Methods] Unselected DD twin pregnancies after 26 weeks of gestation were recruited for this retrospective study (N=144), which was conducted at a tertiary referral perinatal center in the south part of Japan. Perinatal mortality was compared between DD twins with at least one fetal growth restriction (FGR) and without fetal growth restriction. [Results] Perinatal outcome data were recorded for 100% of the 72 twin pairs that completed the study (n=39 pairs without FGR, n=33 pairs with at least one FGR). Overall perinatal mortality was the only 1 intrauterine fetal death in this study. The risk of cerebral palsy and developmental disorders fall 5.9% (6/101 infants) among the infants without FGR to 0% (0/40 infants) among infants with FGR. The gestational week at birth is the only one independent factor for perinatal mortality and morbidity with logistic analysis. [Conclusion] In this small study, DD twin pregnancies with FGR did not show the statistically different for perinatal mortality and morbidity compared to without FGR. Further study is needed to determine the optimum delivery timing for DD twin pregnancies with FGR.

ISP-21-4 Interlocking of twins may cause malpresentation and malrotation of the vertex first twin ; Four case reports of failed trial of labor

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Failed trial of labor (TOL) in twin pregnancy has a high risk of complications for both mother and baby. After commencement of the active management protocol in October 2012, 64 twin TOLs were attempted, and 90.6% of cases achieved successful vaginal delivery at our facility. The current protocol consists of 1) induction of labor between 37 to 38 week's gestation, 2) artificial amniotomy after the engagement of the fetal head, 3) use of neuraxial analgesia, and 4) appropriate informed consent. Among 6 cases of failed TOL, cesarean sections were performed for both twins in 4 cases, and for the second twin in 2 cases. Herein we analyzed former the 4 cases of failed TOL. All cases were primipara, and interestingly, failed TOL because of obstructed labor of the first twin. Induction of labor was performed for diamniotic twins with vertex-vertex (case 1-3) and vertex-transverse (case 4) presentation. In all cases, twin A was overridden by twin B and was in the occiput posterior position. Moreover, internal rotation of twin A was blocked by twin B, leading to obstructed labor. No deceleration of fetal heart rates was observed. Emergent cesarean sections were performed with good fetal outcomes. Interlocking of twins can cause malpresentation and malrotation of the vertex first twin. Monitoring the positional relation of twins may be important for early detection of obstructed labor.

ISP-21-5 Retrospective analysis of 27 cases transported from local clinic due to massive postpartum hemorrhage

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[Objective] We analyzed cases transported from local clinic to our perinatal center due to massive postpartum hemorrhage. [Methods] From Jan. 2012 to Jul. 2015, we chose 75 cases who matched the criteria of postpartum hemorrhage defined by the Perinatal Committee in JSOG. Of which, we selected 27 cases who were transported from local clinic and analyzed cause of bleeding, conditions including shock index (SI) and outcomes of those patients. We got IC from these patients. [Results] In 27 cases, total amount of blood loss was estimated at 4871ml and transfused RBC and FFP was 12.2 and 14.0U, respectively. Out of 27 patients, TAE and ATH was performed to 4 (15%) and 2 (7%) patients respectively. The most frequent case of bleeding was trauma to birth canal including vaginal and vulvar hematoma found in 8 (30%) cases. In these 8 cases, 6 (75%) cases were delivered with vacuum or forceps under epidural anesthesia. Before blood transfusion, we administrated colloid solution as early as possible. Consequently, average SI at the time of transportation and start of blood transfusion were improved from 1.22 to 1.08. [Conclusion] In a case of vacuum or forceps delivery under anesthesia, we should manage more carefully to prevent birth canal trauma. When a doctor in a local clinic encounters massive postpartum hemorrhage, colloid solution transfusion must be done as early as possible.

ISP-21-6 Transcatheter arterial embolization as first-line rescue in intractable primary postpartum hemorrhage : assessment, outcome, and subsequent fertility

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[Objective] To assess the risk factors for intractable and controllable postpartum hemorrhage (PPH) and to evaluate the safety, efficacy and outcome of transcatheter arterial embolization (TAE) in treating intractable PPH. [Methods] An emergency PPH rescue system including the 24-hour available TAE was established in a geographic area with about 7 million people in 2004. TAE with gelatine sponge particles placed on bilateral uterine or internal iliac arteries served as the first-line treatment for intractable PPH. Delivery methods, parity, causes of bleeding, clinical vital signs, coagulopathy, success rate, resumption of menstruation, and subsequent pregnancy outcome after TAE were recorded and compared with the χ^2, student t-test and multivariate logistic regression analysis. [Results] From 2005 to 2013, 301 women experienced PPH, of whom 178 had controllable PPH and 123 intractable PPH. Tachycardia and disseminated intravascular coagulation (DIC) were significant risk factors for intractable PPH. All of the women with intractable PPH underwent TAE, and 89 (72.3%) were transferred by ground transport from other clinics/hospitals to receive treatment in this system. The mean travel distance was 15 ± 12.5 km. The mean time of order to angiography room was 24.9 ± 14.2 minutes. The mean blood loss due to PPH before TAE was 2247 ± 1482 ml (range, 900-11,110 ml). First TAE successfully controlled bleeding in 118 of the 123 (95.9%) women with intractable PPH. Of the 70 women with complete followed up, 69 (98.6%) recovered menstruation. Twenty-three women tried to get pregnant after TAE and 19 (82.6%) of them became pregnant, giving birth to 12 term live infants. [Conclusion] TAE was safe and effective in treating intractable primary PPH with a high success rate and preservation of menstruation and fertility.

ISP-21-7 To assess cervical dilatation and position of fetal head during labor using wireless mobile ultrasound device

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[Objectives] Digital vaginal examination has always been the gold standard to evaluate fetal status during labor. However it can be inaccurate, subjective and uncomfortable for mother. Also, there is a risk of introducing infection with frequent examinations. Recently accumulated data on intrapartum sonogram seems very promising as a substitute of digital examination. However, the working of the ultrasound has raised several concerns as the machines are usually heavy and have disadvantage on immediacy. To overcome such disadvantages, a wireless mobile ultrasound device 'Sonon' operating on the mobile display systems has been introduced. In this study, we have evaluated the possibility for the replacement of intrapartem sonogram to vaginal examination. [Material and Methods] To evaluate Sonon, first, we have investigated correlation between conventional sonography and Sonon by fetal biometry. Second, we have investigated sonopartogram using transperineal assessment of cervical dilatation, effacement and fetal head station. After obtaining informed consent from all participants, 23 pregnant women were enrolled to comparative study using fetal biometry between conventional ultrasonography and Sonon during antepartal period. Since this portable ultrasound machine 'Sonon' is developed recently, there were not enough to reliable data in obstetric fields, so it was important to investigate the collections and analyses of raw values of fetal biometry. After then we had measured fetal weight in pregnant women during labor and compared with birth weight of neonate. We recruited 8 women, who were in the labor process, to participate in serial comparison of cervical dilatation, length, Angle of progression (AOP) and head symphysis pubis diameter (HSD) with sonopartogram using Sonon by one examiner and serial digital vaginal examination consisting of cervical dilatation effacement, and station by another one examiner. Bivariate correlation analysis, linear regression, Pearson correlation, and Spearman's rank correlation were performed to analyze the data collected. [Results] Compared to conventional sonography, Sonon had revealed good correlation in estimated fetal weight ($p < 0.001$) and true neonatal birth weight ($p < 0.001$). The intrapartum sonogram consisting of cervical dilatation ($p < 0.001$), cervical length (P=0.032), AOP (P=0.001) and HSD (P=0.008) had shown strong correlation to the digital vaginal examination. [Conclusion] A newly developed wireless mobile ultrasound device 'Sonon' showed good correlation with conventional ultrasonography and vaginal digital examination. Considering its convenience, Sonon can be a good alternative to reduce frequent vaginal examinations.

ISP-21-8 Consecutive change of cervical length in placenta previa for the prediction of emergent cesarean delivery

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[Objectives] To assess the predictive performance of serial cervical length measurements as a predictor for emergent cesarean section in women with placenta previa. [Methods] This was retrospective cohort study including 93 women with placenta previa. Cervical lengths were measured transvaginal ultrasound from early gestation until delivery. We compared clinical characteristics, serial change of cervical length, and outcomes between emergent cesarean delivery group (case group) and elective cesarean delivery group (control group). Predictive value of cervical change in predicting emergent cesarean delivery was evaluated. [Results] A total of 93 women were analyzed ; 31 women had emergent cesarean delivery due to massive vaginal bleeding. Case group had abrupt cervical change during early third trimester compared with control group. On univariate analysis, hospitalization, cervical change between 2nd and third trimester, and nullipartiy were significantly associated with emergent cesarean delivery. On multivariate analysis after adjusted by maternal age, hospitalization, placenta totalis, ant placenta, cervical change, nulligravidity, nulliparity, previous cesarean delivery, previous preterm delivery, only hospitalization, cervical change remained significantly associated with emergent cesarean delivery. Analyses of the ROC curve showed that cervical change could be the predictor of emergent cesarean delivery (area under the curve 0.676, $p = 0.041$) with optimal cutoff for predicting emergent cesarean delivery of 1.40. [Conclusions] Tranvaginal sonography for CL measurement can be helpful for predicting emergent cesarean delivery.

ISP-22-1 Relationship between serum D-dimer levels and placental findings in pregnant women with fetal growth restriction

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[Objective] Serum D-dimer levels show a gradual increase in the late stages of gestation. The main cause of this elevation is thought to be D-dimer production in the placenta. We investigated the relationship between the D-dimer level and placental findings in cases of fetal growth restriction (FGR). [Methods] We enrolled 83 pregnant women with FGR, who underwent blood D-dimer level testing at 35 or 36 weeks of gestation and delivered within 14 days of the test. Twenty-six of 83 subjects had pregnancy induced hypertension (PIH ; PIH group), and the remaining 57 subjects were in the non-PIH group. In 64 of 83 subjects, the placenta was examined pathologically. Serum D-dimer levels, placental weight, and pathological findings such as fibrin deposition, infarction, and chorangiosis were evaluated retrospectively. [Results] D-dimer levels were positively correlated with placental weight in the non-PIH group ($R = 0.41$, $p < 0.01$). Serum D-dimer levels in the PIH group (3.6 ± 2.9 μg/mL) were significantly greater than those in the non-PIH group (2.2 ± 1.4 μg/mL) ; however, placental pathology did not affect the D-dimer levels. [Conclusion] Placental D-dimer production may increase serum D-dimer levels in pregnant women with FGR. Moreover, in the PIH group, elevation of D-dimer levels may be affected by the D-dimer produced not only in the placenta but also in the systemic circulation.

ISP-22-2 Nuchal cord complication combined with small for gestational age increases the risk of fetal distress during labor

Warabi City Hospital
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[Objective] The aim of this study was to evaluate if a nuchal cord combined with small for gestational age (SGA) will increase the risk of perinatal complications during labor. [Methods] The study was approved by ethics commitee. 1749 singleton term deliveries were enrolled retrospectively. Patients were separated into two groups by occurence of nuchal cord at birth for comparison of perinatal complications. Multivariate logistic regression analyses and odds ratio (OR) and 95% confidence interval (CI) were used to compare the risk. [Results] The risks of augmentation during labor, prolonged second stage of labor, non-reassuring fetal heart rate, instrumental delivery and Cesarean section for fetal distress increased in any nuchal group. There is no significant difference of neonatal outcome between two groups. However, fetus has an obvious higher risk to develop SGA (adjusted OR=1.90, 95%CI, 1.32-2.73) in any nuchal cord group. The risk of fetal distress is affected by fetal sex, where male SGA fetus with any nuchal cord appear to have a significant higher risk in labor compared to control group (adjusted OR=4.30, 95%CI, 1.25-12.98). [Conclusion] Nuchal cord complication combined with SGA increased the risk of fetal distress during labor. Our results suggest that evaluation of fetus body weight is also important in anternal ultrasoundgraphy if a nuchal cord is found.

ISP-22-3 HDlive in assessment of fetal intrathoracic and intra-abdominal anomalies

Kagawa University School of Medicine
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[Objective] To reconstruct fetal intrathoracic and intra-abdominal anomalies reconstructed using HDlive. [Methods] Twelve abnormal cases at 24-34 weeks were included. The study was approved by the IRB. [Results] In situs inversus, mirror image of normal cardiac structures can be recognized using HDlive inversion mode. In meconium peritonitis, small intestinal dilatations were clearly identified, and dilated loops were seen to have irregular calibers. In diaphragmatic hernia, the spatial relationship between the left-sided stomach and right-side-deviated normal heart was noted. In biliary atresia, an oval cyst connected to gallbladder with clear relationship to surroundings was identified by HDlive inversion mode. In enteric duplication cyst, its thick wall and the large amount of thick debris inside it were more discernible using HDlive. In hydronephrosis, HDlive inversion mode realistically showed the anatomical relationship of renal pelvis with spine and stomach. In case of multicystic dysplastic kidney, numerous rounded cysts form the kidneys, umbilical vein and gallbladder were observable. In persistent cloaca, bicornuate uterus with bilateral hydrosalpinx, and ascites were seen. [Conclusion] HDlive is useful in monitoring intrathoracic and intra-abdominal lesions and probable complications that cannot be easily identified using conventional 2D/3D ultrasound.

ISP-22-4 Retrospective study on the association of underlying causes of polyhydramnios with fetal growth

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[Objective] In pregnancy complicated with polyhydramnios (PHA), accurate estimation of its cause is critical in clinical management. This study aimed to clarify the relevance of the causes of PHA to fetal weight. [Methods] This study was conducted under approval our ethics committee. PHA were diagnosed when amniotic fluid index (AFI) is 25 and over. Perinatal records of 41 pregnancies with PHA managed in our hospital from 2011 to 2015 were reviewed. Those pregnancies were categorized based on the birth weight, light for date (LFD), appropriate for date (AFD) and heavy for date (HFD). We also divided AFD/HFD into anomaly group and without anomaly group. [Results] The investigated PHA pregnancies consisted of 12 cases of LFD, 9 cases of HFD and 20 cases of AFD. Chromosomal aberrations (trisomy18) were revealed in all the fetuses of LFD. Fetal anomaly was confirmed in 22 cases of AFD/HFD. Among AFD/HFD, there were no statistical difference in the maximum AFI during pregnancy and the gestational age when PHA was diagnosed. Gestational age at delivery was significantly earlier in the anomaly group. Spontaneous normalization of AFI until delivery occurred in 4.6% of the anomaly group and in 42.9% in the other. [Conclusion] The fetal growth pattern is an important clue to estimate the causes of PHA.

ISP-22-5 Can fetal electrocardiograph find high-risk fetal mice of brain hemorrhage?

Tohoku University[1], National Center for Child Health and Development[2]
Takuya Ito[1], Rika Sugibayashi[2], Takahiro Minato[1], Ken Haneda[1], Naoaki Sato[1], Yupeng Dong[1], Nobuo Yaegashi[1], Yoshitaka Kimura[1]

[Objective] In clinical settings, high-risk fetus of brain hemorrhage with cardiotocomonitors is difficult. In this study, we find the high-risk murine fetus by fetal electrocardiograph (FECG) with short-term variability (STV). [Methods] Mice in Junk group were given unbalanced-nutrients (fat-rich/protein-low) while mice in Normal group were given balanced-nutrients. Both groups were challenged by 3-sets of ischemic-reperfusion. About 80% incidence rate of brain hemorrhage was observed after the 3-sets of ischemic-reperfusion in the Junk group. The ischemic-reperfusion was monitored by the FECG and ultrasound which detected the brain hemorrhage. STV at 3 conditions before the ischemic treatment to the onset of brain hemorrhage (pre-ischemia, 1st ischemia, and 1st reperfusion) was evaluated. [Results] Heart rate reduction at the 1st ischemia was recognized in the same manner in both groups. In the Normal group, STV was increased at the 1st ischemia and reduced at the 1st reperfusion. In the Junk group, STV was reduced at the pre-ischemia without obvious increase at the 1st ischemia, but increased pronouncedly at the 1st reperfusion. [Conclusion] In both groups, transient bradycardia induced by the ischemia was observed while STV showed different dynamics. STV calculated from FECG could be used to find high-risk fetal mice of brain hemorrhage.

ISP-22-6 Prenatal resolution of microcystic congenital cystic adenomatoid malformation (CCAM) : a report of two cases with different initial CVR (CCAM volume ratio)

Okayama Medical Center
Satoe Kirino, Kazumasa Tani, Moe Yorozu, Satomi Yamashita, Mizuho Yoshida, Saya Tsukahara, Yoko Tateishi, Kazumasa Kumazawa, Katsuhiko Tada

[Background] 17% of fetal CCAM are reported to become sonographically undetectable before birth and their related factors are microcystic type and low CVR. [Case report] Case 1 ; A 30-year-old woman G1P0 was referred at 21 weeks of gestation with a hyperechoic lesion (CVR=0.20) in the left lower lung lobe. Without any other abnormalities, MRI confirmed this finding. Repeated ultrasound scans showed the lesion became identical with the normal left upper lobe around 30 weeks. A female baby was delivered vaginally at 36+0 weeks weighing 2568g with Apgar score 7/8. Contrast enhanced thoracic CT at 3 months old revealed no lung mass. Case 2 ; A 30-year-old woman G0 was consulted at 26 weeks on a highly echogenic lesion (CVR=2.60) over the left thorax with cardiac shift. MRI at 26 weeks was consistent with this finding without any other anomalies. The lesion gradually decreased in size and the cardiac shift retuned to the left through the routine sonography scans before 30 weeks. MRI at 36 weeks showed normal thorax. A cesarean section was performed for CPD at 41+4 weeks to deliver a male baby weighing 3014g with Apgar score 8/9. Plain CT on day5 did not reveal any lung abnormalities. [Conclusion] These resolutions may be a part of normal fetal lung development, therefor careful decision-making is needed for microcystic CCAM even with CVR1>6.

ISP-22-7 Effect of ethnicity on fetal behavior : comparison of Asian and Caucasian populations

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[Objective] To evaluate ethnic difference in fetal behavior between Asian and Caucasian populations. [Methods] Fetal behavior was assessed by Kurjak's antenatal neurodevelopmental test (KANET) using 4D ultrasound between 28 and 38 weeks gestation. 89 Japanese and 78 Croatian pregnant women were studied. Total KANET score and values of each parameter were compared.(approved by IRB) [Results] There were significant differences in maternal age, parity, birth weight, and Apgar scores between both groups ($P<0.0001$). No significant differences in birth age and sex ratio between both populations. Total KANET score was normal in both groups. There was a significant difference in total KANET scores between Japanese (median, 14 ; range, 10-16) and Croatian fetuses (median, 12 ; range, 10-15) ($P<0.0001$). When comparing individual KANET parameters, we found significant differences only in 4 fetal movements (isolated head anteflexion, isolated eye blinking, facial alteration or mouth opening, and isolated leg movement). [Conclusion] Ethnicity should be considered when evaluating fetal behavior, especially fetal facial expressions. Although there was a difference in total KANET score between Japanese and Croatians, all scores in both groups were within normal. Ethnical differences in fetal behavior do not affect total KANET score, but close follow-up should be continued in some borderline cases.

ISP-22-8 The study of murine short term variability at each fetal stage

Tohoku University
Takahiro Minato, Takuya Ito, Ken Haneda, Yupeng Dong, Rika Sugibayashi, Naoaki Sato, Yoshitaka Kimura, Nobuo Yaegashi

[Objective] Baseline variability (short term variability) is an important index of fetal condition under hypoxia or brain hemorrhage. It appears to be regulated by autonomic nervous system. As autonomic nervous system matures, STV increases in fetal sheep. This maturation is based on the change of gene expressions. However, it has not been measured numeric data at each growth stage in mouse ; we cannot study the relation between STV and gene expressions during each developmental stage. [Methods] C57BL/6 fetal mice (term 19 days) were used in this study under approval from our University Research Ethics Board. Because their autonomic nervous system develops at the latter half of pregnancy, the STVs with electrocardiogram were measured at the beginning of the latter half period (15.5 days of gestation n=3) and before the delivery (18.5 days of gestation n=3). [Results] For each mouse, we recorded over 1,000 R waves and calculated the RR intervals. The STVs at 15.5 days of gestation were 3.33ms, 2.30ms and 2.32ms. On the other hand, the STVs at 18.8 days of gestation were 4.70ms, 6.05ms and 6.57ms, which were longer than those at 15.5 days of gestation. [Conclusion] STV increased as gestational day proceeds in fetal mice. We would like to make reference value of STV at each pregnant stage for next steps.

ISP-23-1 Vaginal inflammatory preconditioning triggers fetal brain inflammation which contributes to block acute fetal death in response to amniotic LPS

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[Objective] Amniotic infection often has a pathologic maternal source, such as chorioamnionitis (CAM) which is most commonly an ascending disease derived from ongoing bacterial vaginosis (BV). However, there is no evidence to prove whether it is necessary to use different clinical treatments for the CAM patient who with or without subclinical BV respectively. [Methods] An ascending mouse model using two steps of administration LPS into the vagina and the amniotic fluid was developed. On gestation day 18, 460 fetuses derived from 70 pregnant mice were selected from 171 pregnant mice for the highest quality of sample population for analysis. [Results] Vaginal LPS precondition induces a faster inflammatory reaction, different area of brain to active in response to amniotic LPS resulting protect fetus from fetal brain damage. With vaginal LPS precondition, higher survival ratio of fetuses (100% in VAF Vs 59% in AF) in response to amniotic LPS at the endpoint 3 hours (ρ=0.0002, Hazard Ratio : 15.12 (Vs. AF), 95% CI of ratio : 3.587 to 63.76). Supporting data is from FECG data of AF 1.5hs with a continuously extension of the R-R interval by 1.5 folds. [Conclusion] We suggested that anti-inflammation cure should be considered carefully about the pathologic period during treatment ascending CAM patient in obstetrics.

ISP-23-2 The effect of maternal screening for HBV and perinatal HBV prevention program

Kobe University
Yuki Sasagawa, Masashi Deguchi, Akiko Takeda, Kenji Tanimura, Mayumi Morizane, Ichirou Morioka, Hideto Yamada

[Objective] The aim of this study is to assess the effect of maternal screening for HBV and perinatal HBV prevention program. [Methods] With approvals from institutional ethics boards, this study was performed prospectively. 3102 pregnant women delivered at our hospital between Jul. 1, 2008 and Jun.30, 2015 and their neonates were participated in this study. HBs antigen (HBsAg) was measured during the first trimester as a maternal screening. HBe antigen (HBeAb) was measured for the HBsAg positive patients. All neonates delivered from HBsAg-positive women were given HBIG and HB vaccine based on the Japanese HBV prevention program after birth. [Results] Of 3102 pregnant women, 33 were positive for HBs antigen. 10 of the 33 were positive for HBe antigen. Two exacerbation cases were observed among the patient with positive for HBeAg, HBsAg and HBeAg, AST, ALT and HBV-DNA titers increased in both exacerbation cases. HBV prevention program was accomplished for all neonates, and consequently, vertical infection was not observed. [Conclusion] We find that perinatal HBV prevention program is so effective. HBsAg, HBeAg, AST, ALT and HBV-DNA titers seem useful for evaluating patient's condition, but it seems difficult to predict exacerbation by these factors. Careful follow up is necessary to exclude exacerbation, for the women with HBeAg positive result.

ISP-23-3 Maternal blood screening for congenital cytomegalovirus infection of the infants

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[Objective] The aim of this study was to evaluate usefulness of blood antibody screening for congenital cytomegalovirus (CMV) infection using maternal serological tests. [Methods] The institutional ethic boards approved this prospective cohort study and informed consent was obtained. Women underwent measurements of the CMVIgG early in pregnancy and IgG avidity (AI) at 16–18 gestational weeks (GW). The IgG-negative women received educational enterventions and IgG was measured at 35–36 GW. Women with AI＜45% underwent measurements of CMVIgM, antigenemia, and PCR analysis. All neonates underwent urine PCR analysis for CMVDNA. [Results] Of a total of 1,940 women, 561 (28.9%) were IgG-negative ; 5 had IgG seroconversion ; and one neonate with asymptomatic infection was detected. Of 1,379 IgG-positive women, 142 had AI＜45%, and two neonates with congenital infection (1 asymptomatic and 1 symptomatic) were detected. Of 1,237 women with AI＞45%, 6 neonates with congenital infection (4 symptomatic and 2 symptomatic) were detected. [Conclusion] The present study demonstrated that 3 of 9 neonates with congenital infections were caused by CMV primary infection of mothers, and the remaining 6 were non-primary infection. The results suggest maternal antibody screening has limitations. Neonatal urine CMV screening might be useful to detect effectively congenital infection caused by non-primary infection.

ISP-23-4 A case of fetal cytomegalovirus infection in which maternal IgM antibodies were absent

Kyushu University
Minoru Kawakami, Emiko Hara, Nobuhiro Hidaka, Yuka Sato, Yukiko Kondo, Masaharu Murata, Yasuyuki Fujita, Kiyoko Kato

Cytomegalovirus (CMV) infection is the most common intrauterine infection worldwide, and the clinical manifestations are potentially severe. Typically, the diagnosis of acute CMV infection in pregnancy is based on positive results for maternal IgM. Herein, we present a case of a fetal CMV infection in which maternal CMV-specific IgM antibodies were absent. The patient was a 29-year-old primipara. At 24 weeks' gestation, she was detected fetal ascites, growth restriction (-2.3 SD), and a hyperechoic bowel by ultrasound scan. Fetal anemia was strongly suspected based on the markedly elevated fetal MCA-PSV value at 84.6 cm/s (2.5 MoM). We performed umbilical cord sampling ; mild anemia was noted (hemoglobin level, 9.2 g/dL). Maternal blood tests for IgM against TORCH revealed negative results. But we strongly suspected congenital CMV infection based on the sonographic and cord blood examination findings. PCR using amniotic fluid drained at 25 weeks and 3 days revealed CMV-DNA ; congenital CMV infection was diagnosed definitely. Fetal condition became worse, and at 26 weeks and 2 days, fetal death was noted. The pathological examination of the placenta after stillbirth revealed CMV placentitis. This case suggests that maternal CMV-specific IgM antibodies are not reliable for excluding CMV infection in cases of fetal infection with characteristic sonographic findings.

ISP-23-5 Malignant tumor in pregnancy : A clinical study of 22 patients

Jikei University
Momoko Inoue, Akiyo Oonota, Naomi Tagawa, Akiko Konishi, Eri Yoshii, Michiko Suzuki, Hiroaki Aoki, Tomohiro Tanemoto, Osamu Samura, Aikou Okamoto

[Objective] Malignant tumor in pregnancy is uncommon. The incidence is approximately 1 in 1,000 pregnancies. The most common malignancies found in pregnancy women include cervical cancer, breast cancer, melanoma, and malignant lymphomas. The objective of this study was to investigate the clinical characteristics in coexistence of pregnancy and malignancy. [Methods] The clinical records of 22 pregnant women with malignancies treated at multi-center between January 2006 and September 2015 were reviewed. [Results] The mean age of all cases was 35 years old (range 21–39). Seventeen cases (77.3%) continued pregnancy, and 5 cases (22.7%) were terminated by therapeutic abortion. Treatment during pregnancy was performed in 10 cases. Of these, 6 cases received chemotherapy, and 4 cases received surgery. Type of malignancy was as follows : cervical cancer, 6 ; ovarian malignancies, 6 ; breast cancer, 4 ; leukemia, 2 ; lymphoma, 2 ; thyroid cancer, 1 ; gastric cancer, 1. Eight cases (57.1%) had preterm delivery. Of these, 6 cases were iatrogenic preterm delivery. There were no severe complications of the newborn baby in fifteen cases. [Conclusion] Management of the pregnant woman with cancer must be individualized. Discussion must be undertaken with the patient, her family, oncologists, maternal fetal medicine specialists, and neonatologists.

ISP-23-6 Adenocarcinoma Located in Pancreatic Tail During Pregnancy：A Case Report and Literature Review

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Pancreatic cancer is the sixth most common cause of cancer-related death in the Japanese women and the prevalence of pancreatic tail cancer is almost 5% in the whole pancreatic cancer. The antepartum diagnosis of pancreatic tail cancer is extremely rare, and, to our best knowledge, with only one case previously reported in the English literature. Optimizing both maternal and fetal health outcomes is especially challenging because the interventions during pregnancy often pose significant risks to both the mother and the developing fetus. Here, we report a 32yo Japanese woman, G3P2, complicated by DD twins, was transferred to our tertiary center at 26 weeks of gestation, who was diagnosed having adenocarcinoma located in pancreatic tail. We review the literature on the management issues confronted in this unique clinical situation.

ISP-23-7 Factors associated with depressive symptoms during mid-pregnancy at a Japanese University Hospital

Tokyo Medical University
Hideto Shimada, Hiroe Ito, Keiichi Isaka

[Objective] Depression during pregnancy can have clearly harmful effects on both mothers and children. It is necessary to examine the factors associated with depressive symptoms in order to better understand pregnant women, which could then lead to improvements in obstetrics and general hospital psychiatry. Because previous studies have examined women in late pregnancy, the present study examined relevant factors of depressive symptoms in mid-pregnancy. [Methods] Pregnant women between 12-23 weeks gestation and aged＞20 years were recruited at a University Hospital from April 2014 to September 2014. Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale. [Results] Among 369 eligible pregnant women, 72 participated in the study. In multivariate logistic regression analysis, depressive symptoms were significantly associated with psychiatric history and unplanned pregnancy. [Conclusion] Depressive symptoms during mid-pregnancy were associated with psychiatric history and unplanned pregnancy among pregnant women who visited a university hospital. We recommend multiparas as well as primiparas be asked about unplanned pregnancy in clinical settings. Due to some major limitations, further studies are needed to replicate our findings.

ISP-23-8 A case of successful live birth in a woman on long-term hemodialysis

Kyushu University
Yurie Nakamura, Kenta Murakami, Yukiko Kondo, Yuka Sato, Emiko Hara, Masaharu Murata, Nobuhiro Hidaka, Yasuyuki Fujita, Kiyoko Kato

Pregnant women with end-stage renal disease have increased risk of adverse outcomes at all trimesters. Major maternal complications include spontaneous abortion, premature delivery, polyhydramnios and hypertension. A 40-year-old woman requiring hemodialysis for end-stage diabetic nephropathy with type 1 diabetes mellitus was transferred to our hospital at 17 weeks of gestation. Because her glycemic control was poor and HbA1c level was around 7%, we administered insulin dosage by using sliding-scale based on food intake. Obstetricians, renal physicians, diabetologists and neonatologists discussed and decided management policy as follows：1. increase dialysis time from 15 hours to 20 hours per week, 2. maintain pre-dialysis blood urea nitrogen level at less than 50 mg/dL, 3. increase dry weight at 200-300 g per week. 4. maintain hemoglobin level at 10-11 g/dL. We administered nifedipine as a tocolytic agent for increased uterine contraction from 21 weeks of gestation. After around 30 weeks of gestation, hypertension was worsened. At 33 weeks 5 days of gestation, we performed cesarean section because of non-reassuring fetal status. A female infant weighing 1,820g with Apgar scores of 8 and 9 points was delivered and started neonatal care. Well-coordinated and efficacious teamwork is essential for successful outcome of pregnancies with chronic hemodialysis.

ISP-24-1 Impact of a history of myomectomy on cesarean section

The University of Tokyo
Asuka Yoshiara, Seisuke Sayama, Rieko Shitara, Toshio Nakayama, Takayuki Iriyama, Atushi Komatsu, Atushi Nagamatsu, Yutaka Osuga, Tomoyuki Fujii

[Objective] Women with a history of myomectomy often undergo a cesarean section in consideration of the risk of uterine rupture due to myomectomy surgery. This study aimed to clarify the impact of prior myomectomy on cesarean section (C/S). [Methods] This study was conducted under approval of our ethics committee. Clinical data including gestational age, infant weight, intraoperative blood loss and operation time were analyzed in 56 women of singleton pregnancy who underwent elective C/S with a history of myomectomy (group M). Group M were categorized based on the procedures into laparoscopic myomectomy (LM, n=19), laparoscopic assisted myomectomy (LAM, n=19) and, abdominal myomectomy (AM n=18). As a control, 122 women receiving elective C/S for breech presentation were chosen (group C). [Results] The infant weight and the gestational age were comparable between group M and C. Regarding blood loss and operation time (presented as median, 10–90 percentile) were 1490ml (862–2398) and 77 min (69–85) in group M and 1000ml (510–1854) and 69 min,(54–88), showing significant difference in both parameters ($p<0.01$). In comparison with group C, there were especialy larger only in AM ($p<0.01$) but not in LM and LAM. [Conclusion] Pregnancy with a history of myomectomy, especially a removal by abdominal myomectomy, is associated with an increase in blood loss and operation time at cesarean section.

ISP-24-2 Comparative analysis of 15–years ago and the current cesarean delivery rates using 10–group classification

Osaka University
Takao Owa, Kazuya Mimura, Aiko Kakigano, Yuri Matsumoto, Tomomi Takata, Shinya Matsuzaki, Keiichi Kumasawa, Masayuki Endo, Takuji Tomimatsu, Tadashi Kimura

[Objective] Cesarean delivery rates continue to rise throughout the developed world. The aim of this study was to examine the transition of cesarean delivery rates in the same institution by using 10–group classification. [Methods] We used the Robson's 10–group classification which is based on obstetrical parameters (parity, previous cesarean delivery, gestational age, onset of labor, fetal presentation and number of fetuses). Cesarean delivery rates of 2000 and 2014 were examined. Total delivery numbers were 615 in 2000 and 524 in 2014. [Results] From 2000 to 2014, overall cesarean delivery rates increased from 15.6% (96/615) to 35.1% (184/524). Of 10–group classification, cesarean delivery rates increased from 10.9% (32/294) to 21.9% (50/228) among term, singleton, and cephalic nulliparous women, from 31.4% (16/51) to 56.7% (38/67) among preterm singleton cephalic women, and from 45.5% (25/55) to 100% (56/56) among previous cesarean delivery, term, singleton, cephalic women. [Conclusion] The increase in cesarean delivery rate of term, singleton, cephalic nulliparous women and previous cesarean delivery, term, singleton cephalic women correlated with the increase in current overall cesarean rates throughout 15 years. By using this objective classification system, we can analyze trends of cesarean delivery over time in the same institution and between different institutions.

ISP-24-3 Risk factors for birth canal trauma with forceps delivery

Juntendo University
Yasuko Sano, Chihiro Hirai, Xianglan Li, Jun Takeda, Youta Shimanuki, Shintaro Makino, Atsuo Itakura, Satoru Takeda

[Objective] Forceps delivery (FD) is associated with perineal and vaginal trauma. To clarify the risk factors for birth canal trauma associated with FD, we retrospectively evaluated the medical records of FD cases in a single hospital. [Methods] Data of 558 delivered women who underwent FD at term with singleton cephalic position were obtained from 2010 to 2014. The relationship between clinical characteristics and birth canal trauma was analyzed. Birth canal trauma included third and fourth perineal laceration as well as hematoma in vagina and perineum. Univariate and multivariate models of logistic regression were employed. Statistical significance was defined when $p<0.05$. [Results] The incidence of severe laceration and hematoma were 11%, 5%, respectively. Fetal station, maternal gestational weight gain, and birth weight were higher ($p=0.014$, 0.016, 0.025, respectively) among women with severe laceration, whereas the rates of obstetrical analgesia was lower among women with such lacerations ($p=0.015$). Maternal age was higher among women with hematoma ($p<0.001$). Neither indication for FD nor nulliparous showed any influence on the rate birth canal trauma. [Conclusion] Birth canal traumas with FD were associated with higher fetal station, gestational weight gain, birth weight and maternal age. Obstetrical analgesia may reduce severe lacerations.

ISP-24-4 Safety and reliability of forceps delivery based on novel fetal head evaluation：Analysis of 1532 cases

Saitama Medical Center
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[Objective] To evaluate the maternal-neonatal complications of forceps deliveries using trapezoidal-station (t-St), a new concept to assess fetal descent, and comparison with DeLee St (d-St). [Methods] t-St, defined as fetal station based on the trapezoidal plane consisting of the ischial spines and the lower edge of the pubic symphysis, and "UTokyo Naegele Forceps", a thinner and lighter forceps, has been clinically used since 1985. This is a retrospective analysis of 1532 forceps deliveries over 28 years period. With following groups, (1) Normal vs Forceps delivery, (2) St+2 vs St+3/lower, and (3) t-St vs d-St, characteristics and complications were assessed. IC was obtained. [Results] Forceps deliveries showed significantly more bleeding, lower pH, and lower Apgar scores compared with normal deliveries. There were 4 severe neonatal complications in forceps deliveries. Two cases were failed forceps. Comparison between St+2 and St+3/lower groups among forceps deliveries, no significant differences were found in blood loss and serious maternal injuries (3rd or 4th degrees). The incidence of serious maternal injuries and lower Apgar score were significantly lower in t-St, compared with Cochrane report (OR 1.88 and OR 2.20, respectively). [Conclusion] Minimally invasive and safe forceps were performed using t-St, probably reflect of correct assessment of fetal descent.

ISP-24-5 Vaginal versus Cesarean Breech Delivery：Maternal and Neonatal Outcome at Bulacan Medical Center, A Two-Year Retrospective Study

Bulacan Medical Center, Philippines
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[Objective] To compare the maternal and neonatal outcome of vaginal and cesarean breech deliveries at Bulacan Medical Center. [Materials and Methods] A two-year retrospective descriptive study on all patients who delivered breech by vaginal or cesarean section from January 1, 2012 to December 31, 2013. The maternal and neonatal outcomes were compared and analyzed. [Results] There were 165 deliveries included during the study period. There were 83 cases of vaginal breech delivery and 82 cases of cesarean breech delivery. The incidence and risk of postpartum hemorrhage is higher among cesarean breech delivery (7%). Febrile morbidity (p=.0223) is significantly lower for vaginal breech births. Cesarean breech delivery is correlated with longer hospital stay (p=＜0.0001). There were no significant differences on the incidence of asphyxia (5% vs 2%, RR =0.51, RD=-2%, p=0.4141), birth trauma (2% vs 1%, RR=0.51, RD=1%, p=0.5673) and sepsis (12% vs 9%, RR=0.71, RD=-4%, p =0.4582) for vaginal or cesarean breech delivery. Prolonged hospital stay is 2.10 times more likely to occur for cesarean breech deliveries compared with vaginal breech deliveries. Thus, shorter hospital stay means lesser hospital costs for both mother and babies. [Conclusion] There is no significant difference in maternal and perinatal morbidity and mortality between vaginal and cesarean breech delivery except for longer hospital stay and increased febrile morbidity for cesarean births. It is therefore safe to recommend vaginal breech delivery under hospital-specific guidelines for labor management such as strict selection of patients, high quality fetal monitoring and high level of competence among obstetricians to deliver breech.

ISP-24-6 Cervical varix complicated by placenta previa：a case presentation and literature review

Osaka University
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[Background] Uterine cervical varix during pregnancy is rare. Moreover, complicated by placenta previa is extremely rare. Although cases of uterine cervical varix have been reported in the context of massive antepartum or intrapartum hemorrhage, there have been limited reports on imaging findings, outcomes, or clinical course. [Case] We describe the clinical course and imaging results for a 35-year-old woman who was diagnosed with placenta previa complicated by a cervical varix. Investigation by speculum, serial ultrasonography, and magnetic resonance imaging confirmed the diagnoses. A healthy baby was successfully delivered at 36 weeks gestation by cesarean section and speculum examination after surgery indicated that the engorged varix had disappeared. An electronic search from January 1990 to July 2015 identified 8 previous cases of cervical varix complicated by placenta previa in the literature. [Conclusion] Clinicians should be aware of cervical varices when managing placenta previa, to avoid iatrogenic rupture.

ISP-24-7 Rule out the adherent placenta：evaluation with magnetic resonance imaging

Osaka University
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[Objective] Rule out the placenta accreta before delivery allows to minimize potential maternal or neonatal morbidity and mortality in the case of placenta previa. However, such method is not established. We review the magnetic resonance image (MRI) findings to rule out the placenta accreta in a single-institution experience. [Methods] From January 2008 through August 2015, we conducted a retrospective review of the prenatal MRI examinations of 70 patients who underwent MRI evaluation of the placenta in patients with placenta previa. We focused on the characteristic findings of placenta accreta on MRI, such as uterine bulging, a heterogeneous placenta, an intraplacental T2 dark band, and the placental protrusion sign. We investigated the negative predict value of each finding to rule out the placenta accreta. [Results] Of the 70 reviewed cases, 47 cases did not have clinical placenta accreta. The remaining 23 cases were diagnosed with placenta accreta, which was confirmed by an evaluation of the histopathological exmanination. To rule out the placenta accreta on MRI, an intraplacental T2 dark band had the best negative predictive value (83%) and its combination without the presence of protrusion sign on T2-weighted images improved the negative predictive value to 90%. [Conclusion] To rule out the placenta accreta, an intraplacental T2 dark band was the most effective MRI findings.

ISP-25-1 Increased expression of SOCS3 may contribute to decreased expression of TNF alpha in the placenta of gestational diabetes mellitus

University of Occupational and Environmental Health
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[Objective] Suppressor of cytokine signaling 3 (SOCS3) may increase insulin resistance while reducing inflammatory cytokine signaling. Here we examined the expression levels of SOCS3 in the placenta of gestaional diabetes mellitus (GDM), as well as the pro-inflammatory cytokine TNF-alpha, and molecular markers of oxidative damage. [Methods] Immunohistochemistry (IHC) was performed on 20 normal and 17 GDM placentas using antibodies against SOCS3, TNF-alpha, Heat shock protein (Hsp27), and 8-Hydroxy deoxy-guanosine (8OHdG). IHC staining was scored across five fields per slide. Score 0 (no signal), 1 (weak signal detected), 2 (moderate), 3 (strong). This study was approved by Institutional Review Board. [Results] SOCS3 expression was localized to the endothelium of fetal vessels, interstitial cells of the villus, and the Syncytial trophoblast (ST). TNF-alpha was primarily found in the ST. Hsp27 IHC staining was nuclear (with some weak cytoplasmic signal) in the ST. 8OHdG expression was nuclear in the ST. Relative expression levels of these proteins were as follows (control vs cases) SOCS3：0.7 ± 0.4vs 1.4 ± 0.3 P＜0.001, TNF alpha：1.4 ± 0. 9 vs 0.7 ± 0.6 P＜0.001, Hsp27：0.8 ± 0.5 vs 0.9 ± 0.6 P=0.4, 8OHdG：1.9 ± 0.7 vs 1.7 ± 0.7 P=0.5. [Conclusion] Increased expression of SOCS3 may contribute to decreased expression of TNF-alpha, as well as insulin resistance in women with gestational diabetes mellitus.

ISP-25-2 The BMI before pregnancy and vaginal microbiota involved in the development of GDM

Kyorin University
Seishi Furukawa, Mitsutoshi Iwashita

[Purpose] To identify the involvement of obesity and vaginal microbiota developing to GDM. [Method] Cross-sectional study was conducted in pregnant women those were underwent 75g glucose tolerance test. The cut-off values of insulinogenic index (II) and HOMA-R for GDM were obtained. We classified the group of lower II and HOMA-R as type 1 and the group of higher II and HOMA-R as type 2. We compared pre-pregnancy BMI and vaginal microbiota in GDM type 1 and type 2 with those of corresponding group in non-GDM. [Result] 102 cases of pregnant women having factor for GDM were enrolled. The cut-off value of II as 0.83 and HOMA-R as 1.29 were obtained. Nine cases were classified as GDM type 1 and ten cases were as GDM type 2. The BMI of GDM type 1 was significantly higher than that of the non-GDM (n=16) (20.7 ± 1.5 vs.19.1 ± 1.8), and not between the GDM type 2 and non-GDM (n=18) (24.4 ± 4.6 vs.22.9 ± 4.4). There was no difference of the prevalence of Lactobacillus rich community between the GDM type 1 and non-GDM (5/8 vs.13/16). While, GDM type 2 had Lactobacillus poor community (2/10 vs.14/18). [Conclusion]In the group of impaired insulin secretory ability with low insulin resistance, the pre-pregnancy BMI is involved in developing to GDM. In the group of preserved insulin secretory capacity with high insulin resistance, the disturbance of the vaginal microbiota is associated with GDM.

ISP-25-3 Estimating the risk of gestational diabetes in women who are positive for 50g glucose challenge test : Development of the prediction model based on patient characteristics

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[Objective] A 50g glucose challenge test (GCT) is the most widely used screening method for gestational diabetes (GDM) with the posttest probability of approximately 18-24%. In this study, we developed a scoring system made of clinical characteristics that can predict the risk of GDM in pregnant women after 50g GCT. [Study Design] The study population consisted of singleton pregnant women who were positive for 50g GCT (≥140mg/dL) at 24-28 weeks of gestation. In these women 100g GTT were subsequently performed and GDM was diagnosed according to the Carpenter-Coustan Criteria. We collected data on demographic and laboratory characteristics and constructed a model to estimate the probability of GDM using multivariate regression analysis. [Results] During the study period a total of 1488 pregnant women were positive for 50g GCT, and 370 women (24.9%) were diagnosed as GDM by 100g GCT. Of the demographic and laboratory variables analyzed, maternal age, prepregnancy BMI (body mass index), familial history of diabetes, history of previous GDM, and the value of 50g GCT and HbA1c were included in the prediction model for GDM, with a weighted score of 0- 48. The model had an area under the receiver operating characteristics curve of 0.77 (95% CI 0.74 -0.80), and the probability of GDM were 2% in score≤3, 24% in score 4-21, and 89% in score≥22. [Conclusion] A prediction model with a weighted risk scoring system for GDM showed excellent performance in women who were positive for 50g GCT, and may be used to select women for additional testing for GDM.

ISP-25-4 Weight gain during pregnancy and risk of late-onset gestational diabetes

Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Dittakarn Boriboonhirunsarn

[Objectives] To determine the relationship between second trimester weight gain and risk of developing late-onset gestational diabetes (GDM). [Methods] A total of 195 women at-risk for GDM who had normal initial screening results during first trimester were enrolled. Study group consisted of 65 women who had second trimester weight gain of>7 kg. Another 130 women, matched 2 : 1 by BMI category, who had second trimester weight gain of<7 kg were served as comparison group. All women received second GDM screening tests during 26-28 weeks of gestation. Incidence of late-onset GDM were determined and compared between groups. Comparison of various characteristics was also made to determine possible associated factors, including baseline characteristics, weight gain during first trimester, and GDM risks. [Results] Mean age, pre-pregnancy BMI, parity, GDM risks, first trimester weight gain, timing of GDM screening and initial test results were comparable between groups. Incidence of late-onset GDM was significantly higher among study than comparison group (24.6% vs. 10.8%, p=0.012). Logistic regression analysis demonstrated that second trimester weight gain>7 kg and degree of abnormality of initial tests independently increased the risk of late-onset GDM, i.e., second trimester weight gain>7 kg : adjusted OR 2.57, 95%CI 1.12-5.91 ; abnormal GCT but normal OGTT : adjusted OR 2.61, 95%CI 1.03-6.64 ; abnormal 1 value of OGTT : adjusted OR 8.67, 95%CI 2.75-27.35. [Conclusion] Second trimester weight gain>7 kg and degree of abnormality of initial tests independently increased the risk of late-onset GDM.

ISP-25-5 Postpartum screening for glucose intolerance in women with gestational diabetes mellitus

Kobe University
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[Objective] The aim of this study was to evaluate risk factors for glucose intolerance during the postpartum period in women with gestational diabetes mellitus (GDM). [Methods] This prospective cohort study enrolled 72 women with GDM who underwent 75g-OGTT at 12 weeks after delivery, and was approved by the institutional ethic boards. The informed consent was obtained from all participants. According to the WHO criteria, 72 GDM women were divided into glucose intolerance (GI) and normal groups, based on postpartum 75g-OGTT results. Risk factors for GI early in postpartum period included levels of blood glucose (BG), area under the curve (AUC) of glucose, AUC of insulin, HbA1c, HOMA-IR, HOMA-β, insulinogenic index (II), and the oral disposition index (DI) in antepartum 75g-OGTT ; and were analyzed by univariate and multivariate logistic regression analyses. [Results] Twelve of the 72 women (16.7%) had GI and the others were normal. By univariate analyses, fasting BG, AUC glucose, HOMA-β, II, and oral DI in antepartum 75g-OGTT were selected as risk factors for GI. Multivariate logistic regression analysis revealed that the II in 75g-OGTT was a single risk factor (OR, 0.008 ; 95% CI, 0.0001-0.9 ; p<0.05) for GI occurring early in the postpartum period. [Conclusion] The II determined by 75 g-OGTT during pregnancy in GDM women might be useful for the risk assessment of GI in the future.

ISP-25-6 Does low result of one hour 50g glucose challenge test predict adverse fetal and maternal outcomes?

Yokohama City University
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[Objective] To predict fetal and maternal outcomes in women with low 50g glucose challenge test (GCT) result. [Methods] The study groups included women who was offered GCT at 24–28 weeks of gestation, and delivered singleton at term from Aug, 2010 to Aug, 2015. Low GCT is defined as less than 75mg/dL which is less than −1.5SD. Normal GCT is defined between 75 and 139mg/dL. 288 women had low GCT and 4240 had normal GCT. We compared pregnancy outcomes such as neonatal birth weight, large for gestational age (LGA), small for gestational age (SGA), neonatal hypoglycemia, jaundice, NICU admission, pregnancy induced hypertension (PIH), delivery mode. [Results] Low GCT had younger (yr ; 30.6 ± 5 v.s.31.5 ± 5, p=0.001), lower body weight (kg : 50.7 ± 5.7 v.s. 52.0 ± 7.3, p=0.003) and lower BMI (19.9 ± 1.8 v.s. 20.7 ± 2.6, p< 0.001) at first visit. After adjusting these variables, low GCT had significant lower neonatal birth weight (kg : 2968.3 ± 330 v.s 3032 ± 350, p=0.003), lower rate of LGA (1.7% v.s. 5.3%, p=0.005), and higher rate of SGA (12.2% v.s. 8.4%, p=0.039). Categorizing GCT result, there were trends that the lower the GCT result, the lower the rate of LGA, the higher the rate of SGA. Neonatal hypoglycemia, jaundice, NICU admission, PIH, delivery mode were similar in both groups. [Conclusion] Low GCT result is useful to predict fetal outcomes of neonatal birth weight, particularly SGA.

ISP-25-7 In early gestation, maternal smoking leads to increased epigenetic alterations at the promoters of nitrogen compound metabolic and transcriptional regulators

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[Objective] In utero environmental factors are thought to have long lasting effects on epigenetic modification. In early pregnancy, the epigenetic effects of exposure to maternal smoking (MS) in villous tissues are not well known. [Methods] This study was approved by the local ethics committee. We conducted a genome-wide methylation profiles for 22 villous tissues at 7–8 weeks gestation from pregnancies with written informed consent, using Human methylation 450K array. Epigenetic alterations were assessed in the villi under MS, as shown by application of IMA and Smirnov–Grubbs outlier test. [Results] Wilcoxon rank-sum tests didn't detect any specific CpG sites as significantly differentially methylated between two groups. MS significantly increased more hyper-methylated outliers than control. Simultaneously, hypermethylation occurs frequently at the promoter regions of genes related to nitrogen compound metabolic process and transcription, as shown by annotations of the biological processes of loci with altered DNA methylation. [Conclusion] We demonstrated that loci with alterations in the villous DNA methylation under MS were not common among subjects but found to occur preferentially at the CGI promoters of genes encoding metabolic and transcriptional factors. Accumulation of epigenetic modifications associated with in utero exposure to MS may development perinatal disorders.

ISP-25-8 Maternal hemoglobin level might correlate with the fetal hemoglobin level

Aiiku Hospital
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[Objective] The average birth weight has been decreasing in Japan. One of the causes is speculated as the mother's insufficient nutrition intake. In this study, we made a hypothesis that maternal malnutrition during gestation results in an insufficient iron intake, then iron deficiencies for both pregnant women and the fetuses. [Methods] Data were collected from 105 pregnant women who gave birth in April, 2015 in our hospital. The inclusion criteria were singleton, normal pregnancy course, and term delivery. Specific pathological conditions which could affect the mother's hemoglobin level were excluded. We analyzed the correlation between the hemoglobin levels of the mothers at 36 weeks gestation and the umbilical blood at delivery. Generic informed consent to use the data had been acquired from the mothers. We didn't apply this study to the ethics committee because this is a retrospective study of the medical records. [Results] The average hemoglobin level of the mothers at 36 weeks gestation, umbilical artery and vein were 11.0 ± 0.1 g/dL, 15.4 ± 0.1 g/dL, and 15.7 ± 0.1 g/dL, respectively. A weak correlation was observed between maternal hemoglobin level and umbilical vein hemoglobin level ; coefficient of correlation was 0.266 (p=0.006). [Conclusion] In this study, we found the possibility that maternal malnutrition may result in both mothers' and fetuses' iron deficiency.

ISP-25-9 The progression of anemia during pregnancy correlates with the mothers' insufficient weight gain during pregnancy

Aiiku Hospital
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[Objective] The average birthweight has been decreasing in Japan. One of the causes is speculated as the mother's insufficient weight gain during pregnancy. In this study, we made a hypothesis that the less calorie intake during pregnancy results in the less intake of iron and further the anemia during pregnancy. [Methods] Data were collected from 70 pregnant women among 180 women who delivered in May, 2015 in our hospital. The inclusion criteria are singleton, normal pregnancy course, no complications of the mother, and term delivery. We analyzed the correlation between the weight gain till the second trimester and the decrease of hemoglobin concentration (Hb) in the same period. We didn't apply this study to the ethics committee because this is a retrospective study of the medical records. [Results] The maternal weight before the pregnancy and at the second trimester (average 24 weeks) was 51.0 ± 6.2kg (average ± 1.0 SD) and 56.7 ± 5.9kg, respectively. The Hb at the first trimester (average 9 weeks) and the second trimester (average 24 weeks) was 12.4 ± 1.0g/dl and 11.1 ± 0.8 g/dl. The weak negative correlation was observed between the weight gain per week and the decrease of Hb per week ; coefficient of correlation was −0.248 (p=0.04). [Conclusion] In this study, we found the possibility that the more the pregnant women's weight had increased, the lesser her anemia progressed.

ISP-25-10 Distribution of core temperature under maternal abdominal wall during pregnancy

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[Objective] Gene expression of fetal heart in development is known to be related with the surrounding mechanobiological stimulations, such as temperature, shear stress. During pregnancy fetal temperature is depend on maternal core temperature under maternal abdominal wall. But there are no studies about the core temperature. Our aim is to study the temperature during pregnancy. [Methods] Under the informed consent, 22 pregnant women (11w to 38w) participated in this study. Noninvasive core temperature sensor (3M SpotOn system Model 370) was set on the low maternal abdominal wall. Core temperatures under maternal abdominal skin were measured. [Results] Core temperature range was from 33.7℃ to 36.8℃ during pregnancy. Until about 25 weeks the temperatures were high (around 36.5℃). About 30−35weeks those were low (about 35℃). And after 37weeks gestation, the temperatures were high again (around 36.5℃). [Conclusion] We found out that maternal abdominal core temperature was change more than 1℃ during pregnancy. 1℃ change is enough for the change of gene expression of Ca channel (TRPC1) in fetal heart. We suggested that core temperature change will has important mechanobiological influence on developmental heart.

ISP-26-1 Normal ranges of plasma concentrations of pregnancy−associated microRNAs during pregnancy

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[Objective] The aim of this study is to investigate the normal ranges of plasma concentrations of pregnancy−associated microRNAs (miRNAs) change during pregnancy. [Methods] We collected maternal blood samples from 177 uncomplicated pregnant women during pregnancy and after deliverly. 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 Nagasaki University. MiRNAs were measured by real−time quantitative PCR and U6 snRNA was used for internal control miRNA. [Results] Plasma concentrations of placenta specific miRNAs increased during pregnancy and decreased after delivery significantly ($p < 0.05$). Plasma concentrations of fetus−specific miRNAs did not change significantly during pregnancy. The mean values and 95% confidence interval (95% CI) about the logarithm of the plasma concentrations of placenta specific miRNAs were represented as a linear model. The mean value (95% CI) of log miR−515−3p at 12, 23, 30, and 36 weeks of gestation were−2.36 (−3.79−−0.933),−2.19 (−3.60−−0.78),−2.08 (−3.49−−0.67) and−1.98 (−3.41−−0.57), respectively. [Conclusion] Plasma concentrations of placenta−specific miRNAs and fetus−specific miRNAs showed a different transition. We have showed the normal range for the circulating levels of pregnancy−associated miRNAs during pregnancy.

ISP-26-2 Issues for the management of pregnancy of the women with adult congenital heart disease

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[Objective] Prognosis of congenital heart disease has been remarkably improved owing to the advance of medicine and surgery. The opportunity for us to take care of the pregnant women of adult congenital heart disease (ACHD) has been therefore increasing. Most of them have an uneventful pregnancy course. However, we may be sometimes faced on distinctive problems such as arrhythmia, heart failure, cyanosis, etc. even they have not had any events. [Methods] The medical records of pregnancy in the ACHD women were reviewed that were managed at a tertiary center not specialized for ACHD care from 2011 to 2015. The situation of the management, the evaluation, the medication, and the strategy during and after pregnancy were investigated. [Results] Twenty-seven cases and twenty-nine pregnancies were identified. VSD was the most major disease. Seven cases were in postintracardiac repair state. All of the pregnancies were in NYHA I at the first and none of them had cardiac events during and after the pregnancy. Cardiac evaluation before or early in pregnancy was done for twenty of them. Only three of them were followed up three to six months after the delivery. [Conclusion] It did not seem that sufficient checked-up of cardiology for the ACHD women during and after pregnancy which is the period that cardiac volume are supposed to be larger than the non-pregnant state.

ISP-26-3 Successful pregnancy in a woman complicated Stage 4 extracranial arteriovenous malformation with amputated one leg

Osaka University
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Extracranial congenital arteriovenous malformations (AVMs) are rare in the reproductive years. Pregnancy can influence both the development and the progression of AVMs. There is a few data regarding AVMs in pregnancy, especially that of high Stage. We report here a 37-year old primipara woman with congenital AVM in right leg. She underwent amputation of her right lower leg at age of 8 because of necrosis. After she grew up, she suffered from repetitive bleeding from stump and high output heart failure, which was well controlled when she conceived. According to Schobingers classification, her stage was IV. Throughout the course of pregnancy, the maximum BNP was 340pg/ml, and her echocardiographic findings were not altered. She sometimes suffered from large amount of stump bleeding, and we managed by compression each time. Our management dilemma was mode of delivery and timing. MRI revealed subcutaneous abnormal vessels in lower abdomen, but none was found around uterus and vagina. To avoid cardiac burden, we selected labor induction with epidural anesthesia, and she delivered healthy female baby at 37 weeks. High stage AVM may cause maternal and fetal mortality and morbidity, therefore rigorous management is required throughout the pregnancy.

ISP-26-4 Inferior vena cava filter for deep vein thrombosis in early pregnancy：a report of three cases

Akita University
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[Objects] The use of an inferior vena cava filter (IVCF) is a treatment option for deep vein thrombosis (DVT), but no consensus has been reached on its use in early pregnancy. We report our experience with three cases of DVT in our hospital. [Methods] We compared the three cases of DVT treated with an IVCF in terms of differences in the treatment method and time to thrombus reduction. [Cases] 1) A 31-year-old woman with hyperemesis and DVT at 12 weeks of gestation (WG). Anticoagulant was administered, but the thrombus was not reduced in 2 weeks. We placed an IVCF and performed artificial abortion. 2) A 33-year-old woman with pulmonary embolism (PE) and DVT at 14 WG. After placement of an IVCF, anticoagulant and thrombolytic agents were administered. Two days later, the thrombus was reduced markedly with no abnormal bleeding. At 17 WG, we performed artificial abortion. 3) A 34-year-old woman with myoma uteri, PE, and DVT at 10 WG. Her vital signs were normal. We placed an IVCF and administered an anticoagulant. The thrombus was reduced in 4 weeks. At 34 WG, elective cesarean section was performed. The three patients received warfarin after delivery. [Conclusion] We report that the use of IVCF in early or throughout pregnancy can save lives. However, in the cases presented here, permanent IVCFs were used. Methods to avoid the use of a permanent IVCF in early pregnancy should be developed.

ISP-26-5 Pregnant women with inherited thrombocytopenia

Hiroshima University
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[Objective] Management of pregnant women with inherited thrombocytopenia has not been established, because this condition is rare and difficult to diagnose. Autosomal dominant inherited thrombocytopenia caused by integrin αII bβ3 mutation was reported recently. We are currently following up two families with this condition, and herein, we report their perinatal and neonatal courses. [Patients] We enrolled 4 women (7 pregnancies) with this disorder, who gave birth in our hospital during 2007–2015. One of these was a triplet pregnancy. We retrospectively evaluated the platelet counts before and during pregnancy, management of thrombocytopenia, and platelet counts of their infants. [Result] The platelet count before pregnancy was $4.5 \pm 0.5 \times 10^{10}$/L (mean ± SE). During pregnancy, none of the patients experienced a hemorrhagic event. In 2 of 7 cases, γ-globulin had been administered ; however, the platelet counts had remained low. All 7 subjects underwent platelet transfusion before the cesarean section. The median bleeding volume during the surgery was 867 ± 175 mL, and the postoperative courses were uneventful. Five of 9 infants had thrombocytopenia ; however, there were no complications during and after the delivery. [Conclusion] Platelet transfusions were needed before delivery ; however, all perinatal and neonatal courses were uneventful by cesarean section.

ISP-26-6 To assess the management of pregnancies complicated with antithrombin deficiency : A report of 20 cases

Kobe University
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[Objective] To assess the management of pregnancies complicated with antithrombin (AT) deficiency. [Methods] Twenty pregnancies from 18 women genetically diagnosed with AT deficiency and treated from Jan. 2006 to Feb. 2014 were studied. [Results] Eleven cases developed thromboembolism (TE) during pregnancy and were diagnosed with AT deficiency. Of the 11 cases, 6 developed TEs in the first trimester. AT concentrate (3000–6000U/wk) to maintain AT level＞70% and therapeutic dose of heparin (APTT level at 60–90 sec) were administered until 4–6 hrs before delivery. For 9 cases diagnosed with AT deficiency before pregnancy, prophylactic AT medication to maintain AT level＞70% in addition to heparin (10000–15000U) and/or 81–100mg aspirin a day was started at initial visit of the pregnancy. Of 20 cases, 16 delivered vaginally. The median length of gestation was 38 wks (30–40wks) and blood loss at delivery was 572ml (265–2304ml). Heparin-induced thrombocytopenia was occurred in one case. No pregnancy loss, PIH, abruption fetal growth restriction was occurred. AT medication to maintain AT level＞70% continued until 6wks after delivery. Heparin therapy was started 6 hrs after delivery and switched to warfarin at next day. No TEs were occurred in all 9 cases. [Conclusion] Our result supports prophylactic AT medication from early pregnancy is associated with a successful pregnancy outcome.

ISP-26-7 Short umbilical cord length reflective of adverse pregnancy outcomes in a Japanese population

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[Objective] This study aimed to determine the umbilical cord length showing the highest correlation with adverse pregnancy outcomes. [Methods] We retrospectively analyzed data of women who attempted vaginal birth. We excluded patients of preterm birth, multiple gestations, noncephalic presentation, a history of uterine operation, obvious fetal structural abnormalities diagnosed during pregnancy, and elective cesarean delivery owing to maternal complications. The umbilical cord lengths were analyzed and categorized into three groups : less than the first percentile, from the first percentile to less than the tenth percentile, and others. The main outcome was the rate of cesarean delivery. We also evaluated the frequency of operative vaginal delivery, small-for-gestational-age births, neonate resuscitation by intubation, Apgar score less than 7 at 5 minutes, umbilical artery pH below 7.1, manual removal of placenta, placental abruption, preeclampsia and abnormal bleeding during delivery. [Results] The average umbilical cord length was 56.6 cm. Cord lengths of 33 and 43 cm corresponded to the first and tenth percentiles, respectively. A short cord was an indicator of unplanned cesarean delivery, neonate necessitating intubation, and Apgar score less than 7 at 5 minutes. [Conclusion] An umbilical cord length 43 cm and shorter is a clinically useful indicator of adverse pregnancy outcomes.

ISP-26-8 Asymptomatic pyuria in pregnant women during the first trimester is associated with an increased risk of adverse obstetrical outcomes

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[Objectives] Urinalysis is included in the prenatal examination in the first trimester in Taiwan, in contrast to Western countries. We aimed to investigate whether asymptomatic pyuria as detected by urinalysis was associated with adverse perinatal outcomes. [Methods] A total of 1187 singleton pregnant women who received prenatal care at Kaohsiung Chang Gung Memorial Hospital between January 2012 and December 2013 were included for retrospective analysis. We defined asymptomatic pyuria as the presence of 15 or more white blood cells per cubic millimeter in midstream urine without symptoms. Adverse perinatal outcomes including preterm delivery, preterm premature rupture of membrane (PPROM), low birth weight, and low 5 minute Apgar scores were analyzed. Univariate and multivariate logistic regression analyses were used to identify independent predictors. [Results] The prevalence of asymptomatic pyuria was 21.3% in our cohort. Univariate analysis showed that pyuria was the only factor associated with preterm labor, PPROM, and low birth weight. In multivariate analysis, both pyuria (OR：4.89, 95% CI：1.80-13.25, p=0.002) and a maternal age of 35 years or older (OR：3.46, 95% CI：1.11-10.78, p=0.033) were significant independent predictors for a low 5 minute Apgar score (<7). [Conclusion] The identification of asymptomatic pyuria via urinalysis in the first trimester may be a predictor for adverse perinatal outcomes.

ISP-27-1 Pregnancy after uterine artery embolization for the treatment of post-partum hemorrhage：a case series

Kobe University[1], Chibune General Hospital[2]
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[Objective] To report on pregnancies after uterine artery embolization (UAE) for post-partum hemorrhage (PPH). [Methods] Twelve pregnancies after UAE from December 2003 to December 2012 in the single center were studied. [Results] During the study period, 86 women underwent UAE for sever PPH and 12 conceived after UAE. Ten pregnancies were spontaneous while the other 2 required infertility treatment as they did for former pregnancies. In one case, cesarean section was performed at 20 weeks because of massive bleeding during termination of a fetus with multiple malformation. Eight women gave birth (6 cesarean and 2 vaginal delivery) including 2 preterm deliveries. Two pregnancies were terminated at 10 weeks due to miscarriage and the other one was invasive mole. The median interval from UAE to the end of subsequent pregnancy was 3 years (2-7 years). Although pregnancy induced hypertension and fetal growth restriction occurred in one case, the birth weight of the other babies was appropriate for gestational age. The median blood loss at delivery of 9 cases including the case terminated at 20w was 1495ml (395-5450ml). Of 9 cases, 2 had placenta previa, 2 had placenta accreta. Three cases developed severe PPH (blood loss>2000ml). 2 underwent UAE and 1 subsequently required hysterectomy. [Conclusion] There was a higher incidence of severe PPH after UAE in subsequent pregnancies.

ISP-27-2 Pregnancy after laparoscopic myomectomy

Juntendo University
Jun Takeda, Shintaro Makino, Chihiro Hirai, Jun Kumakiri, Mari Kitade, Atsuo Itakura, Satoru Takeda

[Objective] The numbers of pregnancies after enucletic uterine myomectomy has been elevating along with an increase of laparoscopic myomectomy (LM) for the symptomatic uterine myoma. However, the influences on the uterus and subsequent pregnancies have not been fully clarified yet. Thus to elucidate the peripartum risk we analyzed the pregnant cases after LM in a hospital. [Methods] The medical records of pregnant cases after LM were reviewed between January 2010 and August 2015 retrospectively. Details of LM and peripartum outcomes were noted. [Results] We experienced 296 pregnant cases after LM during this period. Fortunately, no rupture has been occurred, but 4 cases (1.3%) of placenta percreta were occurred. We successfully conserved her uterus with wedge resection in a case of partial placenta percreta located at uterine fundus whereas the remaining were turn out to be hysterectomy. The cases with placenta percreta were previously given multiple or large myomectomy which consequently to be severe myometrium defect. [Conclusion] It was low incidence, however, obstetricians and gynecologist should be attentive to the potential risk for placenta percreta in pregnant women after LM. With the preoperative diagnosis and appropriate management, placenta percreta could have a room to save the uterus in the case of fundal attachment.

ISP-27-3 Pregnancy-related cystic ovarian tumor—A case report

Osaka University
Yu Ito, Aiko Kakigano, Tsuyoshi Takiuchi, Yuri Matsumoto, Shinya Matsuzaki, Keiichi Kumasawa, Shinsuke Koyama, Masayuki Endo, Tadashi Kimura

Hyperreactio luteinalis and Luteoma are uncommon condition complicating pregnancy. They are characterized by varying degrees of benign multicystic ovarian enlargement. It is difficult to differentiate from ovarian cancer. We experienced two cases of pregnancy-related multicystic ovarian tumor rapidly growing during pregnancy. The first case is a 38-year old woman, gravida 3, para 2. She was admitted to our hospital at 19 weeks of gestation because of bilaterally enlarged multicystic ovaries. MRI scan demonstrated bilateral ovarian enlargement with mural nodules. Because of the uncertainty in diagnosis of the enlarged ovaries, an exploratory laparotomy with bilateral salpingo-oophorectomy was performed at 24 weeks of gestation. The pathological diagnosis was pregnancy luteoma. The second case is a 33-year old woman, gravid 2, para 1. She was referred to us at 30 weeks of gestation because of multicystic enlargement of the ovaries. On pelvis MRI scan, they had a simple cystic appearance. Serum human chorionic gonadotrophin (hCG) levels were elevated over 200,000 mIU/mL. We suspected hyperreactio luteinalis and employed conservative nonsurgical management. The size of ovaries returned to entirely normal size after the delivery. Knowledge of these rare diseases with findings of clinical imaging might contribute towards preventing overdiagnosis and treatment.

ISP-27-4 3D HD-flow with HDlive silhouette mode in diagnosis of uterine artery pseudoaneurysm during pregnancy

Kagawa University
Kenta Yamamoto, Mohamed Ahmed Mostafa Aboellail, Megumi Ito, Emiko Nitta, Nobuhiro Mori, Uiko Hanaoka, Kenji Kanenishi, Hirokazu Tanaka, Toshiyuki Hata

[Objective] We report an experience using three-dimensional (3D) HDFlow with HDlive silhouette mode to diagnose uterine artery pseudoaneurysm (UAP) during pregnancy. [Case] A-35-year-old primigravida was referred to our clinic because of suspected cervical mass at 34 wks. Transvaginal two-dimensional (2D) sonography showed hypoechoic cervical mass with echolucent center and swirling. Color Doppler showed swirling blood flow within the mass. There were another two cysts without blood flow at cervical lips. 3D HDFlow with glass-body rendering mode and HDlive silhouette mode showed turbulent blood flow inside the mass with clear identification of the feeder artery (right UA), and its exact location on upper surface of the mass. Spatial relationships among the mass, surrounding cervical cysts and tissue, and feeding artery were recognized. Characteristic "Yin Yang" appearance was seen at the periphery of the mass with stagnant flow at its center using HDlive silhouette mode. Diagnosis of UAP was made. Elective Caesarean section was performed at 35w2d to prevent sudden vaginal bleeding. At 11th days postpartum, spontaneous regression of the mass was obvious. [Conclusion] 3D HDFlow with HDlive silhouette mode might be an important adjunctive tool in diagnosis and follow-up of UAP during pregnancy. It may show potential advantages relative to conventional 2D sonography and 2D Doppler alone.

ISP-27-5 Obstetric outcome after laparoscopic removal of rudimentary horn

Osaka University
Masaaki Sawada, Aiko Kakigano, Yuri Matsumoto, Tomomi Takata, Shinya Matsuzaki, Keiichi Kumasawa, Shinsuke Koyama, Masayuki Endo, Tadashi Kimura

[Objective] Rudimentary horn is one type of congenital uterine anomalies, which is at risk of uterine rupture during pregnancy. Therefore currently prophylactic resection is recommended before they consider pregnancy. Here we report obstetric outcome after laparoscopic removal of rudimentary horn. [Methods] A total of 7 cases of pregnancy after resection including 2 pregnancies in 1 woman were encountered in our institution from 2007 to 2015. [Results] There were 2 threatened premature labor out of 7 cases during pregnancy. Mean gestational weeks at delivery were 36.4 weeks. Three cases delivered at term. Three cases delivered vaginally and four by cesarean section. All birth weights were appropriate-for-gestational-age. [Conclusion] Study is limited as for the obstetric outcome of women after prophylactic resection. One previous study has reported that pregnancy after resection is at high risk of preterm birth and that all the cases delivered by cesarean section. We confirmed that approximately 40% of pregnancies in women after resection had term deliveries, which was more frequent than that reported in the previous study. We determined delivery mode by the degree of myometrial injury at resection surgery, and cases with limited deficiency delivered vaginally. If we select the candidate, it might be possible to perform vaginal delivery safely even after resection.(approved by IRB)

ISP-27-6 Rupture of a Bicornuate Uterus in a Primigravida with No Other Risk Factors

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Maggie Dwiggins, Bradley Nitzsche, Susan Catt, Thusitha Cotter

［Background］ Uterine rupture of an unscarred, primigravid uterus is a rare event and generally occurs in the presence of comorbidities such as intrauterine infection, history of surgery or induction of labor. We present a case of uterine rupture at term in a patient with bicornuate uterus and no other comorbid conditions. ［Case］ A 28year-old primigravida at 37 weeks gestation presented with lower abdominal cramping. No contractions were recorded on the monitor, cervical dilation to one centimeter did not change over four hours of monitoring, and she was discharged home with precautions. She was known to have a bicornuate uterus and vertex presentation had been confirmed one week prior. The patient returned, one hour later, with sudden onset, severe abdominal pain. Her abdomen was rigid and exquisitely tender to palpation. Fetal bradycardia was noted, and the patient was emergently delivered by primary cesarean section. A viable fetus was found to be floating in the abdomen with accompanying hemoperitoneum. Uterine rupture along the medial aspect of the left horn was noted at the time of delivery and repair. No other uterine or adnexal abnormalities were noted. ［Conclusion］ The incidence of rupture in any uterine anomaly may be as high as 8%, however this incidence is not defined for bicornuate uterus. We have identified a case of uterine rupture in the absence of known risks factors, and this raises the question of whether bicornuate uterus should be considered a risk factor for uterine rupture.

ISP-27-7 Severe and Short Dizziness in a Pregnant Woman with Type I Arnold Chiari Malformation : A case report and review of the literature

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Symptoms such as dizziness are frequently observed in pregnant women. Since type I Arnold Chiari Malformation (ACM) may cause lethal complications such as central sleep apnea, patients with neurological symptoms require extremely careful management. There are no strict recommendations regarding management of parturients with type I ACM. A 30-year-old pregnant woman was referred to our department at 10 weeks' gestation with complications of type I ACM. At the age of 27 she had complained of dizziness and was diagnosed with type I ACM. Neurological examination confirmed both persistent ataxia and anesthesia of the extremities. Cranial and cervical magnetic resonance imaging (MRI) revealed cerebellar tonsillar herniation through the foramen magnum. An MRI scan at 27 week-gestation revealed a type I ACM, unchanged since at the age 27. For this reason, we chose conservative treatment rather than surgical decompression. Her obstetrical course was unremarkable, and she was delivered of a healthy, term male baby, weighing 3560 g. Pregnant women with known type I ACMs who experience neurological deterioration require prompt evaluation of their anatomic and neurologic status. Further clinical observation and study are necessary for the better understanding of dynamic physiolosy of type I ACMs during pregnancy.

ISP-27-8 Pregnancy outcomes after liver transplantation

Hiroshima University
Naoko Terawaki, Hiroshi Miyoshi, Yuko Teraoka, Suguru Nosaka, Satoshi Urabe, Norifumi Tanaka, Yoshiki Kudo

The number of pregnancies post-liver transplantation (LT) is on the rise, as the number of LT recipient with a good outcome has increased. However, post-LT pregnancy was reported to be associated with a high risk of complications such as gestational hypertension and acute rejection. We retrospectively assessed outcomes of post-LT pregnancies in our hospital. Thirty-five women＜50 years old underwent LT from 1991 to 2014. Ten pregnancies (5 recipients) resulted in 6 live births. The LT to pregnancy period range was 2-19 years. The indications for LT were acute liver failure (2 recipients), congenital biliary atresia, Budd-Chiari syndrome and primary sclerosing cholangitis. Tacrolimus was administered during pregnancy in 5 pregnancies, and discontinued in one. In 2 pregnancies, mycophenolate mofetil was changed. None of the recipients had gestational hypertension, or fetal growth restriction. Condyloma infection and hydramnion were observed. Of 6 deliveries, 2 were cesarean sections, and preterm delivery, occurred in 2 others. Two preterm infants were born with low birth weight, with none having a congenital anomaly. Two patients experienced temperature elevation in the month post-delivery. In conclusion, though we included only a small number of cases, pregnancy after LT, with careful management, was not associated with serious complications or liver dysfunction.

ISP-27-9 Effect of bed rest during pregnancy on thicknesses of quadriceps femoris muscle in pregnant and postpartum women

Tokushima University
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[Objective] The aims of this study were to investigate the changes in the thickness of quadriceps femoris muscle during pregnancy and puerperium and to evaluate the effect of bed rest on it in pregnant and postpartum women. [Methods] (Study1) Fourteen normal pregnant women were recruited. Muscle thicknesses of six sites : proximal, medial and distal parts of rectus femoris and these of vastus intermedius were measured using ultrasonography at 12, 26, 30 and 35 weeks of pregnancy and 4 days and 1 month postpartum. (Study2) We recruited 12 women who were treated by bed rest before 30 weeks for threatened premature delivery and compared the muscle thicknesses in these women with those in 26 normal pregnant women at 30 and 35 weeks of pregnancy and 4 days and 1 month postpartum. The study was approved by IRB. [Results] (Study1) Muscle thicknesses of five sites at 35 weeks were significantly thicker than those at 12 weeks. The thicknesses of those muscles decreased in the postpartum period. (Study2) The muscle thicknesses of four sites at 35 weeks of pregnancy in women with bed rest were significantly thinner than those in normal pregnant women. On the other hand, these changes were disappeared at postpartum. [Conclusion] The thickness of quadriceps femoris muscle increases in normal pregnancy, whereas immobilization due to bed rest during pregnancy suppresses the gain of it.

ISP-28-1 Laparoscopic conservative treatment of an intramural ectopic pregnancy after abdominal myomectomy : a case report

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Intramural ectopic pregnancy is an extremely rare form of ectopic pregnancy. A gestational sac located within the uterine wall and completely surrounded by myometrium and separate from the uterine cavity and fallopian tubes. It may reflect uterine trauma (previous curettage, cesarean section, myomectomy and so on), adenomyosis, and implantation of the embryo. In our patient's case, two risk factors could be involved. A history of myomectomy and an embryo transfer with *in vitro* fertilization (IVF). A 38-year-old woman has a history of an abdominal myomectomy that the uterus endometrium had been ruptured and repaired 1 year ago. Her pregnancy had been established in an embryo transfer in IVF. She was at 5 weeks of gestation, an ultrasound scan showed that the endometrial cavity was empty. An ectopic pregnancy was suspected, the laparoscopic surgery was performed. The gestational sac could not be detected and the transvaginal sonography was performed during the operation. The sonography showed the sac in the anterior wall of the uterus which located the same position of the mass found in the laparoscopy. Chorionic villi was observed in the mass from the anterior uterine wall, establishing the diagnosis of intramural ectopic pregnancy. Ectopic pregnancy after myomectomy, it is necessary to consider the intramural ectopic pregnancy.

ISP-28-2 Perioperative complications after uterine compression sutures

Osaka University
Yosuke Suzuki, Shinya Matsuzaki, Yuri Matsumoto, Aiko Kakigano, Tsuyoshi Takiuchi, Keiichi Kumasawa, Shinsuke Koyama, Masayuki Endo, Tadashi Kimura

[Objective] Uterine compression sutures (UCS) is one of the treatments for postpartum hemorrhage. In this study, we retrospectively examined the perioperative complications of UCS. [Methods] We analyzed cases at our hospital from January 2011 to August 2015. Fifty-seven patients (elective cesarean sections : 22 cases, emergency cesarean sections : 35 cases) underwent a cesarean section with UCS. Another 745 patients underwent a cesarean section without UCS and were enrolled in the study as the control group (elective cesarean sections : 389 cases, emergency cesarean sections : 356 cases). We compared the perioperative complications of the UCS group and the control group. [Results] There were no significant differences in the backgrounds of the patients. The mean amount of blood loss was 2434 ml in the UCS group and 938 ml in the control cesarean section group. There were no significant differences in the rate of postoperative endometritis in the patients who underwent an elective cesarean section in both the UCS and control groups (UCS : 13.6%, control : 8.8%). However, the rate of postoperative endometritis significantly increased in the patients who underwent emergency cesarean sections in the UCS group (UCS : 22.9%, control : 11.3% ; $p<0.05$). [Conclusion] UCS after an emergency cesarean section may increase the rate of postoperative endometritis.

ISP-28-3 Vascular complications of temporary balloon occlusion of the common iliac artery for bleeding control during surgery of placenta accreta：what will be our next step?

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Tu Yi-An, Shih Jin-Chung

[Objective]Temporary balloon occlusion of the common iliac arteries helps us minimize the blood loss during cesarean hysterectomy in cases of placenta accreta. However, it may relate with vascular complications like arterial occlusive disease of the lower extremities. [Methods] Between 2004 and mid-2015, in the single center, we included 37 pregnant women with prenatal diagnosis of morbidly adherent placenta, and performed temporary balloon occlusion of the common iliac arteries during operation for delivery the baby with placenta accreta. Balloon was inflated after delivery, and deflated as soon as hemostasis was secured. Then we closely checked the puncture site, the blood pressure, color, and warmth of both lower legs, to detect possible complications. [Results] Thirty-two (86.5%) patients fulfilled the efficacy of blood loss control less than 2000cc (average 1080 cc). Five patients showed acute complications, including 3 had thrombotic event of iliac arteries, 1 had arteriovenous fistula at puncture site, and 1 had retroperitoneal hemorrhage with symptomatic hypotension. Besides, another 2 patients complained claudication during outpatient follow up for 2 months. Total complication incidence was 18.9% (7/37) with various severity. [Conclusion] Although temporary balloon occlusion of the common iliac artery for bleeding control during placenta accreta operation showed excellent efficacy, vascular complications show relative high incidence. It is probably the time to halt the use of prophylactic balloon occlusion of common iliac artery during the surgery of placenta accreta until we can prove the benefits outweighing the potential risk.

ISP-28-4 Risk stratification score for the prediction of surgical site infections with cesarean delivery

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Natasha Patel, Angelle Brebnor

[Objective] Of all live births reported in the United States, approximately 4 in 10 babies will be delivered via cesarean section. Surgical site infections (SSI) represent a significant and costly complication affecting patients following cesarean section. Up to 3% of women undergoing cesarean delivery will develop a SSI. The aim of this study was to identify the presence of established risk factors associated with poor wound healing in patients who developed surgical site infections following cesarean delivery. Additionally, we propose to develop a scoring system to anticipate the likelihood of developing a SSI given presence or absence of identified risk factors. [Methods] Following IRB approval, female patients over the age of 18 who developed a SSI following cesarean section on labor and delivery between January 2009 and December 2013 at our facility were identified. A retrospective chart review was performed to identify the presence of risk factors associated with poor wound healing in this cohort of patients. Risk factors identified for analysis included, diabetes, tobacco use, obesity, history of MRSA colonization and previous SSI. A chi square analysis was used to calculate the likelihood of developing a surgical site infection based on risk factors identified. Logistic regression and conditional backward stepwise model was used to generate a predictive equation to calculate the risk of developing surgical site infection. [Results] 128 patients who developed a SSI following cesarean delivery were identified. An equal number of control patients who delivered within the same month and did not develop a SSI were analyzed for the presence or absence of risk factors associated with surgical site infection. The presence of diabetes, MRSA colonization or a history of previous infection was identified in the cohort of patients who developed surgical site infections. Obesity (OR=4.89 2.59-9.23) and tobacco (OR=2.33 CI 1.26-4.31) use were found to be the strongest risk factors associated with the development of SSI.. The sensitivity and specificity as determined by a ROC curve of the predictive equation were found to be 0.75 and 0.71, respectively. [Conclusions] In this retrospective analysis, both obesity and tobacco use were independently associated with the development of SSI. Further research with a prospective model is required to validate the positive predictive value of this equation.

ISP-28-5 Adverse Events after Non-obstetric Surgery in Patients with Pregnancy：A Nationwide Study

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Chien-Chang Liao, Ta-Liang Chen

[Objective] To evaluate the adverse events after non-obstetric surgery in patients with pregnancy. [Methods] Using claims data of Taiwan National Health Insurance system, we conducted a retrospective cohort study of 5591 pregnant women underwent non-obstetric surgeries in 2008-2012. We selected 22364 women without pregnancy for comparison by matching procedure with the propensity-score. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of postoperative complications and mortality associated with pregnancy were calculated in the multivariate logistic regressions. [Results] Pregnant women had higher risks of 30-day postoperative septicemia (OR 1.76, 95% CI 1.48-2.09), pneumonia (OR 1.48, 95% CI 1.01-2.15), urinary tract infection (OR 1.31, 95% CI 1.09-1.09), and in-hospital mortality (OR 4.19, 95% CI 2.76-6.38) compared with women without pregnancy. Pregnant women also had longer length of stay and higher medical expenditure after non-obstetric surgery than women without pregnancy. The association between pregnancy and the adverse events after non-obstetric surgery was significant in every age group. [Conclusions] Surgical patients with pregnancy had more adverse events with four-fold 30-day mortality after non-obstetric surgery compared with those without pregnancy. Our findings suggest the urgency revising the protocol of postoperative care for this specific population.

ISP-28-6 Efficacy of a 40 mg single intravenous Parecoxib for postoperative pain control after elective cesarean delivery：a double blind randomized controlled trial

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Tripop Lertbunnaphong, Atthapon Jaishuen

［Objectives］ To determine the efficacy of a single intravenous dose of 40 mg Parecoxib for postoperative pain control after elective cesarean delivery. ［Methods］ A total of 82 low-risk term pregnant women who were scheduled for elective cesarean delivery between January 2014 and June 2015 were enrolled. They were randomly assigned to receive either intravenous injection of 2 mL (40mg) of Parecoxib (Study group, N=41) or 2 mL of normal saline solution (Control group, N=41). Intravenous meperidine was used as an additional standard postoperative pain control in all cases. Pain score using visual analog scale was recorded blindedly at 6th, 12th and 24th hour postoperatively. ［Results］ The characteristics and pregnancy outcomes of both groups were comparable. The total dosage of meperidine were not different between groups. Compared with control, study group had significant less postoperative pain score at 6th and 12th hour (median score 0 vs. 2, $p < 0.01$; and 0 vs. 1, p=0.03, respectively). Study group were also significantly less likely to experience severe postoperative pain (score ≥ 4) at 6th hour (0% vs. 21.9%, p=0.002). They also reported higher satisfaction with Parecoxib treatment (median score 8 vs. 6, $p < 0.01$). ［Conclusion］ A 40 mg single dose intravenous Parecoxib had higher efficacies than meperidine in controlling acute postoperative pain after elective cesarean delivery.

ISP-28-7 Tranexamic acid for prevention of postpartum haemorrhage in cesarean section：A meta-analysis

St. Martin de Porres Charity Hospital, Philippines
Andrew Putranagara, Johan, Dionisius Aryo Purnomo

[Objectives] The aim of this paper was to evaluate the efficacy of tranexamic acid in postpartum hemorrhage prevention in cesarean section patients. [Method] A computer-aided systematic search of medical databases (PUBMED, MEDLINE, Cochrane Database) was performed. We also contacted pharmaceutical companies and experts in the field. We did not apply language restrictions. [Selection Criteria] Inclusion criteria for the studies were as follows：(1) randomized controlled trials Tranexamic acid used as prophylaxis for Postpartum hemorrhage, (2) patients was term and scheduled for elective cesarean section, (3) singleton pregnancy, (4) regular prenatal care, and (5) informed consent obtained. Exclusion criteria were as follows：(1) severe medical and surgical complications involving the heart, liver or kidney, brain disease and blood disorders, (2) allergy to tranexamic acid, (3) history of thromboembolic disorder, (4) abnormal placenta：such as placenta previa, placental abruption, placental adhesion due to repeated surgical abortions, (5) severe pregnancy complications such as severe preeclampsia, (6) multiple pregnancies, macrosomia, polyhydramnios, (7) complication with leiomyoma, (8) not a randomized controlled trial. [Data collection and analysis] A computer-aided systematic search of medical databases (PUBMED, MEDLINE, Cochrane Database) was performed. We searched for randomized controlled trials using the following keywords：(1) cesarean section [MESH] AND (2) Surgical Blood Loss [MESH] AND Tranexamic acid [MESH]. We also searched unpublished trials in clinicaltrials.gov, and did free hand search from references of our literature. Two reviewers (AP, J) will assess the retrieved eligible articles for validity and if it met the inclusion criteria. In case of differences in opinion, a third reviewer (DAP) will resolve the difference. One author will extract the data (AP), while another one will check the accuracy (J). [Results] four studies (n=1237) reported on the total blood loss, which was significantly reduced by an average of 84.87ml when tranexamic acid was administered (Mean Difference (MD) -84.87ml；95% confidence interval (CI) -105.98, -63.77). Five studies (n=740) reported on the blood loss from placental delivery to the end of cesarean section, which was also significantly reduced by an average of 125.77ml when tranexamic acid was administered (Mean difference (MD) -125.77ml；95% confidence interval (CI) -144.82, -106.72). Four studies (n=528) reported on the blood loss from the end of cesarean section to two hours post partum, which was significantly reduced by an average of 44.55ml when tranexamic acid was administered (Mean Difference (MD) -44.55ml；95% confidence interval (CI) -51.02, -38.08).

ISP-28-8 Evaluation of hypogastric artery ligation as a lifesaving method of controlling pelvic hemorrhage in obstetrics and gynecology

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［Objectives］ To evaluate internal iliac artery ligation as a lifesaving procedure in cases of intractable pelvic hemorrhage in obstetrics and gynecology. ［Method］ Total six cases, five of obstetrics and one of gynecology who underwent ligation of hypogastric arteries as a method of controlling intractable hemorrhage in a period of one year were studied and various parameters such as number of transfusions, febrile morbidity, wound and other complications and duration of stay were evaluated. In the obstetric cases two were cases of previous caesarean section with central placenta praevia, two were cases of rupture uterus and one was a case of previous caesarean section who had intractable hemorrhage during surgery. The gynaec case had avulsion of the tubo ovarian pedicle during vaginal hysterectomy. ［Results］ All except one patient who was referred with ruptured uterus in irreversible shock survived and were discharged without complications. ［Conclusion］ Ligation of hypogastric vessels is found to be a very good method of controlling intractable pelvic hemorrhage in emergency situations. In a backward rural area as ours with a large number of unbooked patients coming in emergencies it would be advisable to train the postgraduates in the procedure.

ISP-28-9 Bakri balloon tamponade for reducing blood loss during delivery and postpartum of patients with placenta previa

National Defense Medical College
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[Objective] To reduce blood loss during delivery on patients with placenta previa, various procedures for the control of uterine hemorrhage have been performed. Recently Bakri balloon was reported as an effective and safe method for reducing amount of hemorrhage at cesarean delivery of the patients with placenta previa. We retrospectively evaluated the effectiveness of Bakri balloon on the control of uterine hemorrhage during delivery and postpartum of the patients with placenta previa. [Methods] One hundred and sixteen patients with placenta previa during past six years were retrospectively evaluated. All patients were analyzed about amount of hemorrhage, methods for bleeding control, requiring blood transfusion, and occurrence of complications. This study was approved by the Institutional Review Board. [Results] Fifteen patients with placenta previa were received cesarean delivery and Bakri balloon tamponade during past two years. The amount of hemorrhage, addition of uterine artery embolization and incidence of blood transfusion after cesarean section for placenta previa decreased gradually since the administration of Bakri balloon tamponade. No complication was associated with its use. [Conclusion] It is effective and safe for using Bakri balloon tamponade to reduce blood loss during delivery and postpartum of patients with placenta previa.

ISP-28-10 Quantified Blood Loss：An Alternative Method in correlating change in pre-delivery and post-delivery hematocrit

Florida State University College, USA
Caitlin Dunham, Brittney Williams

[Objective] Obstetric hemorrhage contributes to significant maternal morbidity and mortality in the United States and worldwide. In Florida, hemorrhage caused 15% of pregnancy related deaths from 2005-2009. Few studies have assessed the correlation between estimated or quantified blood loss with change in hematocrit postpartum. Our study prospectively examined blood loss using quantification methods to better understand the change in hematocrit. [Method] A prospective observational study was conducted by reviewing the obstetric records for patients with vaginal and cesarean deliveries from March 2014-July 2014. Patients delivered at Sacred Heart Hospital were included. Patients transferred to Sacred Heart Hospital after delivery, data sheets without patient identifying information and patients without quantified blood loss calculations were excluded. Quantified blood loss was calculated using weight-based methods. [Results] During the study period, 54 patients with both visually estimated blood loss and quantified blood loss were included. Estimated blood loss and change in hematocrit have a weak correlation；however, it is not statistically significant. In comparing change in hematocrit to quantitative blood loss, a Pearson test for correlation reaches statistical significance. [Conclusion] Quantitative blood loss provides a method to correlate postpartum change in hematocrit with greater precision than estimated blood loss. Utilizing quantitative blood loss can heighten awareness of postpartum hemorrhage and lead to more timely interventions to diagnose and manage postpartum hemorrhage.

ISP-29-1 The expression of fibrosis related factor in villous stroma of placenta complicated with preeclampsia is induced by hypoxia and TGFβ stimulation

Kyushu University
Takako Ohmaru, Kazuo Asanoma, Yukiko Kondo, Nobuhiro Hidaka, Yasuyuki Fujita, Kiyoko Kato

[Objective] Fibrosis are known as one of the characteristic pathological findings of placenta in preeclampsia (PE). We focused on the relationship between pathogenesis of preeclampsia and placental fibrosis. [Methods] The expression levels of the fibrosis related factors (FRF) were compared between placentas in PE and normal pregnancy (CTL). The mRNA and protein expression levels of FRF were examined by real-time RT-PCR and immunohistological stain with Hybrid Cell Count software (Keyence), respectively. Changes in expression levels of these factors in mesenchymal cells isolated from term placentas under hypoxic condition or TGFβ stimulation were evaluated by real-time RT-PCR. This study was approved by the ethics committee in our institute. [Results] The mRNA levels of collagen fiber (COL), connective tissue growth factor (CTGF) and fibronectin (FN) in PE placentas were higher than those in CTL. The protein levels of COL, CTGF and FN in CTL were 22, 9 and 5%, respectively；in PE, 33, 12 and 13%, respectively. These protein levels of FRF in PE were significantly higher than those in CTL ($p<0.05$). The mRNA expression of FRF by hypoxic or TGFβ stimulation were more prominent in the mesenchymal cells of PE compared with CTL placentas. [Conclusion] The villous stromal cells of PE are more sensitive to hypoxic or TGFβ stimulation than those of CTL, and are prone to produce fibrosis.

ISP-29-2 Enhanced expression of lysophosphatidic acid receptors in preeclamptic placentas

The University of Tokyo
Tatsuya Fujii, Takeshi Nagamatsu, Mayuko Ichikawa-Matsubara, Takayuki Iriyama, Atsushi Komatsu, Kei Kawana, Yutaka Osuga, Tomoyuki Fujii

[Objective] Lysophosphatidic acid (LPA) is a representative lipid mediator. Six specific receptors (LPARs) have been identified so far. We previously reported reduced production of LPA producing enzyme ATX in the placenta of women complicated with preeclampsia (PE). This study aimed to investigate the expression of LPARs in the placenta with PE. [Methods] Under the approval by IRB and patient's consent, placentas were collected from pregnant women with preeclampsia (n=26) and uncomplicated pregnant women (n=20 in the first trimester and n=22 at term). The expression of LPARs in the placentas was analyzed by quantitative RT-PCR and western blotting. [Results] The mRNA expression levels of LPARs except for LPAR4 were significantly higher at term pregnancy compared to that in the first trimester ($p<0.001$). In the preeclamptic placentas, mRNA expressions of LPAR1, LPAR2, LPAR3 and LPAR4 were significantly elevated compared to normal term placentas ($p<0.05$). The increased expression of LPAR3 but not LPAR1 and LPAR2 was revealed by Western blotting analysis ($p<0.05$). [Conclusion] Our findings suggest that the altered LPA-LPAR signaling might be involved in the impaired placentation of preeclamptic pregnancy.

ISP-29-3 Cytokine levels in serum, placenta and amniotic membrane of the preterm mouse model with chronic odontogenic *porphyomonas gingivalis* infection

Hiroshima University
Yuko Teraoka, Hiroshi Miyoshi, Haruhisa Konishi, Satoshi Urabe, Mutsumi Miyauchi, Takashi Takata, Yoshiki Kudo

[Objective] It is now widely accepted that inflammation induces preterm delivery. However, the mechanism is uncertain. We found that the odontogenic *Porphyromonas gingivalis (P.g)* infection induces preterm delivery in mice. This study aimed to analyze the relationship between *P.g* infection and pro-inflammatory cytokines. [Methods] We observed *P.g* in the placenta using immunohistochemistry. We also measured TNF-α and IL-1β levels in the blood serum using ELISA and in the amniotic membrane, placenta, and myometrium using real-time PCR at day 18 of gestation in control and *P.g* mice. This study was carried out in accordance with guideline from the committee of research facilities for laboratory animal science at our University. [Results] Immunohistochemistry revealed that the *P.g* colonies were expressed primarily in the placenta at the embryo side. Serum TNF-α and IL-1β levels were 1.9 and 2.7 fold elevated in the *P.g*-infected mice. IL-1β levels in the placenta and amniotic membrane were 2.3 and 5.7 fold increased but not in the myometrium. The TNF-α level increased 2.2 fold in the placenta but not in the amniotic membrane and myometrium. [Conclusion] The high pro-inflammatory cytokine level supposed to be associated with *P.g* infection plays a role in promoting preterm delivery. However, the origin of cytokines and the mechanism leading to preterm delivery have not been confirmed.

ISP-29-4 Risk factors for retained products of conception after mid-trimester abortion

Wakayama Medical University
Tomoko Noguchi, Michihisa Shiro, Naoyuki Iwahashi, Sakiko Nanjo, Madoka Yamamoto, Nami Ota, Yasushi Mabuchi, Shigetaka Yagi, Sawako Minami, Kazuhiko Ino

[Objective] Retained products of conception (RPOC) is one of the cause of post-partum hemorrhage. Some cases of retained placenta are shown after mid-trimester abortion. We conducted a retrospective study on risk factors of RPOC after mid-trimester abortion. [Methods] This was a retrospective cohort study of 55 patients who had medical abortion between 12 weeks 0 day and 21 weeks 6 days gestation (IUFD : 19 cases, Artificial abortion : 36 cases) in our hospital. We evaluated maternal age, gestational age at delivery, null or multi parous, past history of abortion, past surgery of uterus, the number of gemeprost administration, and the period of 3rd stage labor, and analyzed their correlation with RPOC. [Results] RPOC was shown in eight cases (15.1%) of all medical abortion. Comparing the group of RPOC with non-RPOC, there were statistically significant differences in gestational age at delivery (13.4 weeks vs 18.3 weeks, $p=0.001$), the period of 3rd stage of labor (25.0 min vs 7.0 min, $p=0.019$). Multivariate analysis showed that early gestational age (less than 16 weeks) was a risk factor for RPOC. [Conclusion] The early gestational age weeks may be a risk factor of RPOC after mid-trimester abortion. Evaluation of RPOC by ultrasound after delivery is important in medical abortion at early gestational age.

ISP-29-5 Decreased expression of indoleamine 2, 3-dioxygenase in placenta with preeclampsia and/or fetal growth restriction

Wakayama Medical University
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[Objective] The objective of the study was to determine the differences in Indoleamine 2, 3-dioxygenase (IDO), a tryptophan-catabolizing enzyme, fms-like tyrosine kinase receptor-1 (Flt-1), and TGF-β expressions among normal, pleeclampsia (PE), and fetal growth restriction (FGR) placentas. [Methods] Immunohistochemistry was performed in placentas from the 3rd trimester of pregnancies complicated with either FGR alone (n=19), PE alone (n=20), or both PE/FGR combined (n=39) compared to gestational age-matched controls (n=23). Informed consent was obtained from patients for the use of materials. [Results] Flt-1 was mainly located on trophoblasts, while IDO and TGF-β were located on endothelial cells in villous stroma. Flt-1 and TGF-β were strongly expressed in FGR alone, PE alone, and PE/FGR combined groups compared to controls. PE alone group showed significantly lower IDO expression compared to FGR alone and controls, and PE/FGR combined group showed significantly lower IDO expression compared to FGR alone group. High Flt-1 and low IDO were concerned with severity of maternal hypertension or proteinuria. [Conclusion] Higher Flt-1/lower IDO expression seems to be related to PE and FGR, and also related to severity of clinical symptoms of PE. These findings suggest that IDO may play a role in pathophysiology of PE and FGR.

ISP-29-6 Gene expression profiling in the process of human cytotrophoblast differentiation into syncytiotrophoblast

The University of Tokyo
Kazuki Morita, Takeshi Nagamatsu, Atsushi Komatsu, Takayuki Iriyama, Yutaka Osuga, Tomoyuki Fujii

[Objective] In human placenta, genes and proteins involved in the cell differentiation from cytotrophoblasts (CTs) to syncytiotrophoblast (ST) are not fully elucidated. This study aimed to clarify the shift of gene expression profile in the course of the differentiation. [Methods] This study was conducted under approval of our ethics committee. CTs were isolated from the placentas of women undergoing elective caesarean section at term pregnancy (purity＞98%). Cell fusion of the isolated CTs occurred spontaneously within 72 h, forming ST in culture. Measurement of hCG secretion and desmoplakin staining were conducted to confirm CT differentiation into ST. Messenger RNA were isolated at 24h and 96h in culture and the shift of gene expression profile were evaluated by RNA sequencing (RNA-seq) technology. TopHat2 was used to align the sequence reads to the human genome. The gene expression level and the statistical significance between the samples were determined by Cuffdiff. [Results] In comparison of the expression data at 24h with that at 96h, 1768 genes showed significant alteration of gene expression levels with p-value＆1；0.05. Among them, the expression levels were elevated in 852 genes and were decreased in 916 genes. [Conclusion] Using RNA-seq, we succeeded in detecting dynamic shift of gene expression pattern in the process of cell differentiation from CTs into ST.

ISP-29-7 Transcriptome profiling of purified human trophoblast cells

Tohoku University Hospital[1], Department of Informative Genetics, Environment and Genome Research Center, Tohoku University Graduate School of Medicine[2]
Hirotaka Hamada[1], Takahiro Arima[2], Nobuo Yaegashi[1]

[Objective] Trophoblast cells in the human placenta are classified into three main types：cytotrophoblast cells (CTs), syncytiotrophoblast cells (STs) and extravillous cytotrophoblast cells (EVTs). CTs are stem/progenitor cells of STs and EVTs. STs play roles in hormone production and the exchange of nutrients and gases and EVTs invade the maternal decidua and remodel uterine spiral arteries to ensure sufficient blood supply to the fetus. It is not fully understood how the proliferation and differentiation of trophoblast cells are regulated *in vivo*. [Methods] We performed transcriptome profiling of uncultured CTs, STs and EVTs, using RNA-sequencing technology. [Results] The expression levels of more than 1000 genes dramatically changed (＞10-fold increase or decrease) during differentiation of CTs to EVTs or STs. In STs, genes encoding hormones and other pregnancy-specific secretory proteins were strongly induced and genes regulating the cell cycle were downregulated. In EVTs, immune-related genes such as chemokines and the human leukocyte antigens were significantly induced. We also identified 100 genes specifically expressed in CTs, some of which are known to be essential for the maintenance of mouse trophoblast stem cells. [Conclusion] These data will increase our understanding of normal placental development and the pathogenesis of pregnancy complications.

ISP-29-8 The investigation of placental carucium transport system

University of Occupational Environmental Health
Toshihide Sakuragi, Eiji Shibata, Satoshi Aramaki, Chiharu Tomonaga, Yukiyo Aiko, Hirohide Inagaki, Kimi Nakashima, Toru Hachisuga

[Objective] The TRPV (Transient Receptor Potential Vanilloid) 5 and 6 are members of a highly conserved family of Calcium channels sensitive to intracellular Ca2+. Recent reports describe TRPV 5 and 6 expression in human placenta, as well as kidney and intestinal epithelium. Here we compared kidney and placenta calcium transport machinery by immunohistochemistry (IHC) in order to elucidate calcium transport mechanism in the placenta. [Methods] Human placenta (10) were examined for common calcium transporting proteins found in the kidney, including TRPV 5, TRPV 6, Calbindin, PMCA ATPase, NCX1. We analyzed localization and intensity of expression. Expression signals were scored at five fields per slide. Score 0 (no signal), 1 (weak signal detected), 2 (moderate), 3 (strong). [Results] TRPV 5, TRPV 6, and Calbindin were identified in the syncytiotrophoblastic layer. PMCA ATPase was observed in the basement membrane. Overall, expression in the placenta was found to be similar to the calcium transporter localization in the kidney. However expression of NCX1, seen in kidney, was not observed in the placenta, and thus appears not to be involved in placental calcium transport mechanisms. [Conclusion] The localization of TRPV 5, TRPV 6, Calbindin, and PMCA ATPase in the human placenta suggests that they play an important role in regulated calcium transport.

ISP-29-9 Sonic hedgehog pathway may play an important role in placental function

Kyoto University Graduate School of Medicine
Hiroshi Takai, Eiji Kondoh, Mai Sato, Kaoru Kawasaki, Hikaru Kiyokawa, Mari Ujita, Yoshitsugu Chigusa, Ikuo Konishi

[Objective] We previously reported that Sonic hedgehog (=Shh) pathway was involved in preeclamptic placentas. The aim of this study is to elucidate the role of Shh pathway in placental function. [Methods] The study protocol was approved by the Ethics Committee. 20 placental samples were collected from normal and preeclamptic singleton pregnancies (n=10, respectively). The expression of Patched homolog 1 (=PTCH1), a Shh receptor, was examined using qPCR. Clinical data including placental weight and fetal birth weight were collected from medical records to investigate their association with PTCH1 expression. Primary cytotrophoblasts (=CTs) were treated with or without cyclopamine, a Shh pathway inhibitor or forskolin, an inducer of syncytialization. Moreover, primary CTs were cultured under normoxia or hypoxia ($1\%O_2$) for 24h. Alterations in the PTCH1 expression in primary CTs were evaluated by qPCR. [Results] PTCH1 expressions were significantly down-regulated in preeclamptic placentas ($P<0.0001$). 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 expressions were significantly down-regulated by cyclopamine (n=5, $P=0.0079$), while they were up-regulated by forskolin (n=6, $P=0.0411$). Hypoxia increased the expression of PTCH1 in primary CTs (n=4, $P=0.0286$). [Conclusion] Shh pathway may play an important role in placental function.

ISP-29-10 Circulating levels of C19MC-cluster microRNAs in pregnant women with abruptio placenta

Nagasaki University
Yuri Hasegawa, Kiyonori Miura, Ai Higashijima, Yuko Murakami, Ozora Tsukamoto, Shuhei Abe, Naoki Fuchi, Shoko Miura, Masanori Kaneuchi, Koh-ichiro Yoshiura, Hideaki Masuzaki

[Objective] The aim of this study was to clarify the association between circulating C19MC microRNAs in maternal plasma and abruptio placenta (AP). [Methods] All samples were obtained after receiving written informed consent and the study protocol was approved by the IRB of our university. Maternal blood samples (7 ml) at 26-40 weeks of gestation were obtained from 17 pregnant women with AP and 21 uncomplicated pregnant women (NP group). The plasma concentrations of C19MC microRNAs (miR-518b, -517a, -517c, -515-3p) were measured by quantitative real-time RT-PCR. [Results] The circulating levels of all four C19MC microRNAs in maternal plasma were higher in the AP group compared with the NP group. Plasma concentrations of miR-517c were significantly higher in the AP group compared with the NP group (41989.6 copies/μL vs 12593.1 copies/μL), while others were not significantly increased in the AP group compared with the NP group. [Conclusion] Increased levels of C19MC microRNAs in maternal plasma may be a characteristic phenomenon of established AP. This study demonstrated for the first time that the up-regulation of miR-517c occurred as a consequence of AP.

ISP-30-1 Endoplasmic reticulum (ER) stress induces vascular endothelial growth factor (VEGF) production in granulosa cells : implications for a novel therapeutic approach for OHSS

The University of Tokyo[1], The University of Toyama[2]
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[Objective] Given the emerging role of unfolded protein response (UPR), activated by ER stress, in regulating angiogenesis, we examined whether ER stress activated in granulosa cells (GC) regulates VEGF expression and whether tauroursodeoxycholic acid (TUDCA), an ER stress inhibitor already in clinical use for liver diseases, exerts a preventive effect on developing OHSS. [Methods] Cultured human GC were treated with hCG, tunicamycin (Tm), an ER stressor, and TUDCA. VEGF mRNA expression and protein secretion were examined by quantitative RT-PCR and ELISA, respectively. OHSS was induced in rats and TUDCA was injected i.p. Vascular permeability (VP) was measured and ovarian VEGF mRNA expression were examined. The study was approved by IRB. [Results] Tm increased the basal and hCG-induced VEGF mRNA expression and VEGF protein secretion in cultured human GC. Pretreatment of GC with TUDCA abrogated the effect of ER stress on the hCG-induced VEGF production. Administration of TUDCA suppressed the increase in VP observed in OHSS rats, with a concomitant reduction in VEGF mRNA expression in the ovary. [Conclusion] ER stress upregulates the hCG-induced VEGF production in GC and TUDCA prevents the development of OHSS by reducing VEGF production in GC. ER stress might be a novel therapeutic target for preventing OHSS, given its stimulatory effect on VEGF production in GC.

ISP-30-2 Fertilization of dysmorphic human oocytes and subsequent embryo development

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[Objective] To investigate the fertilization potential and subsequent embryonic development of dysmorphic mature oocytes with specific morphological abnormalities in intracytoplasmic sperm injection (ICSI) cycles. [Methods] From 35 consecutive ICSI cycles during a period of 5 years, in which at least one dysmorphic mature oocytes was obtained, the fertilization rate (FR) and embryonic development of 58 dysmorphic and 42 normal form oocytes (control 1) were compared. The FR and embryonic development of 441 normal form oocytes from another 119 ICSI cycles without dysmorphic oocytes served as control 2. Dysmorphic oocytes were classified as having a dark cytoplasm, cytoplasmic granularity, cytoplasmic vacuoles, refractile bodies in the cytoplasm, smooth endoplasmic reticulum in the cytoplasm, an oval shape, an abnormal zona pellucida, a large perivitelline space, debris in the perivitelline space, or an abnormal polar body. [Results] Overall, the FR was significantly lower in the dysmorphic oocytes group than in the normal form oocytes from the control 1 and 2 groups. Development up to the day-3 cleavage stage was significantly lower in the dysmorphic oocytes group than in the normal form oocyte group from control 2. However, the percentage of ≥6-cell embryos, and the percentage of grade A or grade B embryos at day-3 were similar between the dysmorphic oocyte group and the normal form oocyte groups. Dysmorphic oocytes with a dark cytoplasm or an abnormal polar body had a relatively good prognosis because they exhibited a 50% or greater chance of grade A embryo formation. [Conclusion] The fertilization potential of dysmorphic oocytes is lower, but their subsequent embryonic development was relatively good. Dysmorphic oocytes with a dark cytoplasm or an abnormal polar body develop into satisfactory quality embryos.

ISP-30-3 Assisted Reproductive Technology (ART) in Japan 2013. Annual report of Japan ART registry

Tokushima University[1], Tokyo Medical and Dental University[2], Saitama Medical University[3], Tokyo Metropolitan Bokutoh Hospital[4], Nippon Medical School[5], Keio University[6], National Center for Child Health and Development[7]
Akira Kuwahara[1], Tomonori Ishikawa[2], Osamu Ishihara[3], Koji Kugu[4], Rintaro Sawa[5], Kouji Banno[6], Hidekazu Saito[7], Minoru Irahara[1]

[Objective] This is the 26th report of Japan ART Registry that include results of initiated ART cycles in 2013. [Methods] Each ART cycles were directly registered through Web-based registry by all of 587 ART units existing in Japan and analyzed. [Results] 557 units reported 368,764 initiated cycles (IVF 89,868, ICSI 137,479, GIFT 67, frozen embryo transfer (FET) 141,213, oocyte freezing 15, embryo transfer with frozen oocyte122) and 41,216 live deliveries. Egg donation and PGD were not included in this data. Number of cycles increases with 13.0% compared to 2012 and 4.13% of neonates were estimated to be conceived with ART in Japan. In fresh embryo available cycles, 51.3% of cycles were decided to "freeze all". As most of these cycles were preferable cycles, the clinical pregnancy rates (PR) per aspiration and per transfer were relatively low as 6.7% and 20.8%, respectively. In contrast, PR per transfer in FET was 32.8%. As a result, 75.5% of live deliveries were delivered from FET. Single embryo transfer were performed 77.2% of fresh ET and 80.0% of FET, and multiple pregnancy rate was 3.54%. Live deliveries were done with 39,569 single, 1,479 twin and 9 triple pregnancies. [Conclusion] Number of ART was increased. ART pregnancies were reached to 4% of general conception in Japan, and 75% were derived from FET. SET was common as 75% and multiple pregnancy rate was low as 3.5%.

ISP-30-4 A trial to predict blastocyst formation by the respiratory activity of human embryos

Tohoku University[1], Akita University[2], Yamagata University[3], Hirosaki University[4], Fukushima Medical University[5]
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[Objective] To define and predict developmental competence of human embryos promptly, we investigated a correlation between respiratory activity and embryo growth. [Methods] Redundant 30 human embryos which frozen-thawed on 2nd day after fertilization, were utilized for this study under informed consent. The respiratory activity of embryos was measured at 6, 24, 48, 72 and 96 hours, followed by thawing. This experiment was approved by the ethics committee of our institution. [Results] Of 30 embryos, 9 developed to blastocyst stage (blastocyst group) and 21 arrested at various stage (arrested group). The respiratory activity in blastocyst group was significantly higher than those in arrested group at day 4 or later. Respiratory activities at day 3 tended to be high, albeit with not statistically significant. [Conclusion] We demonstrated that respiratory activity of the day 4 embryo correlated to blastocyst formation. The respiratory activity at day 3 could possibly be a useful parameter too. Though further investigation is required, we conclude that developmental competence of human embryos to blastocyst stage can potentially be predicted by measuring of the respiratory activity.

ISP-30-5 Field Survey of Reproductive Medicine in Educational Establishments for Medical Residency Programs in the Kanto Society of Obstetrics and Gynecology

Juntendo University
Yuko Ikemoto, Keiji Kuroda, Keisuke Murakami, Rie Ozaki, Yuki Ujihira, Makoto Jinushi, Jun Kumakiri, Mari Kitade, Satoru Takeda

[Objective] The Japan Society of Obstetrics and Gynecology requires educational establishments that provide medical residency programs to include the broad area. From 2016 onward, assisted reproductive technology (ART) will be demanded as essential training for doctors specializing in obstetrics and gynecology ; however, training in ART is not provided in a proportion of educational facilities. We conducted a research survey to analyze the significance and problems associated with reproductive medicine in the training system. [Methods] In 2014, we conducted a questionnaire survey regarding reproductive medicine in universities and general hospitals. This study was approved by the local ethical committee. [Results] Out of 141 facilities, we collected questionnaires from 66 (47%). Among the respondents, timing of intercourse, artificial insemination with the husband's semen, and ART were provided in 60 (91%), 45 (68%), and 31 (47%) hospitals, respectively. Junior and senior residents could not receive ART education in 27 (41%) and 19 (29%), respectively. Of 35 facilities without ART, 21 (60%) had no affiliated hospital that provided ART. [Conclusion] Although universities and general hospitals can cover comprehensive treatment, some of them do not provide satisfactory ART education. Rearrangement in the educational environment is necessary for ideal residency training programs.

ISP-31-1 Effect of S100A6 over-expression on β-catenin in endometriosis

Jiangxi Maternal and Child Health Hospital, China
Zequn Liu, Xiaoling Zhang, Meihong Chen, Qing Cao, Donghua Huang

[Objective] S100A6 is over-expressed in several human tumors, including pancreatic carcinoma, malignant fibrous histiocytoma, breast, colon, and gastric carcinoma. However, little is known about the role of S100A6 in endometriosis. The aim of the present study was to investigate the effect of S100A6 over-expression on β-catenin in endometriosis stromal cells. [Methods] Endometriotic stromal cells were transfected with an hS100A6-expressing recombinant lentivirus construct. The expression of β-catenin was assessed by western blot and reverse transcription-polymerase chain reaction. [Results] S100A6 over-expression promoted β-catenin expression at the RNA and protein levels, in endometriosis stromal cells. [Conclusions] S100A6 induces the expression of β-catenin in endometriosis stromal cells.

ISP-31-2 Increased secretion of monocyte chemoattractant protein-1 (MCP-1) in endometriotic stroma cells is mediated by cell-extracellular matrix adhesion and focal adhesion kinase (FAK)

Nagoya University
Takashi Nagai, Akira Iwase, Chiharu Ishida, Zenta Maseki, Yukiyo Kasahara, Ken Shimizu, Tomohiko Murase, Satoko Osuka, Tomoko Nakamura, Sachiko Takikawa, Maki Goto, Fumitaka Kikkawa

[Objective] Integrins have been demonstrated to regulate cell survival, proliferation and invasion via FAK in many types of cells including endometriosis. MCP-1 is one of the highly upregulated chemokines in endometriotic tissues. In the current study, we investigated that FAK and adhesion-mediated MCP-1 secretion from endometrial and endometriotic stromal cells. [Methods] We purified and cultured stromal cells from surgically removed specimens of endometrium and endometriotic cysts. All human samples were obtained with informed consent. We assayed the concentrations of MCP-1 in the culture media of endometrial stroma cells with or without endometriosis (eESC and ESC, respectively) and endometriotic cyst-derived stromal cells (CSC). [Results] The concentration of MCP-1 was more than 10-fold in CSC culture media compared to ESC and eESC. MCP-1 secretion was increased by attachment to collagen and fibronectin, although significance was only found in the fibronectin. FAK inhibitor and Jnk inhibitor inhibited secretion of MCP-1 from CSC, while MEK inhibitor did not show any inhibition. [Conclusion] Increased secretion of MCP-1 from endometriotic stromal cells was mediated via FAK which was stimulated by integrin-extracellular matrix adhesion. These results suggest that inflammatory response and cell adhesion is interrelated and implicated in the development endometriosis.

ISP-31-3 SR-16234, a selective estrogen receptor modulator, represses development of endometriosis-like lesions in rat model

Tottori University
Fuminori Taniguchi, Khine Yin Mon, Kei Nagira, Eriko Hirakawa, Yukihiro Azuma, Tasuku Harada

[Objective] Selective estrogen receptor modulators (SERM) have tissue-selective actions. SR-16234 (SRI licensed to Nobelpharma for endometriosis) is a newly developed SERM, which has an estrogen receptor (ER) αpure antagonist and ERβpartial agonist activity. We investigate the efficacy of SR16234 for the treatment of endometriosis by using the rat model. [Methods] A rat endometriosis model was established by transplanting autologous endometrial tissue (7 weeks, CD rat : n=36). All rats were ovariectomized and had subcutaneous estradiol (E2) injections. The lumen of one uterine horn was opened longitudinally and divided into two pieces. Two everted segments were sutured to the parietal peritoneum. After 4 weeks of oral SR-16234 (0.1-1 mg/kg/day) treatment, the endometriosis-like lesions were evaluated. Gene expression in the lesions was analyzed by real time RT-PCR. [Results] SR16234 decreased the weight of endometriosis-like lesions. Maximal dose (1mg/kg) of this drug completely inhibited the formation of lesions. By E2 treatment, IL (interleukin)-6 and MCP (monocyte chemotactic protein)-1, PEDF (pigment epithelium-derived factor) mRNA expression in the lesions was upregulated. Among them, SR16234 repressed E2-induced IL-6 mRNA expression and showed tendency to increase PEDF expression. [Conclusion] SR16234 had a regressive effect on the development of rat endometriosis-like lesions.

ISP-31-4 Upregulation of versican in apparently normal peritoneum in women with endometriosis is not be secondary event but may be the cause

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Hirohiko Tani[1], Akihito Horie[1], Yukiyasu Sato[2], Koh Suginami[1], Yumiko Miyazaki[1], Masashi Ueda[1], Asuka Okunomiya[1], Ikuo Konishi[1], Tamayuki Shinomura[3]

[Objective] In development of peritoneal endometriosis, we hypothesized that upregulation of versican, a major proteoglycan component of ECM, in the normal peritoneum plays an essential role. Because, our microarray analysis showed versican mRNA expression in apparently normal peritoneum is significantly higher in women with endometriosis than those without. In vitro studies showed that versican V1 enhances the attachment of primary endometrial stromal cells (ESCs) to normal peritoneal mesothelial cells (HMrSV5), and increased the invasiveness of ESCs. In present study, we examined the possible regulators in the microenvironment of women with endometriosis. [Methods] Under approval of the Ethical Committee of Kyoto University, peritoneal fluid of endometriotic women (PF, n=3) was obtained at laparoscopy. HMrSV5 cells were incubated for 24 hours in the presence or absence of PF or various cytokines. mRNA levels of versican and various cytokines in HMrSV5 cells were assessed by RT-PCR. [Results] Treatment with PF upregulated the expression of IL-6 and IL-8, but did not alter the expression of versican V1 in HMrSV5 cells. Among the factors examined, only activated TGFb1 significantly increased versican V1. [Conclusion] Upregulation of versican in the apparently normal peritoneum of women with endometriosis may not be the result of stimulation by the endometriotic peritoneal fluid.

ISP-31-5 New diagnostic interface of endometriosis：NMS-E（Numerical multi-scoring system of endometriosis）

Nippon Medical School
Masao Ichikawa, Shigeo Akira, Masaki Sekine, Shuichi Ono, Toshiyuki Takeshita

［Objective］NMS-E（Numerical multi-scoring system of endometriosis）is a new diagnostic interface of endometriosis to integrate and manage information which are necessary for an optimal surgery. The purpose of this study is to evaluate the efficacy and accuracy of NMS-E.［Methods］NMS-E integrates echographic information with an internal examination using cubic image and is comprised of the four elements I：the cyst size, II：adhesion, III：pain, IV：uterine or peri-uterine diseases. NMS-E was performed in 64 cases between 2012 and 2015. The four parameters were evaluated, 1：Specificity, sensitivity and accuracy of adhesion score of NMS-E, 2：The rate of agreement of macroscopic views and pathological views, 3：The correlation between NMS-E score and r-ASRM, 4：Postoperative complications.［Results］The mean age, BMI, operative time, and blood loss was 35.8y.o, 21.1kg/m^2, 188.4mins, 75.9ml. The sensitivity, specificity, PVP, PVN, and accuracy of adhesion score were 81.4%, 85.2%, PPV 79.2%, PNV 87.2%, 84.1% respectively. Histopathological endometriosis was found in 74% of the resected lesions. NMS-E score was well correlated with r-ASRM（0.730：P value=7.12E-12）. No one had voiding disorders.［Conclusion］NMS-E is highly effective method to predict the whole image and activity of endometriosis preoperatively and contributes to increase the safety of its surgery.

ISP-31-6 Comparison of clinical efficacy of long-term medical treatment with low dose oral contraceptives or progestin in women with endometriosis

Nagasaki University
Michio Kitajima, Ken Taniguchi, Ayumi Harada, Naoko Murakami, Tsuneo Inoue, Masanori Kaneuchi, Kiyonori Miura, Hideaki Masuzaki

［Objective］Endometriosis is a chronic inflammatory disease. Long-term follow-up is mandatory to alleviate symptom come along with life-stage of women. Although low dose oral contraceptives（OC/LEP）and progestin（P）are frequently used, the knowledge on the efficacy of long-term treatment is limited. Therefore, we investigated the clinical profiles of women who received long-term hormonal therapy.［Methods］From September 2008 to August 2015, 46 women with overt or suspected endometriosis followed-up for more than five years and treated with OC/LEP or P for at least 24 month were enrolled. The changes of clinical symptom or presence of side effects were investigated retrospectively and compared between two groups.［Results］In46 women, 26 cases received OC/LEP and 20 had P, respectively. Duration of medication was significantly longer in OC/LEP than in P（68 ± 25 vs. 51 ± 17 month, P=0.01）. In women confirmed the presence of endometriomas at the start of medication, 50%（7/14）and 46%（6/13）were disappeared during medical treatment in OC/LEP and P, respectively. Major complications were not observed, however, two women developed ovarian cancer during follow-up periods.［Conclusion］Medical therapy with OC/LEP or P should be considered in women with endometriosis as long as possible to avoid disease progression or recurrence. Occurrence of malignancy should be checked thoroughly.

ISP-31-7 Enlarged uterine corpus volume in women with endometriosis：assessment using three-dimensional reconstruction of pelvic magnetic resonance images

Kyoto Prefectural University
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［Objective］There has been few report on direct structural changes in uteri of women with endometriosis. Uterine volume and shape between women with and without endometriosis were compared by using three-dimensional（3D）reconstruction of pevlic MRIs.［Methods］75 nulligravid aged 20-45 years who had no other uterine lesion were enrolled. This study was approved by IRB of our University. Endometriosis group（EG）underwent operations for endometrioma（n=39）, whereas control group（CG）underwent operations for ovarian cysts other than endometrioma（n=36）. Based on the preoperative MRIs, we measured the sizes of uterus and the volume of the corpus using 3D images reconstructed by an image processing software.［Results］The mean uterine volume was significantly larger in EG compared with CG（50.9 ± 14.4 vs. 41.7 ± 14.3［ml ± SD］；P＜0.01）. The longitudinal length and transverse diameter of the corpus, and the longitudinal length of the endometrium were significantly larger in EG（P＜0.01）. However, there were no significant differences between two groups in uterine cavity volume, antero-posterior（AP）diameter of the corpus, diameter of the endometrium, corpus-cervix angle, diameters of anterior/posterior junctional zones, or the length or AP diameter of the cervix.［Conclusion］The volume of the corpus and length of the cavity of the uterus are enlarged in endometriosis.

ISP-31-8 Involvement of Epithelial–Mesenchymal Transition in Human Adenomyosis：role of hepatocyte growth factor and estrogen

Kyoto Prefectural University[1], Saiseikai Nagasaki Hospital[2], Nagasaki University[3]
Khaleque Khan[1], Akira Fujishita[2], Michio Kitajima[3], Hideaki Masuzaki[3], Jo Kitawaki[1]

[Objective] The exact pathogenesis of adenomyosis is elusive. We investigated the role of hepatocyte growth factor (HGF) and estrogen in the occurrence of epithelial–mesenchymal transition (EMT) in human adenomyosis. [Methods] Biopsy specimens from endometrium to myometrium were collected after hysterectomy from women with (n=15) and without (n =12) adenomyosis. The relationship between HGF and E–cadherin/N–cadherin was examined using endometrial epithelial cells (EECs) and tissues by qRT–PCR and immunohistochemistry. The gene and protein expressions of two transcriptional repressors of E–cadherin, SLUG and SNAIL, were examined using Ishikawa cells.(approved by IRB) [Results] HGF down–regulated E–cadherin and up–regulated N–cadherin mRNA expression in EECs and an inverse relationship between HGF and E–cadherin was observed in basalis endometria of women with adenomyosis. HGF induced morphological changes and promoted migration of EECs. Ishikawa cells exhibited up–regulation of SLUG/SNAIL gene expression in response to HGF and estrogen with an additive effect between them. HGF– and estrogen–promoted SLUG/SNAIL gene expression was significantly abrogated after pre–treatment of cells with anti–HGF antibody or ICI 182720. [Conclusion] HGF either alone or in combination with estrogen may be involved in gland invagination deep into myometrium by inducing EMT in women with adenomyosis.

ISP-31-9 Analgesic effects of levonorgestrel–releasing intrauterine system (LNG–IUS) on patients with and without adenomyosis

The University of Tokyo
Yasushi Hirota, Hirofumi Haraguchi, Takehiro Hiraoka, Kaori Koga, Yutaka Osuga, Tomoyuki Fujii

[Objective] LNG–IUS is a treatment for dysmenorrhea and hypermenorrhea. The aim of the study is to clarify whether the presence of adenomyosis influences the efficacy of LNG–IUS in patients with dysmenorrhea and chronic pelvic pain (CPP). [Methods] 22 patients who had started LNG–IUS treatment from 2014 to 2015 were enrolled in this study. Dysmenorrhea and CPP were evaluated by visual analogue scale score (VAS；0–100) before and 3 months after inserting LNG–IUS. This study was approved by the institutional ethics committee. [Results] Patients' ages in adenomyosis group (AM；n=14) and non–adenomyosis group (nAM；n=8) were 41 ± 4 and 40 ± 2 years (mean ± SD), respectively. Pre–treatment VAS of dysmenorrhea were 73 ± 19 in AM and 54 ± 19 in nAM, and post–treatment VAS of dysmenorrhea were 25 ± 20 in AM and 10 ± 18 in nAM (mean ± SD). Pre–treatment VAS of CPP were 33 ± 24 in AM and 36 ± 33 in nAM, and post–treatment VAS of CPP were 22 ± 13 in AM and 15 ± 28 in nAM. LNG–IUS treatment did not reduce severity of CPP but that of dysmenorrhea regardless of the presence of adenomyosis. CPP after the treatment was significantly severe in patients with adenomyosis compared to those without adenomyosis. [Conclusion] CPP severity after 3–month treatment of LNG–IUS was influenced by the presence of adenomyosis. Evaluation of CPP after long–term treatment of LNG–IUS might be required to reveal the efficacy more clearly.

ISP-32-1 Study using Anti–Mullerian hormone (AMH) about the impact of laparoscopic endometrial cystectomy on ovarian reserves

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[Introduction] Endometriosis is often treated surgically. However, ovarian reserves have been reported to decrease as healthy ovarian tissues are detached. [Objective] Anti–Mullerian hormone (AMH) levels in the blood are reported to reflect ovarian reserves, so we evaluated changes in ovarian reserves after removal of ovarian chocolate cysts by measuring these levels. [Subjects and methods] The Institutional Review Board of our department approved this study, and informed consent was obtained from each patient. The subjects were 15 women who underwent laparoscopic cystectomy with the subcutaneous abdominal wall lifting method at our department starting in October 2014. Blood tests and transvaginal ultrasonography were performed before surgery and after 1, 3, 6, 9 months, and 1 year. [Results] In all the subjects, the AMH levels declined immediately after surgery, although in most of the patients, the levels increased again at 3 months and returned to their preoperative values at 1 year postoperatively. [Discussion] We were unable to compare these patients to patients who underwent the pneumoperitoneum method at our institution, so we could only compare our results with other reports. Still, it appears that the traction methods may be useful for conserving ovarian reserves.

ISP-32-2 Utility of assessment of presurgical serum anti-Mullarian hormone values for prediction of poor ovarian responder after laparoscopic cystectomy for ovarian endometrioma

Juntendo University
Rie Ozaki, Jun Kumakiri, Mari Kitade, Keiji Kuroda, Makoto Jinushi, Yuki Ujihira, Keisuke Murakami, Yuko Ikemoto, Ayako Masuda, Noriko Kato, Satoru Takeda

[Objective] To evaluate the feasibility of prediction for the possibility of being postsurgical poor ovarian responder (POR) according to Bologna criteria after laparoscopic cystectomy for ovarian endometriomas. [Methods] Patients with ovarian endometriomas were prospectively evaluated. The serum anti-Mullarian hormone (AMH) values were measured presurgically and at 6 months after surgery. According to the criteria, postsurgical POR was defined as patient with＜1.1 ng/mL of the AMH values.(approved by IRB) [Results] Among 135 patients who underwent laparoscopic cystectomy, 58 patients were classified as postsurgical POR. Patients who underwent bilateral cystectomy was significantly positive correlation [odds ratio (OR), 2.68 ; p=0.03] and presurgical AMH was negative correlation (OR, 0.39 ; p＜0.001) to being POR. The best cut-off points of presurgical AMH value for prediction of postsurgical POR of the patients who underwent unilateral and bilateral cystectomy were 2.1 and 2.7 ng/mL, respectively. The cumulative spontaneous pregnancy rate of POR group in 46 infertile patients was significantly lower than non-POR group (12.7% vs 40.9%, p=0.03). [Conclusion] Our data suggested that the assessment of presurgical AMH value is beneficial for the prediction of postsurgical POR after laparoscopic cystectomy in patients with ovarian endometriomas according to the Bologna criteria.

ISP-32-3 Hysterectomy does not change recurrence rate of ovarian endometrioma after cystectomy

The University of Tokyo
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[Objective] Recurrence of ovarian endometrioma after cystectomy is a major issue of gynecological surgery. Since it remains unclear that hysterectomy in addition to cystectomy reduces the recurrence rate of endometrioma compared to cystectomy alone, the aim of this study is to clarify the recurrence of endometrioma after cystectomy with or without hysterectomy. [Methods] Endometriosis patients who had undergone the following surgery from 2001 to 2014 were enrolled in this study ; (1) not only cystectomy of ovarian endometrioma but hysterectomy due to the complication of uterine fibroids or adenomyosis, (2) cystectomy without hysterectomy. Recurrence of endometrioma, defined as appearance of ovarian endometrioma larger than 2 cm in diameter after surgery, was investigated retrospectively. This study was approved by the institutional research ethics committee. [Results] In 18 cases with both cystectomy and hysterectomy (Group 1 ; age, 41.6 ± 4.5 years old (mean ± SD) ; follow-up period 63 ± 31 months (mean ± SD)), the recurrence rate was 16.7% (3/18). In 704 cases with cystectomy (Group 2 ; age, 34.0 ± 5.5 years old ; follow-up period 62 ± 35 months), the recurrence rate was 24.6% (173/704 ; P=0.60, Group1 vs Group 2). [Conclusion] Our findings may suggest that simultaneous hysterectomy does not change recurrence rate of endometrioma after cystectomy.

ISP-32-4 Increased uterine artery vascular resistance on the endometrioma side in women with endometriosis

Kyoto Prefectural University
Miyoko Waratani, Taisuke Mori, Fumitake Ito, Yukiko Tanaka, Akemi Koshiba, Izumi Kusuki, Kazuhiro Iwasaku, Jo Kitawaki

[Objective] It is reported that endometriosis causes a decreased endothelial function and has a higher risk of cerebral infarction later in their life course. We examined whether uterine artery vascular resistance (UtA-VR) indices (pulsatility index, PI ; resistance index, RI) were elevated in women with endometriosis. [Methods] UtA-VR indices (pulsatility index, PI ; resistance index, RI) were measured using transvaginal Doppler sonography in 148 women with ovarian endometrioma, non-endometriosis ovarian cyst, fibroids, or normal pelvis. The UtA diameters were measured using magnetic resonance imaging. The diameters of arcuate arteries were measured histologically in excised uterine specimen sections. [Results] The PI/RI on the unilateral endometrioma side was significantly higher than those on the contralateral unaffected side, non-endometriosis ovarian cyst, fibroids, and normal pelvis (P＜0.01). There was a significant reduction of PI/RI after cystectomy of endometrioma (P＜0.01). The UtA diameters were significantly greater (P＜0.01) and the short axis/long axis diameter ratio were significantly smaller (P＜0.01) than those at the unaffected side. [Conclusion] UtA-VR increases on the endometrioma side compared with that on the unaffected side and in normal pelvis. Possible causes include adhesion/physical obstruction, local inflammation, and vessel contractions.

ISP-32-5 Anti-inflammatory effects of drospirenone on endometriosis

The University of Tokyo
Tomoko Makabe, Kaori Koga, Arisa Takeuchi, Fusako Sue, Mariko Miyashita, Gentaro Izumi, Masashi Takamura, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Yutaka Osuga, Tomoyuki Fujii

[Objective] Although Drospirenone/Ethynyl Estradiol is known to control endometriosis, the molecular mechanism has not been well clarified. The aim of this study was to evaluate anti-inflammatory effects of drospirenone on endometriotic stromal cells (ESC). [Methods] Under the IRB approval and informed consents, ESC were obtained from patients with ovarian endometrioma. ESC were isolated and exposed to IL1-β (5 ng/ml) to mimic local inflammation. 1) ESC were treated with drospirenone at the concentrations of 10^{-6} M for 3h. mRNA expressions of cytokines and growth factors were measured by quantitative RT-PCR. 2) ESC were treated with drospirenone at the concentrations of 10^{-9}–10^{-5} M for 24h. Supernatants were collected and concentrations of cytokines and growth factors were measured by ELISA. [Results] 1) Drospirenone decreased IL-6, IL-8, VEGF and NGF mRNA expression in ESC to 89.2% ($p<0.05$), 84.3% ($p<0.01$), 77.4 5.9% ($p<0.01$) and 85.1% ($p<0.01$), respectively. 2) Drospirenone decreased IL-6, IL-8 and VEGF secretion in a dose dependent manner. 10^{-5} M drospirenone decreased IL-6, IL-8 and VEGF secretion to 77.3% ($p<0.05$), 82.2% ($p<0.05$) and 69.4 7.9% ($p<0.05$), respectively. [Conclusion] Drospirenone reduced expression of inflammatory cytokines and growth factors in ESC. This reduction may be associated with the favorable clinical effect of drospirenone on endometriosis.

ISP-32-6 The process of endometrial reconstruction in the mouse model of decellularized matrix transplantation

The University of Tokyo
Takehiro Hiraoka, Yasushi Hirota, Tomoko Saito-Fujita, Tomoki Tanaka, Mitsunori Matsuo, Leona Matsumoto, Hirofumi Haraguchi, Yutaka Osuga, Tomoyuki Fujii

[Objective] Endometrial regeneration is highly potent, but its process is poorly understood. The aim of the study is to clarify the process of endometrial reconstruction. [Methods] Donor mouse uteri were decellularized by SDS treatment, and sutured at the site of artificial defects in recipient uteri. The recipient uteri on post-transplantation days 1, 5 and 90 were histologically examined. [Results] Decellularized tissues before transplantation were composed only of extracellular matrix with no remaining cells. Flat cells rapidly covered the surface of the transplanted matrix on post-transplantation day 1, and the flat cells became columnar shape which reconstitute the normal-appearing epithelium by day 5. Whole endometrial layers with normal structure were reconstructed at the sites of transplantation on day 90. Treatment of ovariectomized mice with vehicle or estradiol-17β (E2) before transplantation revealed that more regenerated epithelial cells were present in the grafts of vehicle group than those of E2 group on day 1, indicating negative impact of E2 on epithelial repair of neighboring defects. [Conclusion] Our findings demonstrated the prominent regenerative capacity of endometrial epithelium, and may provide a clue for clarifying mechanisms of endometrial remodeling which primarily occurs in the menstrual period under lower E2 levels in humans.

ISP-32-7 Hypoxia inducible factor 2α (Hif2α) regulates embryo implantation

The University of Tokyo
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[Objective] Although Hif2α, a major transcriptional factor induced by low oxygen tension, is reported to be strongly induced in the mouse uterus during embryo implantation, its role in pregnancy remains unclear. This study aimed to clarify functions of uterine Hif2α by a genetically-modified mouse model. [Methods] Female mice with deletion of uterine Hif2α (KO) were generated by crossing Pgr-cre and Hif2α-floxed mice to evaluate their pregnancy phenotypes after mating with wild-type males. [Results] KO showed not only an aberrant position of embryonic attachment to the luminal epithelium but implantation failure. Expression of Lif, a critical cytokine for implantation, was reduced in KO compared to the controls. During implantation, epithelial expression of E-cadherin, a tight junction regulator, was eliminated and epithelial alignment was collapsed at implantation sites of the controls, while both E-cadherin expression and epithelial alignment were persistent in KO. Although the treatment of KO with recombinant LIF normalized the location of embryonic attachment, it could recover neither their persistence of E-cadherin expression and epithelial alignment nor implantation failure. [Conclusion] These findings suggest that uterine Hif2α determines the position of embryo attachment by inducing Lif and allows trophoblast invasion by destructing alignment of the luminal epithelium.

ISP-32-8 Leukemia inhibitory factor in the cervical epithelium is a possible biomarker of uterine receptivity

The University of Tokyo
Shota Igaue, Yasushi Hirota, Tomoko Saito-Fujita, Hirofumi Haraguchi, Leona Matsumoto, Mitsunori Matsuo, Takehiro Hiraoka, Tomoki Tanaka, Yutaka Osuga, Tomoyuki Fujii

[Objective] The uterus acquires the capacity to receive the embryo successfully in the periimplantation period, and this capacity called uterine receptivity is critical for embryo implantation. Although several endometrial biomarkers of uterine receptivity such as leukemia inhibitory factor (LIF) have been studied, there are no reports about cervical biomarkers of uterine receptivity. The aim of this study is to examine whether cervical LIF can be a biomarker for uterine receptivity. [Methods] Mouse models of implantation and ovariectomy using C57/BL/6 wild-type mice were used. Uteri and cervices were obtained from pregnant and ovariectomized mice to assess LIF expression. [Results] Cervical LIF mRNA was expressed primarily in the epithelium, and was upregulated in the receptive phase compared to the pre-receptive phase. Two different mouse models of implantation failure induced by a progesterone (P_4) receptor antagonist RU486 or an oxidative stress inducer paraquat revealed downregulation of cervical LIF mRNA. However, RU486 injection did not suppress cervical LIF mRNA levels in the ovariectomized mice treated with estradiol-17β and P_4. [Conclusion] These findings indicate that cervical LIF is expressed in a manner depending on uterine receptivity rather than P_4 signaling, and LIF expression in the cervical epithelium can be a novel biomarker of uterine receptivity.

ISP-32-9 Role of Versican V1 in an Embryo Implantation Model

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[Objective] Versican, a component of an extracellular matrix, can regulate cell-to-cell adhesion mediated by integrinβ1 or CD44. We have shown that versican expression in endometrial epithelial cells was most prominent in the mid-secretory phase. The aim of this study was to investigate a possible role of versican in embryo implantation. [Methods] Endometrial carcinoma cell lines (Ishikawa) and spheroids of choriocarcinoma cell lines (BeWo) were used as a model for endometrial epithelium and embryo, respectively. We established versican V1-overexpressing Ishikawa cells (ISKW). First, the numbers of BeWo cells or BeWo spheroids that attached to ISKW and control Ishikawa were compared in attachment assay. Next, expressions of CD44 and integrinβ1 on Ishikawa and BeWo cells were examined by immunocytochemistry. Finally, versican expression in Ishikawa cells treated with TGF-β1 was evaluated through RT-PCR and immunocytochemistry. [Results] The number of BeWo spheroids that attached to ISKW were significantly higher than that attached to control Ishikawa. This difference was not observed when solitary BeWo cells were used. Integrinβ1 but not CD44 was strongly expressed in BeWo spheroids. TGF-β1 treatment significantly enhanced mRNA as well as protein expression of versican V1 in Ishikawa cells. [Conclusion] Versican may facilitate embryo implantation.

ISP-33-1 Infertility problems after abdominal radical trachelectomy

Kyushu University
Kana Hiasa, Katsuko Egashira, Chihiro Minami, Kaoru Okugawa, Teruhiko Kawamura, Natsuko Yokota, Kiyoko Kato

[Objective] In our facility, oncologic surgeons performed over 140 radical trachelectomy (RT) for the patients of uterine cervical cancer. We cannot estimate accurate conception rate because we do not recognize the number of patients who attempted to conceive. [Methods] We investigated 18 patients who visited our facility for infertility treatment after RT between 2012 to 2015 by medical record. Written informed consent was obtained from all participants of trachelectomy. [Results] Till now there have been a total of 19 pregnancies in 15 patients. Four pregnancies were achieved naturally. Pregnancies after IUIs were 3, and after IVFs or ICSIs were 12. The infertility rate after RT is reported to be high. Some patients complained about oligomenorrhea and had adhesion of endometrium for unknown reason. Thin endometrium despite the sufficient estrogen replacement is also seen. We also experienced some cases of premature ovarian insufficiency. [Conclusion] In our experience, 78% of patients who got pregnant were under infertility treatment. RT is meaningful for young cervical cancer patents. But it is difficult to get pregnant naturally after RT. We must be taken care of uterine body and blood flow from ovarian arteries, and pay attention to condition of endometrial cavity. We think that early application of the artificial reproductive technology is recommended.

ISP-33-2 Successful delivery after abdominal radical trachelectomy and in vitro fertilization treated in the same facility throughout：a case report

Kyushu University
Aya Takayama, Kana Hiasa, Katsuko Egashira, Teruhiko Kawamura, Natsuko Yokota, Chihiro Minami, Kiyoko Kato

The number of uterine cervical cancer patients in their 20's and 30's is increasing, and many of them want to retain their fertility. Rradical trachelectomy is a possible option for patients with early-stage cervical cancer. We experienced a case that the patient delivered after being performed radical trachelectomy and in vitro fertilization all in our hospital. The patient was a 35-year-old Japanese woman, gravida 0, para 0. She was diagnosed with cervical cancer stage Ib1 (mucinous adenocarcinoma, endocervical type). A radical trachelectomy with sentinel node biopsy was performed. Twenty months after operation, we performed egg retrieval and freezed all the embryos for fear of ovarian hyperstimulation syndrome. Five months after that, the patient became pregnant by frozen embryo transfer. From 21 weeks of gestation, she had continuous tocolytic treatment with ritodrine because of threatened premature delivery. At 35 weeks of gestation, she underwent emergency cesarean section because of premature rupture of the membrane. A boy weighing 2272g was delivered, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. Both the mother and the baby were discharged without trouble. We could observe all the course of her treatment from the operation for cancer to successful delivery. This case will help young early-stage cervical cancer patients to keep hopes for childbearing.

ISP-33-3 Survey of attitudes toward uterus transplantation among Japanese women of reproductive age

Keio University
Kiyoko Umene, Iori Kisu, Kouji Banno, Masataka Adachi, Yuya Nogami, Mamoru Tanaka, Daisuke Aoki

[Objective] To clarify the views of Japanese women of reproductive age on uterus transplantation (UTx) for uterine factor infertility. [Methods] A total of 3,892 women aged 25 to 39 years old were randomly chosen by an Internet research company and a questionnaire on UTx was conducted via the Internet in December 2014. Responses were analyzed from 3,098 subjects (mean age 32.1 ± 4.2 years old), after exclusion of inappropriate respondents in screening. The study was conducted with the approval of the institutional review board. [Results] As a result of questionnaires, deceased donors (33.8%) and mothers (19.0%) were favored as donors, and women with congenital absence of the uterus (54.4%) and hysterectomy due to a malignant uterine tumor (20.0%) as recipients. Of the respondents, 62.1%, 34.7% and 18.1% favored adoption, UTx and gestational surrogacy, respectively. In contrast, 7.0%, 21.9% and 63.3% opposed adoption, UTx and gestational surrogacy, respectively, and 89.9% opposed at least one of these options. Regarding societal acceptance for UTx, the answer rates were 15.7% for "should be permitted", 77.6% for "should be permitted with discussion", and 6.7% for "should not be permitted, even with discussion". [Conclusion] Many Japanese women of reproductive age felt that UTx is socially and individually acceptable. They were also more favorable about UTx than gestational surrogacy.

ISP-33-4 Fertility preservation in three AYA women with myelodysplastic syndrome

Nagasaki University
Noriko Nagata, Michio Kitajima, Ken Taniguchi, Naoko Murakami, Ayumi Harada, Masanori Kaneuchi, Kiyonori Miura, Hideaki Masuzaki

[Introduction] Myelodysplastic syndrome (MDS) is characterized by bone marrow failure with pancytopenia and risk of leukemia. The curative treatment approach is hematopoietic stem cell transplantation (HSCT). Fertility preservation should be considered in young women with this condition. [Case 1] 21 years old married woman was diagnosed as MDS with bone marrow chromosome aberration at 12 weeks of gestation. The patient chose to terminate pregnancy to have HSCT. Five weeks after the evacuation, ovarian stimulation was commenced while she received platelet transfusions. Twelve oocytes were retrieved and six blastocysts were vitrified. She received frozen-thaw embryo transfer two years after HSCT. [Case 2]18 years old girl was diagnosed as MDS without chromosomal aberration. Since she sought fertility preservation before progression of disease, ovarian stimulation was commenced and eight oocytes were vitrified. [Case 3] 18 years old girl had been diagnosed as severe aplastic anemia. As she evolved into MDS with bone marrow chromosome aberration, HSCT was planed and ovarian stimulation was commenced. She received frequent blood transfusion and eight oocytes were vitrified by two stimulated cycles. [Conclusions] Women with MDS at reproductive age sometimes require HSCT. Oocyte cryopreservation may be the choice of fertility preservation and could be performed under strict surveillance.

ISP-33-5 The oophorectomies conducted in this hospital for ovarian tissue cryopreservation to avoid iatrogenic sterility in patients received treatment of malignant tumor

Juntendo University Urayasu Hospital
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When young women in cancer receive aggressive chemotherapy, they may suffer from fertility loss due to irreversible reproductive damage. We conducted oocyte retrieval and oophorectomy of ten patients in laparoscopic surgery to perform oocyte and ovary cryopreservation for fertility preservation.(approved by IRB) All the patients underwent Reduced Port Surgery (RPS). The cortex of collected ovaries were sectioned 1cm × 1cm × 1mm. The oocytes and sliced ovaries were frozen with vitrification technique. The patients were admitted to into our hospital on the day before the surgery and discharged on the first day after the surgery. The average age of the patients was 23.5 ± 8.6 years old (14–41). All of them were nulliparous. They were introduced from other hospitals except one patient. The primary diseases were 6 hematopoietic tumors, 2 breast cancers, 1 osteosarcomas and 1 rhabdomyosarcomas. 7 patients had already received chemotherapy before ovarian tissue cryopreservation. The number of collected ovarian cortexes were 9.5 ± 2.3 (4–12). The number of collected oocytes were 4.2 ± 4.5 (0–16). The patient could resume the chemotherapy in 5.6 ± 1.6 days (3–7) postoperatively while taking advantage of minimally invasive surgery as the RPS. We could leave the possibility of pregnancy without delaying the treatment of primary diseases.

ISP-33-6 Study on fertility preservation of young female patients suffering from collagen disease who had led to the administration of Cyclophosphamide

The Jikei University
Eriko Shiraishi, Takayuki Haino, Yuki Ito, Atsuko Kato, Kouhei Sugimoto, Aikou Okamoto

[Study Design] Cyclophosphamide (CPA) is a DNA alkylating chemotherapeutic agent that induces ovarian toxicity and reduction in fertility in young female patients. Recently, fertility preservation consisting of egg, embryo and/or ovarian tissues freezing is recommended for women who receive CPA therapy, including patients with collagen disease. In this study, we surveyed 24 female patients under 45 years of age who were administered CPA therapy at our University Hospital from 2007 to 2014. Data including the CPA total dose, the period until CPA administration from the start of first-line treatment, and the period until CPA administration from when symptoms worsened were assessed. [Patient Characteristics] The mean age of patients was 35.0 y/o. There were 19 SLE patients and 5 others. [Results] The average CPA total dose was 1948 mg, the average period until CPA administration from the start of first-line treatment was 97.3 months, and the average period until CPA administration from when symptoms worsened was 2.3 months. The results of this study indicate that patients had more than two months available for fertility-preservation therapy. However, they would not receive the option due to the complications. Therefore, we should provide young female patient with collagen disease with information regarding fertility preservation before the onset of symptom worsening.

ISP-33-7 Usefulness of the hypersensitive antimüllerian hormone (AMH) assay for detecting very low AMH levels in association with menstrual status

Nagoya University
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[Objective] Measurement of serum concentrations of antimüllerian hormone (AMH) is useful for identifying reduced ovarian follicle pool. We investigated whether a recently developed hypersensitive ELISA kit, picoAMH, would be more effective at detecting very low AMH levels in association with menstrual status. [Methods] We recruited 73 women from previous studies with undetectable AMH levels. Serum concentrations of AMH from the same samples were assayed using ELISA kits, the AMH Gen II, and the picoAMH. [Results] AMH levels were undetectable in 68 out of 73 samples using the AMH Gen II. AMH concentration was detectable in 36 samples using the picoAMH, with 32 samples within and four samples out of the standard range, but still detectable. Thirty-two women whose AMH levels were undetectable all showed amenorrhea. We also found a significant correlation in the classes of serum AMH levels (undetectable, detectable under the limit of quantification, and measurable within the assay range) and menstrual status. [Conclusion] The present study demonstrated that very low levels of AMH, which can be detected using picoAMH, correlated with current and future ovulation status. This suggests serum AMH levels can be useful for the assessment of ovarian reserve and follow-up of women with a declined ovarian reserve.

ISP-33-8 Serum antimullerian hormone in adolescents with PCOS

JIPMER, India
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[Objective] Our study was undertaken to assess serum antimullerian hormone (AMH) levels in adolescents with PCOS in comparison with controls and to evaluate the relationship between serum AMH levels and ovarian ultrasound features in adolescents with PCOS. [Methods] This was a hospital based Case control study. 169 adolescent girls aged 13–19 years attending the Gynaecology outpatient department of a tertiary care hospital in South India from May 2013 to July 2015 were included in the study. On day 3–5 of cycle, 5ml of venous blood was taken for serum AMH levels and transabdominal ultrasound was done and details of antral follicle count, follicle distribution and ovarian volume were noted. [Results] Serum Antimullerian hormone levels were elevated in cases [9.16 (6.09–12.13)] when compared to the controls [5.8 (3.67–7.57)] and this difference was statistically significant (p=0.0001). Serum Anti Mullerian hormone levels had a positive relationship with the follicle count (p=0.0001) and peripheral follicle distribution (p=0.0001). There was a positive correlation between Serum AMH levels and mean ovarian volume (r=0.35, p=0.0001). Serum Anti Mullerian hormone levels for a derived cutoff value of >7.74 had a sensitivity of 58.82% (95% CI, 47.62–69.39), specificity of 79.76% (95% CI, 69.59–87.75), positive predictive value of 74.6%, negative predictive value of 65.6%, positive likelihood ratio of 2.91 and negative likelihood ratio of 0.52. Out of 45 cases with ultrasound features suggestive of PCOS, 27 had serum AMH levels >7.74. But, when we used AMH as a proxy marker for ultrasound features we were able to capture 27 of 45 cases contributing to approximately 60% yield. [Conclusions] Since obtaining high-quality ovarian ultrasound is not possible transabominally and often impaired due to obesity, serum AMH might serve as a surrogate marker for ovarian ultrasonographic features seen in PCOS. Hence serum AMH may therefore be a useful adjunct to assist in the diagnosis and follow-up of PCOS in adolescents.

ISP-33-9 Withdraw

ISP-34-1 A selective hysteroscopic hydro-tubation is a useful item for tubal occlusion therapy

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[Objective] IVF is not necessarily friendly for a tubal infertility patient because IVF itself burden her with a mental and economical difficulty. A balloon dilation technique (FT catheter) for tubal occlusion requires higher skills and running cost. We studied a usefulness of Hysteroscopic selective hydro-tubation (HST) for a tubal infertility patient, who was diagnosed as bilateral tubal occlusion with hystero-salpingography (HSG). [Methods] 20 patients of IVF, 10 of FT and 56 HST patients were employed. HST was performed for 22 patients diagnosed as bilateral tubal occlusion by HST with fully informed consent. We compared clinical outcome, cost, duration of hospitalization between three alternatives. [Results] Eight of ten cases diagnosed as bilateral tubal occlusion with HSG were confirmed tubal patency (7cases ; bilateral, 1 case ; unilateral). The days of visit to our clinic are IVF ; 21 ± 2.5*/**, FT ; 2.1 ± 0.4*, and HST ; 1.2 ± 0.5** (* **p < 0.01) The days of hospital stay are 3.0 ± 0.5*, 4.0 ± 1.5**, and 0.2 ± 0.4*/**. Pains are 40% (8/20) * and 100% (10/10) */** and 8.9% (5/56) **. Pregnancy rate are 30% (6/20) 30.4% (17/56) 10% (1/10) (NS), respectively. [Conclusion] HST can detect tubal patency of 80% patients diagnosed as bilateral tubal occlusion by HSG. HST is a useful item in respective of equivalent pregnancy rate of HST to that of IVF or FT, and its lower cost.

ISP-34-2 What is the most effective indication for falloposcopic tuboplasty to achieve pregnancy?

Keio University
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[Objective] The aim of this study is to clarify the optimal indication for Falloposcopic tuboplasty (FT). [Methods] This study was approved by the institutional review board, and informed consent was obtained from each patient. From 1996 through 2008, 476 patients diagnosed with unilateral or bilateral tubal occlusion or bilateral stenosis underwent FT. Of these patients 3 groups were recruited into this study by the period to conceive : early conceived group (conceived within 6 months, n=89), late conceived group (conceived over 12 months, n=32), non-conceived group (n=355). Patients who had laparoscopically assisted FT or conceived by in vitro fertilization were excluded from this study. We retrospectively analyzed the association between tubal occlusion site and pregnancy rate. [Results] The cumulative probability of conception was 32.9%, 59.8%, and 85.4%, respectively, at 3, 6 and 12 months after FT. The pregnancy rate in the patients with bilateral tubal occlusion at intramural segment (IS) was significantly high compared to patients without bilateral tubal occlusion at IS (P=0.007, odds ratio 1.82). The rate of patients with a single occlusion at IS was 26% in the early conceived group, 17.6% in the late conceived group and 7.1% in the non-conceived group. [Conclusion] The present study suggests that bilateral tubal occlusion at IS is the most suitable indication for FT.

ISP-34-3 Establishment of a mouse model for psychologically-induced miscarriage

The University of Tokyo
Takaaki Nagasaka, Takeshi Nagamatsu, Eri Inoue, Mari Hoya, Takayuki Iriyama, Atsushi Komatsu, Kei Kawana, Yutaka Osuga, Tomoyuki Fujii

[Objective]Psychological stresses caused by past episode of miscarriage can be a hidden factor to induce additional miscarriage in women with recurrent pregnancy loss. This study aimed to establish a mouse model to investigate the molecular mechanism that underlies psychological stress-induced miscarriage. [Methods] Based on the fact that DBA/2J male and CBA/J female mating is prone to develop miscarriage, psychological stress was given to pregnant CBA/J mice by restraining in an instrument, usually used to keep mice still temporarily. After repeated physical restraint for 4 hr/day from day 5 pc to 7pc, the rate of in-utero fetal absorption was assessed at day 13pc. Peripheral corticosterone level was evaluated at 7 pc to assess the mental stress following the physical restriction. [Results] Prior to the stress, the serum corticosterone was lower than the detectable limit. Following the restraint stress, the corticosterone level increased rapidly and the increment was sustained for two hours. The miscarriage rate was increased significantly (p=0.042) after the restraint stress (34.1 ± 20.1%) compared to that of control (25.0 ± 14.2%). [Conclusion] Enhanced miscarriage rate demonstrated by physical restraint model suggested that mental condition during pregnancy can affect the gestational outcome, and serum corticosterone level can be a biomarker for psychological stress in this model.

ISP-34-4 Studies on the chromosomal abnormality in patients with recurrent abortion and the prognosis of patients with inversion (9) of chromosome

Niigata University
Taro Nonaka, Makiko Takahashi, Chika Nonaka, Koichi Takakuwa, Takayuki Enomoto

[Objective] The chromosomal abnormality is one of the risk factors for recurrent abortion (RA). The inversion (9) (inv (9)) of chromosome is considered to be normal variant, and the inv (9) shown in the patients or husbands with RA is believed to be innocent. There are few reports concerning the outcome of pregnancy in patient population with RA, in which a patient or a husband possesses the inv (9). We analyzed the incidence of various chromosomal abnormalities in the patient population with RA, and also analyzed the outcome of pregnancy with inv (9). [Methods] Chromosomal karyotype was performed in 1567 couples with RA under informed consent, and the frequency of various chromosomal abnormalities in patient population was analyzed. Moreover, the outcome of pregnancy in the patients with inv (9) was investigated. [Results] Of 1567 patient couples, any chromosomal abnormalities were detected in 154 (9.8%). Of these 154 couples, inv (9) was detected in 43 couples. Thus, the frequency of inv (9) in whole patients with RA was 2.7% (43/1567). Of 43 couples, 30 patients conceived repetitively which resulted in live birth in 22 cases and spontaneous abortion in 8 cases. Of the 8 cases, 4 obtained good outcome in pregnancy afterward. [Conclusion] It is suggested that the inv (9) of chromosome has little association with the genesis of RA and adverse effects on perinatal prognosis.

ISP-34-5 Protein S deficiency complicated pregnancy in women with recurrent pregnancy loss

Kobe University
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[Objective] To evaluate whether low dose aspirin (LDA) and LDA plus heparin (LDA/H) therapies are effective in pregnant women with a history of recurrent pregnancy loss (RPL) and protein S (PS) deficiency. [Methods] In this prospective cohort study, with the agreement of institutional ethics committee and informed consents, clinical characteristics, pregnancy outcome and complications of 38 women with a history of PRL and with＜60% of plasma free PS antigen, were compared among the 3 groups ; antiphospholipid antibody (aPL)-negative women who received LDA alone (group A, n=8), aPL-negative women who received LDA/H (group B, n=22), and aPL-positive women who received LDA/H (group C, n=8). [Results] The gestational week (GW) at delivery in group C (median 32 GW, range 26-40) was earlier than 40 (34-41) GW in group A, or 38.5 (34-41) GW in group B ($p<0.05$). The birth weight (1794g, 750-3384) in group C was less than 2855 g (1716-3890) in group B ($p<0.05$). The incidences of pregnancy complications in group C were higher than that in group B ($p<0.05$). [Conclusion] Women with RPL, PS deficiency, and a positive test for aPL had high risks of pregnancy complications even when they received LDA/H therapy. Among women with RPL, PS deficiency, and a negative test for aPL, there were no differences in pregnancy outcome or pregnancy complications between LDA alone and LDA/H therapies.

ISP-34-6 Analysis from the nationwide data collection of preimplantation genetic diagnosis (PGD) outcome for recurrent pregnancy loss with translocation in Japan

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[Objective] By analyzing all the PGD data using the FISH method for recurrent pregnancy loss with translocation performed in Japan, we examined the national characteristics and considered future issues. [Methods] The 266 cases in 12 facilities from 2006 to September 2014 were compared with the ESHRE consortium data using the FISH method. The study was supported by a Ministry of Health, Labor and Welfare grant with the approval of the Institutional Review Board. [Results] The mean number of oocytes per oocyte retrieval (OR) was 6.96 (4,926/708), and the number of transferable embryos per OR was 0.77 (543/708), both of which were less than the ESHRE data (12.3 and 1.31). The pregnancy rate (PR) per OR (19.9% [141/708]) was lower, and the PR per embryo transfer (ET) (48.1% [141/293]) was higher than the ESHRE data (24.4% and 39.6%). The transferable embryo rate per number of biopsied embryos was 23.7% (543/2,290) and the miscarriage rate excluding ectopic pregnancies was 36.0% (50/139), both of which were equal to the ESHRE data (22.6% and 36.8%). [Conclusion] The number of transferable embryos was＜1 in Japan, which should be disclosed to the patients undergoing ET. Although the comprehensive array CGH method is expected to reduce the miscarriage rate, whether or not it contributes to successful pregnancies should be discussed because the number of transferable embryos will be little.

ISP-34-7 Treatment for patients with recurrent fetal losses positive for anti-cardiolipin beta2 glycoprotein I antibody and/or lupus anticoagulant using Sairei-to and low dose aspirin

Niigata University
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[Objective] It is widely accepted that anti-CL-beta2-GPI and lupus anticoagulant (LAC) are representative anti-phospholipid antibodies (APL), which correlates with generation of diversity of adverse pregnancies. The main mechanisms of this generation are considered to be direct damage to chorionic villi by APL, as well as formation of thrombi intervillous spaces. Taking account of these mechanisms, the application of immune suppressive and anti-coagulation therapy should be considered as a treatment option. In this study, we investigated the efficacy of such treatment for the patients with recurrent fetal loss (RFL) positive for APL. [Methods] Twenty-two patients with RFL were treated with the medication using Sairei-to and low-dose aspirin. In patients who revealed high titer of APL, ACH was also adopted. Of 22 cases, anti-CL-beta2-GPI was positive in 14 cases, LAC was positive in 5 cases, and remaining 3 cases were positive for both.(with patient's IC) [Results] Of 22 patients who were treated by the current protocol, the pregnancy successfully continued in 18 patients (81.8%). When 2 cases with chromosomal abnormality in chorionic villi were excluded from the study, pregnancies are successfully continued in 16 of 18 cases with the present protocol. [Conclusion] The efficacy of the current treatment for patients with RFL positive for APL was indicated.

ISP-35-1 The suppressive effect of immune stress on LH secretion is absent in the early neonatal period in rats

Tokushima University
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[Objective] Some physiological functions display weak responses to stress in the early neonatal period ; i.e., they exhibit stress hyporesponse periods (SHRP). In this study, we evaluated whether gonadotropin regulatory factors exhibit SHRP in rats. [Methods] Rats were intraperitoneally injected with lipopolysaccharide (100 μg/kg) (LPS group) or saline (control group) on postnatal day (PND) 5, 10, 15 or 25. The serum LH concentrations and hypothalamic mRNA levels of pro-inflammatory cytokines were measured at 2 hr after the injection. [Results] The serum LH concentration of the LPS group was lower than that of the control group at PND25 in both sexes, but such difference was not seen at PND5, 10, or 15 in either sex. In both sexes, the TNFα and IL-6 mRNA expression levels of the LPS group were higher than those of the control group at PND25, but not at PND5 or 10. The IL-1β mRNA expression level of the LPS group was higher than that of the control group at all time points. [Conclusion] These findings suggest that gonadotropin regulatory factors exhibit SHRP. The HPG might become responsive to immune stress between PND15 and 25, which could be related to enhanced hypothalamic cytokine expression. The avoidance of infectious stress during the early neonatal period might be important for normal development of the HPG axis.

ISP-35-2 Difference in myeloperoxidase between women with and without amenorrhea

Kanazawa Medical University
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[Objective] Myeloperoxidase is one of the enzymes derived from neutrophil, and produces reactive oxygen species to kill bacteria. Myeloperoxidase activity in female reproductive cycle was investigated to know association between inflammation and ovulation. [Methods] Blood samples were collected from 71 women aged 40 or younger to examine myeloperoxidase activity in neutrophil. The samples were from the women with (1) amenorrhea (amenorrhea group) and (2) with normal menstrual cycle (normal group) in state of (i) menstrual ; (ii) early follicular ; (iii) late follicular ; (iv) ovulatory ; and (v) luteal phase. This study was conducted using a stock data of myeloperoxidase in blood samples in the clinical laboratory after being approved by the Ethics Review Board in our institute. [Results] Myeloperoxidase index in normal group was 3.8 ± 3.5 (SD), and that was about 7.0 fold higher than that of amenorrhea group (−0.6 ± 6.4) (P=0.025, Welch's t-test). Myeloperoxidase was the highest in the ovulatory phase (5.1 ± 2.8), but it did not significantly differ to those of other phases within normal group (P=0.352, ANOVA). [Conclusion] Myeloperoxidase activity in neutrophil was highest in the ovulatory phase, suggesting that presence of inflammation is important in ovulation, although further research is needed to clarify it.

ISP-35-3 PAI-1 in granulosa cells is suppressed directly by statin and indirectly by suppressing TGF-β and TNF-α in mononuclear cells by insulin sensitizing drugs ; a new therapy for PCOS

University of Toyama[1], The University of Tokyo[2], University of Nagoya[3]
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[Objective] Plasminogen activator inhibtor (PAI)-1 is elevated with polycystic ovary syndrome (PCOS). The regulation of PAI-1 in granulosa cells (GC) was examined using human GC cell line (HGrC1). [Methods] the protocol was approved by the institute. Ovarian sections were used for immunohistochemistry. Peritoneal fluid mononuclear cell (PFMC) were obtained from ovarian tumor patients. HGrC1 were cultured with TGF-β (1 ng/ml) and/or TNF-α (5 ng/ml), and PFMC were treated with LPS (1 μg/ml) with insulin-sensitizing drugs (metformin, pioglitazone and rosiglitazone). The mRNA levels were evaluated by quantitative PCR. PAI-1 activity in HGrC1 supernatant was measured. [Results] Little expression of PAI-1 in GC in normal ovary whereas GC of PCOS exhibited distinct expression in vivo. In HGrC1, with TGF-β or TNF-α, PAI-1 mRNA levels were 10- fold or 5-fold higher than control, respectively (P＜0.01). PAI-1 activity had same tendency as mRNA levels. Simultaneous stimuli of TGF-β and TNF-α induced PAI-1 levels synergistically, which was suppressed with p38 MAPK inhibitor, ALK-5 inhibitor or simvastatin (P＜0.01). Insulin sensitizing drugs suppressed LPS-induced TGF-β and TNF-α mRNA levels in PFMC (P＜0.01). [Conclusion] We firstly found statin and insulin sensitizing agents provide a therapy for PCOS by down regulation of PAI-1 in GC and down regulation of TGF-β and TNF-α in PFMC, respectively.

ISP-35-4 Role of CD59 in remodeling of the maternal spiral artery

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[Objective] Human extravillous trophoblast (EVT) invades maternal decidua (interstitial EVT, iEVT) as well as the spiral artery (endovascular EVT, eEVT). Although eEVT can make direct contact with complement components contained in the maternal blood, eEVT is not eliminated by complement activation. CD59 is an 18–20 kDa glycosylphosphatidylinositol–anchored protein that inhibits formation of membrane attack complex (MAC), a final product in the complement activation. In the present study, we investigated the expression and the function of CD59 in EVT. [Methods] Tissue samples of early embryo implantation sites were collected from therapeutic hysterectomies during pregnancy and were subjected to immunohistochemistry using anti–CD59 antibody. All the samples were approved by the Ethics Committee of our Hospital. Human immortalized EVT cell line (Swan71) and CD59–silenced Swan71 (Sw/CD59–sh), which was established by shRNA knockdown approach, were subjected to WST assay and invasion assay. [Results] In immunohistochemistry, CD59 expression was higher on eEVT than on iEVT. Down–regulation of CD59 expression was achieved in more than 90% of Sw/CD59–sh cells. In WST and invasion assays, there was no significant difference between Swan71 and Sw/CD59–sh. [Conclusion] High expression of CD59 on eEVT suggests that CD59 contributes to protection of eEVT from complement system.

ISP-35-5 Perinatal effects of hormonal change on neuronal morphology and expression of estrogen receptor α in the amygdala of female Wistar rats

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[Objective] During pregnancy from the first trimester to a few months after delivery, some of the women suffer from depression. Amygdala is the central regions to regulate emotion. We investigate the effects of hormonal change during pregnancy and postpartum on the neuronal morphology and its relationship with the expression of estrogen receptor α (ERα) in the amygdala. [Methods] We used female Wistar rats at gestational day 15 [G15], 20 [G20], 4 days after delivery [P4], and normal estrous [E] to perform the Rapid Golgi Stain and immunohistochemistry. 1) The rat brains were stained by using the Rapid Golgi Stain protocol. The dendritic spines were counted along the first branch and spine density was determined by counting the number of the spines in 10 μm. 2) The rat brains were sectioned and incubated with anti–ERα antibody. [Results] At P4, the number of mushroom type spine density in the amygdala was significantly decreased comparing to G15, G20 and estrous rats ($p<0.05$). Similarly, the number of ERα immunoreactive cells in the central amygdala was remarkedly decreased at P4 comparing to G15, G20 and estrous rats ($p<0.05$). [Conclusion] These results suggest that the perinatal dynamic changes of the estradiol concentrations may affect the morphological changes in the amygdala via down regulating ERα expression. These findings may be related to emotional instability after delivery.

ISP-35-6 The expression of orexigenic and anorexigenic factors in middle–aged female rats that had been subjected to prenatal undernutrition

Tokushima University
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[Objective] Orexigenic and anorexigenic factors regulate food intake and energy expenditure. We studied how the expression of factors was affected by food deprivation (FD) in middle–aged female rats that had been subjected to prenatal undernutrition. [Methods] Eight pregnant rats were divided into normal nutrition (NN) or undernutrition (UN) (n=4), which received 50% of daily food intake from day 13 of pregnancy to delivery. The pups from dams were defined as the maternal NN (mNN) and maternal UN (mUN), respectively. At the age of 6 months, pups were sub–divided into : Fed and subjected to 24h or 48h FD (n=7–8). Serum leptin, hypothalamic mRNA expression levels of orexigenic or anorexigenic factors were measured. [Results] In mNN and mUN rats, serum leptin levels of the 24h and 48h FD groups tended to be lower than those of the Fed. NPY mRNA expression levels of the 24h and 48h FD groups were significantly higher in the mUN rats than in the mNN rats. OBRb mRNA expression levels of the mUN rats in the 24h and 48h FD groups were lower than those of the corresponding mNN rats. [Conclusion] These findings indicate that rats that are subjected to prenatal undernutrition exhibit upregulated expression of orexigenic factors and are more sensitive to FD in middle age, which might increase risk of developing metabolic disorders in later life, if they are housed in hypernourished condition.

ISP-36-1 A case of a marked decrease in bone mineral density during long-term administration of Dienogest

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Dienogest is a 4th generation progestin, which is effective for the treatment of endometriosis by suppressing endometrial proliferation and reducing pain. Long term administration is often performed to prevent postoperative recurrence, because it is not thought to affect bone metabolism. A 39 year-old women, 0G0P, with 9P-syndrome, had regular menstrual periods and developed endometriosis. She had undergone a left salpingo-oophorectomy because of an endometrial cyst at age 26. She developed recurrence of the endometrial cyst 6 months after surgery. Dienogest treatment was started following GnRHa therapy. Before treatment, her bone mineral density (BMD) was 0.985 g/cm^2 (YAM 102%). During Dienogest treatment her BMD gradually decreased, reaching 0.752 g/cm^2 (YAM 74%) after 7 years. Serum E_2 was 208 pg/mL before treatment, and it also fell to below 20 pg/mL. Dienogest treatment was discontinued for a while, but was started again at a half dose together with activated VitD to maintain BMD because her pain worsened. In general, Dienogest does not fully decrease serum E_2 level, but maintains it at 30 to 50 pg/ml. However, in this case E_2 levels significantly decreased. Since she did not take any medicine affecting BMD, this marked E_2 decrease would affect BMD. In this regard, serum E_2 levels and BMD should be monitored in patients receiving long-term Dienogest administration.

ISP-36-2 Effect of the dipeptidyl peptidase-4 inhibitor teneligliptin on glucose metabolism in ovariectomized mice on a high-fat diet

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[Objective] A decrease in serum estrogen in menopause is closely associated with the development of obesity and the onset of type 2 diabetes. Recently, incretin based therapies are used as a novel approach for the treatment of diabetes. In this study, we investigated the effects of DPP-4 inhibitor, teneligliptin in a mice model of postmenopausal obesity. [Methods] We prepared and analyzed three groups of mice. Control : sham-operated mice fed a regular diet, OVX-HF : ovariectomized mice fed a high-fat diet, Tene : OVX-HF mice treated with teneligliptin at 60 mg/kg/day. [Results] OVX-HF showed increased body weight, fat accumulation, hepatic steatosis, and elevations of blood glucose in GTT, while these metabolic abnormalities were significantly ameliorated in Tene. Chronic inflammations in the visceral adipose tissue such as infiltration of M1 macrophages and increased expressions of TNFa and MCP1 in OVX-HF were significantly ameliorated in Tene. Importantly, decreased energy consumption, reduced locomotor activity, and lowered body temperature in OVX-HF mice were ameliorated in Tene. [Conclusion] Teneligliptin effectively improved obesity and glucose metabolism in postmenopausal obese mice. Since obesity and reduced energy metabolism are a common physiology of menopause, teneligliptin appears to be beneficial as a treatment for type 2 diabetes in postmenopausal obesity.

ISP-36-3 Palpitation in middle-aged women is associated with anxiety

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[Objective]Palpitation is included in most of menopausal symptom inventories, whereas the precise underlying mechanism is not known. This study aims to investigate factors associated with palpitation in middle-aged women. [Methods] The records of 305 women aged 40 to 59 years who enrolled in a health and nutrition education program at a menopause clinic were analyzed cross-sectionally, approved by institutional review board. The prevalence of palpitation was estimated based on women's response to the Menopausal Symptom Scale. Effects of background characteristics, including age, menopause status, body composition, basal metabolism, cardiovascular parameters, physical fitness, life style, and psychological symptoms, on palpitation were assessed using multivariate logistic regression analysis. [Results] Palpitation was reported by 35.8% of women. Factors associated with palpitation were : resting energy expenditure ; systolic blood pressure ; pulse rate ; cardioankle vascular index ; hand-grip strength ; body ante-flexion ; regular exercise ; depression and anxiety. Multiple logistic regression analysis revealed independent association between palpitation and Hospital Anxiety Subscale (adjusted odds ratio 1.22 [1.15-1.32]). [Conclusion] Palpitation is highly prevalent in middle-aged women, and is associated with anxiety. Treatment of anxiety could relieve palpitation in this population.

ISP-36-4 Modified Gilliam–Doleris Uterine Suspension for Pelvic Organ Prolapse in a Young Nullipara

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[Introduction] Pelvic organ prolapse (POP) is a common condition in parous patients, obese patients and those at advanced age, and it is rare in patients who are nulliparous, young or thin. Uterus–sparing surgery for reproductive–age POP patients offers the potential for preserving fertility. We report the case of a young nulliparous POP patient treated with a modified Gilliam–Doleris uterine suspension. [Case] A 19–year–old Japanese woman was referred to our hospital with the complaint of failure of the vaginal pessary treatment she had received for her uterine prolapse. A magnetic resonance imaging identified an ovarian tumor measuring 17 cm diameter. Her body mass index was 23 kg/m^2. The POP quantitation score was stage III. We performed an abdominal modified Gilliam–Doleris uterine suspension and right ovarian cystectomy. The pathology of the ovarian tumor was mature teratoma. The patient has been free from recurrent prolapse for 5 years after surgery. [Discussion] Isolated POP in young and nulliparous women is rare but it occurs with a cumulative background risk. Though the original Gilliam–Doleris technique was designed for patients with uterine retroflexion, a modification of this technique should be considered a treatment option for young POP patients.

ISP-36-5 Obliterative LeFort colpocleisis for pelvic organ prolapse in elderly women aged 70 years and over

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[Objective] Treatment of genital prolapse in elderly women is challenging. The aim of this study was to evaluate the long term postoperative patient's satisfaction and objective improvement in women aged 70 years and over with high stages of pelvic organ prolapse treated with obliterative LeFort colpocleisis. [Materials and methods] From January 2003 to December 2013, female patients aged 70 years and over, who underwent colpocleisis surgery were included in this study. We reviewed the charts for preoperative and postoperative medical history, severity of prolapse, urodynamic studies, and early postoperative complications related to this procedure in these patients. Subjective outcomes were assessed by a nursing coordinator who interviewed patients by telephone in June 2014. [Results] Colpocleisis was performed in 22 elderly patients and 59% patients were of advanced age (≧80years). The mean post–operative follow up duration was 48.1 months (range 7–118). Six patients (27.3%) had died of medical problems at the time of the telephone interview. Fourteen patients (87.5%) reported a successful outcome after the operation and 2 patients (12.5%) reported improvement. For present time satisfaction, 93.8% patients reported they were satisfied. [Conclusion] Colpocleisis should be considered as one of the surgical options for treating advanced pelvic organ prolapse in elderly patients who do not wish to preserve vaginal function for sexual intercourse.

ISP-36-6 The role of physiotherapy in women with dysfunctional voiding presented as over–activity bladder—A case report

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[Objectives] Voiding dysfunction (VD) is common among women. Previous studies reported 2–25.5% prevalence rates referred for the evaluation of lower urinary tract symptoms (LUTS) with variable diagnostic criteria. Our study reported an incidence of 6.1% among women with LUTS. The major clinical presentation is irritative symptoms such as overactive bladder in 137 (63.1%) women with VD. The purpose of this report is to share our experience of physiotherapy intervention for the management of dysfunctional voiding (DV). [Methods] This 31 year–old woman suffered from LUTS for about 3 months with small bladder capacity and voiding up to 30 times per day. Urodynamic study revealed detrusor overactivity and dysfunctional voiding (low MFR and high PdetQmax). Pelvic floor muscle (PFM) examination shows hypertonic PFM with taut muscle band over left side with insufficient relaxation. The patient received pelvic floor muscle biofeedback (PFBF) emphasize on relaxation training, electrical stimulation to re–educate and strengthening the PFM and to inhibit involuntary detrusor contraction. Supervised PFM training (PFMT) performed twice weekly, and bladder retraining with urge strategy to improve OAB symptoms. Short term medication were prescribed for symptoms relieve. [Results] The symptoms got improved after one month of PFMT with decrease of daytime frequency and nocturia. After training, the PFM strength improved with adequate relaxation. [Conclusions] PFM training should emphasize on PFM relaxation in patients with VD. Teaching volitional relaxation of PFM as the initiating event in voiding will be beneficial.

ISP-36-7 Attitudes among Japanese Obstetrician/Gynecologists toward HPV vaccination, and the vaccination status of their daughters

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[Objective] Most adolescents in Japan have recently been refraining from receiving the HPV vaccine, following media reports of adverse medical events and a suspension of the governmental recommendation. We have previously reported HPV vaccination of girls is heavily influenced by their mothers' knowledge and attitudes towards cervical cancer. However, it has been unclear how the obstetricians and gynecologists themselves were affected by the negative media reports. [Methods] A questionnaire was distributed by mail to obstetricians and gynecologists previously trained at a university hospital. [Results] None of the responders' daughters received HPV vaccination after the suspension of the governmental recommendation. The number who received the HPV vaccine in 6th to 9th grade in 2014 was significantly lower than those in 2012 ($p=0.012$). However, 64% of the responders whose daughters were eligible still had the intention to vaccinate their daughter in the future. 65% of the responders also intended to recommend to their teen patients. [Conclusion] Our study revealed that obstetricians and gynecologists were negatively influenced by media reports of the adverse events of the HPV vaccine and the suspension of the governmental recommendation. However, their intention to vaccinate their daughters was much higher than that of the general population which we previously reported.

ISP-36-8 Sharing family tree between midwife and genetics team

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[Objective] Family history is very important as a part of maternity assessment. It provides information regarding the risks of inherited conditions and adverse pregnancy outcomes. In Japan, midwives routinely perform maternity risk assessments at first antenatal appointments. We believe this is a good opportunity to evaluate health risks other than maternity care. [Methods] We analysed 100 midwifery records, which were randomly chosen from 2500 cases since 2013. Records include all information collected by midwives during patient interviews. We also analysed the style of family tree used. [Results] Records are comprised of past medical history, family history, previous delivery/operation, condition of previous children, breastfeeding and social status. Most records include a family tree of three generations, however, not for families of siblings. The style of family tree used is similar to genetics standard and the information is socially focused. [Conclusion] From a genetics viewpoint, midwifery records are very useful to evaluate health risks. Unfortunately, genetics has not been considered a key focus in midwifery education in Japan. However, through sharing family information between midwife and genetics team, assessment of genetic conditions could be added to maternity care, and it would contribute to women's health.

ISP-36-9 A concept paper on human reproduction in inter-generational inter-stellar space travel—Recognising the obstetric and gynaecology issues and carcinogenesis

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［Objective］ To bring to scholarly discussion on issues pertaining to human reproduction in inter-stellar space which will require inter-generational time and exposure to carcinogenesis. Space travel and planetary colonization may one day be possible. Just like breaking the sound barrier, we have to think forward. Space colonization is worthwhile only if reproduction is attainable as journeys will last for years (inter-generational) with current technology and exposure to cosmic irradiation （carcinogenesis）; unless hibernation techniques, shielded fertilized embryo freezing - regrowth at destination or super quantum leap vehicles or other methods that transpire time evolve. ［Methods］ Many issues were identified on literature review including animal litter sizes. There are no real human studies to date. Primary issues current : zero-gravity, radiation exposure (carcinogenesis/mutations), osteoporosis, cancer formation, practicality of physical copulation-Newton's 3rd. Law and space-suits, mother-fetal-placental circulation and embryogenesis. Secondary effects : cell division, clonal expansion, sperm travel in space with coitus, white cell dysfunction-fetal immunity, radiation effects on developing embryo/shielding, artificial gravity, lowered blood pressure-lesser erection, extra-terrestial environment, cyto-skeletal effects, metabolic changes, length of gestation, if need for Caesarean delivery arises - operative and anaesthetic （gas behavior） procedural rethinking, neonatal resuscitation in weightlessness or in artificial gravity, blood transfusion, blood will float, liquids behaviour in space, APGAR score value in space, second stage maternal expulsive efforts - zero gravity of fetal weight versus volume of fetus, higher infection risks among others. Studies of human group male-female behavior/bonding in Antartica reveal male/female rivalry that jeopardises the team ; for prolonged periods in confined spaces with limited partner choices. Prolonged travel with radiation exposure-human carcinogenesis. Semen & menstrual blood will float. Radiation protection new materials that are not as cumbersome nor dense as lead that will affect spaceship designs as to lift-off weights ; assembled in space ; no-re-entry vehicle ; extra gravity （many G's） in new planetary systems among other issues. What forms of carcinogenesis - leukaemia, solid organ malignancies or other malignancies like skin cancer can occur with more frequency. ［Results］ At the current moment, human reproduction in inter-stellar space is not practicable and conceivable. Radiation effects are ovum & sperm toxic with embryotoxicity even if fertilization is successful -unless better shielding from cosmic rays materializes. There are many other issues including carcinogenesis and shielding of space travelers from irradiating cosmic rays. Simple vaginal delivery, neonatal resuscitation, anaesthetic gas behaviour, new LSCS methods/instruments in the weightlessness of space (unless artificial gravity created) need to be rethought. Neonatal vaccination issues ; new diseases are other issues. ［Conclusion］ Economics, environmental issues, political domination, major natural up-heavals, minerals in space and scientific-based endeavor may be the determinants to drive research in human reproduction in inter-stellar space and the avoidance of space travel induced cosmic radiation exposure/carcinogenesis. How present day Obstetricians & Gynaecologists pre-learn/adapt would be akin to the realization that IVF/cloning/survival from cancer was not possible years ago nor conceivable. Dare we to think?

ISP-36-10 Effect of vaginal estriol treatment for total laparoscopic hysterectomy

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［Objective］Uterine shrinkage induced by gonadotropin-releasing hormone (GnRH) agonist may facilitate total laparoscopic hysterectomy （TLH）, although GnRH agonist have side effects of vaginal atrophy, which may cause difficulty in uterine removal through vagina. This study aims to evaluate the effect of vaginal estriol therapy in TLH with GnRH agonist treatment. ［Methods］ We retrospectively reviewed 27 cases of TLH with preoperative GnRH agonist treatment, and compared surgical outcome with or without vaginal estriol use （1mg） before TLH, with informed consent to the patients. ［Results］ 12 cases （44%） used vaginal estriol. No significant difference exist in age （44 vs 45, p=0.11）, rate of nullipara （58% vs 40%, p =0.29）, uterine weight （633 vs 855, p=1）, GnRH agonist treatment cycle （3 vs 3, p=0.62） between the groups. By vaginal estriol treatment, there were no improvements in uterine removal time through vagina （18.5 min vs 11 min, p=0.24）, rate of perineal laceration （33% vs 33%, p=0.66）, in addition, there were no difference in rate of uterus size reduction by GnRH agonist （22% vs 18%, p=0.4）. ［Conclusion］ Vaginal estriol treatment before TLH with GnRH agonist therapy did not improve surgical outcome, although vaginal estriol can be used to atrophic vaginitis without reducing the effect of GnRH agonist therapy before TLH.

ISP-36-11 Foreign Body in Metrocolpos and Undesirable Consequences

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[Objective (s)] To study foreign body in metrocolpos. [Method] Prospective case collection of foreign bodies (FB) in premenarcheal children to postmenopausal women irrespective of age or parity was conducted from Jan 2002 onwards till 2015 Sept, mainly from TUTH operation and outpatient record, with only few additional special cases from other three hospitals, inclusive of health camps. [Results] There were two cases of intrauterine fetal bones retention in normal (1) and one of the obstructed didelphic uterus ; besides SPONTANEOUS FB ENTRY in 19 : {paddy grain : 18 [children (3), uterovaginal prolapse, UVP (15)] ; fruit seed retained in an adolescent for 8 years)}. SELF INSERTED FB were nail (1) in 3 year child ; stone (1) in 16 year old ; penetrating stick (2) for procurement of abortion and appliances for relief from UVP : 8 [fruit seed balls (3), sand bag (1), thyme (jwano)-(1) ; glass bangle (1) and rubber ball (1), green leaves (1)]. FB INSERTED FOR MEDICAL PURPOSES : Excluding a plastic piece deceptively kept in vagina ensuring fertility by a quack (1), remaining had medical personnel involvement. Encountered were impacted vaginal ring pessary (≥5) ; missed IUCD : 16 : retrieved from vagina (10) ; by laparotomy (2) for uterine perforation ; at hysterectomy 3 : [abdominal (1) /Saf T coil ; and vaginal[(2) ; Saf T coil (1) and Cu T (1)]or self-expelled at vaginal delivery (1). MVA cannula as retained FB : 2 [stuck in the uterine cavity (1) ; and perforating the uterus (1) that was removed by laparotomy followed by successful birth]. Persistent foul smelly vaginal discharge, bleeding or peritonism were known morbidities blown out of proportion by pyoperitoneum due to stone with fortunate survival after laparotomy/drainage of 1300 ml pus along with salphingo-oophorectomy despite prolonged hospitalization for 26 days. This appeared trivial compared to one each of VVF/RVF that resulted on removal of impacted sand bag and vaginal ring pessary besides fatal hemorrhagic sequel on rubber ball extraction from vagina. [Conclusions] Foreign body in metrocolpos and its undesired consequences must be avoided by understanding child-women psyche, provision of counseling and qualitative services, be it as simple as pregnancy termination, contraception or uterovaginal prolapse management.

ISP-37-1 Progressive direction of endometriosis evaluated by the density of follicles in the lesions of ovarian endometrioma

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[Objective] To clarify the progressive mechanism of endometriomas, we pathologically evaluated the follicle density to quantify the focal area of endometrioma. [Methods] Women who underwent laparoscopic salpingo-oophorectomy due to endometriomas were subjected (n=22) and compared to women who underwent laparoscopic risk-reducing salpingo-oophorectomy (RRSO) due to hereditary breast and ovarian cancer as control (n=10). To evaluate normal ovarian area, we defined follicle density (number of follicles in cm^2) and quantified the number of follicles. We pathologically compared between near and far side from intraoperative rupture foramen of endometrioma in each surgical specimen, and further compared to those in control cases. [Results] Median (range) age of patients with endometrioma and control were 44 (35-52) and 49 years-old (42-57), respectively. The follicle density of near and far side from rupture lesion of endometrioma were 0.9/cm^2 (0-6.8) and 2.2/cm^2 (0-7.4) (p=0.06). In control, the follicles in ovary were evenly distributed. [Conclusion] It is estimated that the normal ovarian tissue of near the rupture lesion was less than that of far side. Because endometriosis induces the inflammation near the legion and the number of follicles will decrease, the lesion of rapture during operation might be close to the origin of endometriosis, and the disease progressed to the far side.

ISP-37-2 A case report of multiple adenomyotic cysts derived from uterine serosa

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It is reported that adenomyotic cysts are usually found in the context of diffuse adenomyosis in a diameter of less than 5 mm and most of reports are demonstrated in single or a couple of cysts. Herein we report a rare case of multiple adenomyotic cysts which were derived from uterine serosa. A 34-year-old nulliparous woman came with chief complain of hypermenorrhea. She had experienced a chlamydia trachomatis infection and had surgical history of appendectomy and left salpingo-oophorectomy before 17 years. No malignant finding was detected from cervical and endometrial cytology. CA125 score was slightly increased at 78.8 U/ml. Ultrasonography and MRI showed that about twenty of cysts whose diameter ranged from 5 to 30 mm surrounded the uterine body without invading myometrium, while uterine hypertrophy caused by typical adenomyosis was not found. Considering inclusion cyst or pseudomyxoma peritonei as differential diagnosis, we selected the operation of tumor resection with fertility preservation by laparotomy. Almost all of cysts contained transparent fluid except only one cyst colored bloody. They were diagnosed as adenomyotic cysts by pathological analysis that they consisted of endometrial tissue (CD10+ and AE1/AE3+) and were covered in myometrium (α-actin+). This experience drove us to indicate that adenomyotic cysts might have a potential to show a variety of image.

ISP-37-3 Follow-up study of symptomatic submucous fibroids after hysteroscopic myomectomy

Iizuka Hospital
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[Objective] The aim of this study is to estimate the effectiveness of hysteroscopic myomectomy for symptomatic submucous uterine fibroids and identify prognostic factors for persistent or recurrence of symptoms. [Methods] 237 patients who underwent a hysteroscopic myomectomy were divided into 3 groups according to the classification of the European Society for Gynaecological Endoscopy. Type 0 (116 patients), Type I (97 patients), Type II (24 patients). The medical records and videotape records of all patients were retrospectively reviewed. [Results] Symptom improvement was achieved in 100% of Type 0 and I, 66.7% of Type II. Five-year cumulative symptom free rate after hysteroscopic myomectomy was 96.7 ± 1.9%, 87.8 ± 6.7%, and 44.5 ± 12.7% in Type 0, I, and II, respectively. Mean symptom free time is 46.2 ± 2.6 months, and 47.7 ± 2.7 months, and 24.7 ± 6.3 months in Type 0, I, and II, respectively. Logistic regression analysis revealed that co-existent of other myoma and Type II were independent prognostic factor for symptom recurrence. [Conclusion] Type I fibroids are recognized as a good indication for hysteroscopic myomectomy. In Type II, a number of patients felt their symptom was improved, but it will be better to think that curative effect is temporary.

ISP-37-4 Twisted adnexa—A Gynecological emergency and its laparoscopic manegement

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Jyoti Chaubey, Sanjay Chaubey

Twisted adnexa presents as acute abdomen. Here we present and discuss eight cases of a twisted adnexa presented as acute abdomen in our hospital. Usually these cases come to our emergency in odd hours. Few modes of investigations are available at that time and urgent intervention is needed due to acute presentation. In six cases it was twisted ovarian cyst and in two cases it was due twisted hydrosalphinx. All eight cases were delt with minimally access surgery which not only confirms the diagnosis but also have therapeutic benefits. We found that laparoscopy is a good modality to confirm the nature of gynecological emergencies and to treat the pathology. It has significantally low morbidity and promising results.

ISP-37-5 Laparoscopic creation of neovagina—Early experience from a developing country

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Sanjay Chaubey, Jyoti Chaubey

Mullarian anamoly is an uncommon congenital malformation encountered. It can manifest from septal defect to the agenisis of uterus and vagina, which can lead to severe physiological social and psychological impact on the person. Laparoscopic creation of neovagina was performed in nine patients and out come was analysed. We did slight modifications in the Vecchiett's method to utilize the available instruments, material and to reduce the cost of the procedure. Veres needle was used to pass the sutures as this helped in avoiding the injury to the pelvic organs and the blunt tip in the dissection in the avascular tissue. A suture grasping needle was used to pullout the traction sutures and tied to the locally developed traction device with a locking bolt to apply gradual traction on the glass olive placed at the hymen dimple. An invagination was created in the vesicorectal space in 10 to 12 days. The space thus created maintained with regular mould application till the patient became sexually active. The procedure is simple and safe as no need of laparotomy, bowel anastemosis or skin grafting is needed. The procedure can be performed with commonly used laparoscopic instruments and locally available materials there fore not increasing the cost of this laparoscopic procedure. Which is inhibiting in developing countries due to poor socioeconomic status of the masses. Follow up of the patients showed that it gives anatomically and functionally gratifying results.

ISP-37-6 Surgical method of laparoscopic gonadectomy and histological examination for the 3 cases of AIS (Androgen Insensitivity Syndrome)

Juntendo University
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[Objective] Androgen Insensitivity Syndrome (AIS), is caused by mutation of the gene encoding the androgen receptor. Localization of internal genitalia of AIS is intra-pelvis, intra-inguinal and intra-labia. Here, for 3 cases of AIS performed by laparoscopic gonadectomy, whose internal genitalia existed on different area. We are reporting on our findings regarding of them to demonstrate the procedure of laparoscopic surgery with VTR and analyze histological examination. Case1) There is a gonad and para-gonadal cyst intra peritoneum around inguinal. In the histological finding, there were testis consisted of seminiferous tubules, testicular artery and vas deferens. Case2) This case is an elder sister of case 1. Both gonads were could be seen in the pelvis and they were connected by cord-like tissue. In histology, the testis, fallopian tubes and rudimentary uterus were also existed in the removed masses. Case3) Both gonads existed deep in the back of the inguinal duct. In the gonads, there were testis and fallopian tubes as well. [Conclusion] laparoscopic gonadectomy could be performed anywhere the gonads existed in the pelvic cavity and some cases of AIS may have remnants of Mullerian and Wolffian duct in histology.

ISP-37-7 Laparoscopic diagnosis and treatment of 46, XY disorders of sex development

Kobe University
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Three cases of 46,XY disorder of sex development (DSD) were treated. [Case1] 18y.o.woman with primary amenorrhea visited. After accepting an informed consent blood chromosomal test showed 46XY (90%)/45X (10%). Based on hypergonadotropic hypogonadism (HH) and on genital findings, she was diagnosed as mixed gonadal dysgenesis. She received laparoscopic gonadectomy followed by Kaufmann treatment. [Case2] 19y.o.woman with primary amenorrhea visited. The defect of upper vagina and uterus was pointed out. After accepting an informed consent blood chromosomal test showed 46XY. Based on hormonal pattern and genital findings, she was diagnosed as androgen insensitivity syndrome. She received laparoscopic gonadectomy followed by estrogen replacement therapy. Vaginoplasty was scheduled later. [Case3] 18y.o. woman with primary amenorrhea visited. After accepting an informed consent blood chromosomal test showed 46XY. Based on HH pattern and genitalia findings, she was diagnosed as XY pure gonadal dysgenesis. Though informed about the risks of malignancy, it took 3years to get consent. On laparoscopy, both ovaries shrank, however histological examination revealed dysgerminoma 1a. She was followed up receiving Kaufmann treatment. [Conclusions] Only with image examination, internal gonad is difficult to examine. Laparoscopy is useful to confirm the findings and to treat with 46,XY DSD.

ISP-37-8 Ischemic heart disease and risk of perinatal factors

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[Objective] The relationship between perinatal factors and ischemic heart disease (IHD) have not been well known. [Methods] We retrospectively examined past perinatal factors for women over 40 years old, admitted in cardiovascular section in 2015. Perinatal factors were as follows ; Times of pregnancy and delivery, Method of delivery, Birth weight, Hypertensive disease in pregnant period, GDM, preterm labor and delivery, and placenta abruption. Those women were divided into two groups : IHD and non-IHD and compared perinatal factors. [Results] The incidence of perinatal factors in each groups was as follows ; Hypertensive disease (20.2% vs 18.9%) delivery of low birth weight (LFD) infant (21.5% vs 16.2%) delivery of heavy-for-date weight (HFD) infant (24.0% vs 13.5%) PTL (21.5% vs 13.5%). Each perinatal factor was higher in IHD group, but there was no significant difference. But the women who have at least one perinatal factor were significantly higher in the IHD group (p=0.045 Fisher's exact test). Furthermore, women with histories of abnormal birth weight (LFD +HFD infants) had significantly relationship to IHD. [Conclusion] The study demonstrates the risk of IHD was much higher in women who have at least one of the perinatal factors.

ISP-37-9 Clinical Examinations on a delivery of placenta and its outcomes

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[Objective] This investigation is aimed to find out the outcomes related to the delivery of placenta. [Methods] We compared 23 cases from January 2013 to August 2015 with placenta delivery time of more than 30 minutes. We classified the placenta delivery into a naturally delivered group (N group) and an artificially delivered group (A group). Artificially delivered group are defined as either using curettage, manually, or hysterectomy. [Results] Patients were 9 primiparas and 13 multiparas with two and six curettages in the past respectively. The artificial placenta deliveries were done by 4 curettages, 13 manually removed, 2 hysterectomies. All 7 patients of N group did not have curettages in the past. 7/16 patients in A group had curettages in the past. An average placenta delivery time were 352 minutes in total, 108 minutes for N group, and 210 minutes for the A group. An average of total blood losses before interventions (an average total blood losses for N group) were 1582mL in total, 1310mL for N group, 1672mL for A group. [Conclusion] From this examination, we can conclude that most of the placenta can be delivered within four hours either naturally or artificially. Even if the delivery is done in the artificial ways, most of them can be removed manually. There are also a chance for a placenta to be delivered naturally if there are no curettages in the past.

ISP-37-10 Challenges in providing maternity care in remote areas and islands for primary care physicians in Japan : A qualitative study

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[Objective] Maintaining the maternity care system is one of the biggest issues due to the decrease of the number of obstetricians, especially in remote areas and islands. This qualitative study aimed to clarify the challenges and problems for primary care physicians (PCPs) and obstetricians, and to reveal the needs to develop a better system. [Methods] We conducted semi-structured interviews to 12 PCPs and obstetricians who were practicing maternity care at a clinic/hospital in remote areas and islands across Japan. The interview data were analyzed qualitatively to elucidate the problems. This study had been approved by an ethics committee and we obtained informed consent from each participant. [Results] PCPs who engage in maternity care recognized the following problems : lack of enough OBGYN training, unclearness of the goal in OBGYN training, difficulties in consulting OBGYN doctors, lack of preparation for medical accidents, and lack of continuing training system in maternity care. [Conclusion] Developing a system in which PCPs and obstetricians can collaborate each other to assure the provision of maternity care in remote areas and islands will be needed. Development of a maternity care training program to certify PCPs, and the use of information and communication technology at remote clinics to consult OBGYN doctors may also be suggested.

ISP-37-11 The two cases of vaginoplasty and formation of new canal to vagina from uterine body in women vaginal atresia with functional uterus

Kyushu University Hospital
Kumiko Tanaka, Chihiro Minami, Kana Hiasa, Katsuko Egashira, Kiyoko Kato

The congenital agenesis of the vagina occurs in 1 in 4,000-10,000 live female births, and normal development of the uterine corpus is observed in＜10% of these patients. The traditional treatment is hysterectomy due to molimina in puberty. Here we present two cases of successful treatment for congenital vaginal agenesis with hematometra, which makes it possible to discharge menstrual blood and to preserve fertility. Case 1 ; A 14-year-old girl was referred to our hospital because of primary amenorrhea and periodic lower abdominal pain. Initial investigation revealed normal vulva, 1-cm-length vagina, no communication between uterus and vagina, and hematometra. On laparotomy, we found a normal sized uterine corpus without uterine cervix. An neovagina was created and canalized to the uterine cavity. The prosthetic device with an artificial skin graft was inserted in it. She has regular menstruation after the operation. Case2 ; A 13-year-old girl who experienced primary amenorrhoea and periodic pelvic pain was sentto our hospital. Initial investigation revealed normal vulva, no vagina, and hematometra. Laparoscopic surgery revealed normal sized uterine corpus and enlarged cervix in which chocolate-like fluid was pooling. An neovagina was created and canalized to the uterine cervix. Although vaginal dilatation was needed because of stenosis. She has regular menstruation.

ISP-38-1 Neonatal outcomes after the implantation of human embryos vitrified using a closed-system device

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[Objective] An open vitrification system : OVS maximized cooling and warming rates be by direct contact to liquid nitrogen. However, there are drawbacks of the OVS, such as the risk of contamination. To avoid the possible risk of contamination, several closed vitrification systems : CVSs have been developed. However, new concerns such as a decrease in the cooling rate have emerged. We compared the neonatal outcome and clinical safety using the CVS with the OVS. [Methods] This was a retrospective cohort study that was approved by the ethics committee of our facility. The data pertaining to a total of 875 blastocysts were divided into two groups according to the day of blastocyst vitrification. Developmental competence of blastocysts vitrified by CVS after implantation, including gestational age, birth weight, sex, Apgar score, and anomalies of newborn was compared with that obtained in the case of OVS. [Results] One hundreds thirteen of 313 patients in CVS and 206 of 562 patients in OVS had deliveried. There were no differences between the use of CVS and OVS in gestational age, birth weight, proportion of Caesarian sections, sex ratio, Apgar score, and congenital anomalies of newborns. [Conclusion] Our study offers some insights into the safety of CVS. There were no differences in the developmental characteristics after implantation or in the neonatal status between CVS and OVS.

ISP-38-2 Multiple steroidogenic pathways underlie androgen excess in polycystic ovary syndrome

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[Objective] To clarify the origin of androgens in polycystic ovary syndrome (PCOS) patients. [Methods] Blood samples were obtained form 28 PCOS patients and 31 control females. We measured serum levels of steroid metabolites in the conventional steroidogenic pathways and non-conventional pathways, i.e., a so-called backdoor pathway [pregnenolone>17-OH allopregnanolone (AP) >androstanediol (3αdiol) >dihydrotestosterone (DHT)]and a pathway from androstenedione (δ4A) to DHT via androstanedione (5α-dione). [Results] Blood levels of 17-OH progesterone (17-OHP), δ4A, testosterone (T), 5α-dione, androsterone (ADT), and 3α-diol were elevated in the PCOS group than in the control group, while the values of remaining steroids did not differ between the two groups. In the PCOS group, DHT values were correlated with T values, but not with androstanedione or 3α-diol values. Blood levels of δ4A and T paralleled those of 17-OHP. Quantitative correlations were observed between ADT and 5α-dione and between ADT and 17-OHAP. [Conclusion] The results indicate that multiple steroidogenic pathways operate in PCOS. In Japanese patients, androgens seem to be synthesized predominantly via the conventional pathways and, to a lesser extent, via the backdoor and 5α-dione-mediated pathways.

ISP-38-3 Separated double embryo transfer (s-DET) is a novel embryo transfer method to prevent multiple gestations in Assisted Reproductive Technology (ART) treatment

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[Objective] To get better results, double embryo transfer (DET) has been tried, but twin pregnancies are also increased. It is concerned that DET might disturb a suitable position for implantation, and we focused on the distance of each embryo on DET. In this study, we use a novel ET method which two embryos transferred to the separate position on DET (s-DET) and evaluated the outcomes of the s-DET compared to those of the conventional DET (c-DET). [Methods] Between May and August 2015, 174 cycles which received thawed ET were enrolled. This was a prospective randomized trial, and informed consent was obtained from all patients. The ovulatory or hormone replacement cycle were used for the endometrial preparation. Ninety-four cycles were performed c-DET, and 80 were done s-DET. The ART outcomes between two groups were evaluated. [Results] The clinical pregnancy and implantation rates in the s-DET group were 25.0 and 13.1%, respectively, these were similar to those of the c-DET group (27.6 and 17.5%). However, the twin rate was 3.5% in the s-DET group and significantly lower than that in the c-DET group (25.0% ; $p<0.05$). [Conclusion] Although s-DET is almost similar to c-DET except two embryos were transferred separately, the twin rate in s-DET group was significantly lower than the c-DET group. Therefore, s-DET may become a novel embryo transfer method to prevent multiple gestations.

ISP-38-4 The case that led to an emergency surgery to the pregnancy after IVF-ET at the uterus inside and outside same time

Ehime Rosai Hospital
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A case report of emergency surgery of normal pregnancy and ectopic pregnancy. By the progress of the assisted reproductive technology, it is said that a tendency to increase includes the incidence of pregnancy at the uterus inside and outside same time with increase in multiple pregnancy. Here, we report a case of the pregnancy at the uterus inside and outside same time led to an emergency surgery after in vitro fertilization-embryo transfer (IVF-ET) ; The patient was 23-year-old primiparous woman. She was getting infertility treatment. She subsequently became pregnant through freeze blastocyst transplant in a natural ovulation period because an uterine tube factor. At 6 weeks of pregnancy, she consulted a doctor for lower abdominal pain, cold sweat, sexual organs bleeding. ultrasonography revealed a foetal sac, a fetus heartbeat to the uterus and the right adnexa, and the pregnancy was diagnosed at the uterus inside and outside same time. It became the introduction to our course. We performed an emergency operation of extirpation of gestational sac and right fallopian tube plasty. After 5 days of operation, we confirmed fetus and a fetus heartbeat in the uterus by ultrasonography. After 16 days of operation, She became the discharge. This case suggests the importance of the follow-up of the pregnancy at the uterus inside and outside same time in case of the artificial pregnancy.

ISP-38-5 Preformed Wolffian duct regulates Mullerian duct elongation independently of canonical Wnt signaling or Lhx1 expression

Kumamoto University
Masahiko Chiga, Takashi Ohba, Hidetaka Katabuchi

[Objective] The Mullerian duct gives rise to female reproductive organs, such as the oviduct and uterus. During embryogenesis, the Wolffian duct, which generates male reproductive organs and the kidney, is formed, and the Mullerian duct then elongates caudally along the preformed Wolffian duct. However, the precise mechanisms of Mullerian duct elongation remain largely unknown. In this study, we addressed the role of Wolffian duct for the development of the Mullerian duct. [Methods] We genetically ablated the Wolffian duct by Wolffian duct-specific expression of a diphtheria toxin subunit, and examined the effects on Mullerian duct elongation. [Results] While genetic ablation of the Wolffian duct resulted in kidney hypoplasia in both male and female mutant mice, the female mutant mice lacked the uterus. At mid-gestation, the Mullerian duct was truncated at the level where the Wolffian duct was prematurely terminated in the mutant mice, meaning that Mullerian duct elongation was dependent on the preformed Wolffian duct. However, the cell proliferation, cell apoptosis and expression of Wnt9b and Lhx1 in the Wolffian duct and Mullerian duct were not affected in the mutant mice. [Conclusion] Our results suggest that the Wolffian duct regulates Mullerian duct elongation by currently unidentified mechanisms that are independent of canonical Wnt signaling or Lhx1 expression.

ISP-38-6 Platelet aggregation in citrated whole blood of the first trimester of pregnancy

Hokkaido University
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[Objective] It was recently suggested that platelet reactivity is reduced in early pregnancy. This study was performed to investigate changes in platelet reactivity in the first trimester. [Methods] This study was conducted after approval by institutional review board. Thirty-three pregnant women in first trimester and 11-non-pregnant women provided blood specimens. Platelet count and number of platelet aggregates (PA) were serially determined in the same citrated whole blood specimens at 15, 30, 45, 60, 75, and 90 minutes after blood sampling using a hematology analyzer. [Results] The number of PA (/μL) was significantly higher at 30 minutes and thereafter in both groups, but was consistently lower for pregnant than non-pregnant women over the 90-minute observation period. The platelet count decreased in a time-dependent manner in both groups, but was significantly lower at 30 and 90 minutes for non-pregnant than pregnant women. The number of PA-showed a significant positive correlation with net decrease in platelet count for both pregnant and non-pregnant women. PA counts were also significantly positively correlated with the mean platelet volume. [Conclusion] Platelet reactivity monitored by the increase in number of PA and fall in platelet count was reduced in early pregnancy compared with non-pregnant healthy controls.

ISP-38-7 Prevention strategies in perinatal women with group B streptococcal infection

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[Objective] Newborns are initially colonized with bacteria during passage through the birth canal, and Group B streptococci (GBS) are the leading cause of life-threatening neonatal bacterial infections. We investigated the actual prevention strategies used for perinatal women with GBS. [Methods] From April 1, 2004 to April 1, 2015, 18,472 full-term infants were vaginally delivered in our hospital. We found no randomized trials of standard vaginal screening for GBS and with IC between 35 and 36 weeks of gestation. GBS+ women were initially treated with Prophylactic intravenous ampicillin (PIA) in the intra-partum term. All of infants get underwent GBS screening after delivery. [Results] Of the women in the study, 15.4% (2,844) were GBS+ and treated with intravenous ampicillin, and 9.6% (232) of infants were colonized at birth. PIA of<3 g in GBS+ women reduced the risk of early-onset neonatal GBS infection to 9.9%. Additionally, PIA of>4 g in GBS+ women reduced the risk of early-onset neonatal GBS infection to 4.4%. Regarding GBS screening after delivery, 2.7% (498) of infants were GBS+, and 1.7% of GBS+ infants were born to untreated GBS- women. [Conclusion] GBS screening for newborns is an effective method of preventing GBS infection. PIA of>4 g in GBS+ women reduced the risk of early-onset neonatal GBS infection. Remarkably, 47.8% of GBS+ infants were born to GBS- women.

ISP-39-8 An internet survey intended to find ways to improve the dismal cervical cancer screening rate in young Japanese women

Osaka University
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[Objective] The cervical cancer screening rate is low in Japan. Our preliminary research in Japan has shown that many 20 year-old daughters asked their mothers for their initial cervical cancer screening, but their mothers fail to encourage them. The objective of our research is to reveal the factors that are affecting these mothers advice to their daughters. [Methods] We conducted our internet survey from February 20th to 25th, 2015. The targets of the survey were mothers who had their 20 year-old daughters still living at home with them. A 28-question questionnaire was prepared. We analyzed the correlation between mothers knowledge about cervical cancer and their daughters screening rates. The Institutional Ethics Committee. approved this research. [Results] Mothers who had their own cervical cancer screening had significantly more knowledge about cervical cancer than did the mothers who had not had a cervical cancer screening. They tended to significantly more often encourage their daughters to have cervical cancer screening. When mothers were educated with information about cervical cancer, they were significantly more likely than before to recommend that their daughters have it (all, $p<0.05$). [Conclusion] The combination of knowledge and personal experience by the mothers may provide the impetus for them to encourage their daughters to have cervical cancer screening.

ISP-39-9 Estrogen-related receptor alpha promotes angiogenesis and proliferation in uterine endometrial cancer

Kyoto Prefectural University of Medicine
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[Objective] Estrogen dependency is a common feature of most endometrial cancers. Estrogen-related receptor α (ERRα) is structurally similar to ERα. However, it is considered as an orphan receptor due to the lack of identified physiological ligands. This study aimed to investigate the role of ERRα in tissues derived from uterine endometrial cancer. [Methods] After obtaining informed consent and IRB approval, immunohistochemistry was performed on 56 specimens collected from endometrial cancer patients. Cell proliferation, cell cycle, angiogenesis, sensitivity to anti-tumor drugs and protein expression levels, in vivo tumorigenecity were analyzed using WST-8 assay, flow cytometry, luciferase assay, real-time PCR, and western blot analysis. [Results] ERRα was positively expressed in all tissues examined. This expression pattern was associated with advanced clinical stage and serous histological type ($P<0.01$). With a negative prognostic significance, knockdown of ERRα suppressed angiogenesis via VEGF, inhibited cell proliferation ($P<0.01$), induced cell cycle arrest at the mitotic phase, and caspase-3 dependent apoptosis. A significant reduction of tumor growth and angiogenesis was observed in xenografts ($P<0.01$) with ERRα knockdown. [Conclusion] We propose that ERRα may be a potential therapeutic target for endometrial cancer.

ISP-39-10 Identification of microRNA as a biomarker in primary ovarian cancer

Fukuoka Medical University
Satoshi Fukagawa, Kohei Miyata, Fusanori Yotsumoto, Shingo Miyamoto

[Objective] The aim of this study is to identify a micro RNA (miRNA) which is associated with clinical prognosis in patients with primary OVCA. [Methods] The sera in 12 patients with primary OVCA were used in microarray analysis. The association between the expression of these analyzed miRNAs in the use of qRT-PCR and clinical stages were examined in 98 patients with primary OVCA. In vitro, WST8 assay in the absence or presence of cisplatin or paclitaxel was performed, using SKOV-3 cell lines with or without the transfection of miRNA or siRNA for miRNA. In vivo, stable overexpression miR-135a in SKOV-3 cells was injected subcutaneously into SHO mice. This study approved by IRB. [Results] In the microarray analysis and the analysis for 98 patients with primary OVCA using qRT-PCR, miRNA-135a indicated the significantly lower expression in the patients with advanced OVCA. In WST8 assay, the number of transfected cells with miR-135a significantly decreased. Additionally, the number of transfected cells with siRNA for miR-135a significantly increased. In the presence of cisplatin or paclitaxel, the number of transfected cells miR-135a significantly suppressed. In vivo stable overexpression miRNA-135a in SKOV-3 cells inhibited tumor growth in SHO mice. [Conclusion] miRNA-135a may be involved in chemo-sensitivity and be recognized as a candidate of significant biomarker in primary OVCA.

ISP-39-11 Efficacy of weekly paclitaxel and carboplatin for neoadjuvant chemotherapy of epithelial ovarian cancer with poor condition patients

Kinki University
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[Objective] Ovarian cancer is often diagnosed at advanced stage and patients have poor performance status (PS) with progression, so less toxic therapy is required for successful treatment and improvement of prognosis. The purpose of this study is to assess if weekly paclitaxel and carboplatin (wTC) is useful as neoadjuvant chemotherapy (NACT) for epithelial ovarian cancer with poor condition patients. [Methods] Patients with stage III/IV epithelial ovarian cancer who underwent NACT by wTC (n=20) and triweekly TC (twTC) (n=18) were analyzed about the efficacy and toxicity. [Results] All of wTC patients presented with PS 2 or 3, which was poor compared with twTC patients. In wTC patients, 80% of patients could be performed interval debulking surgery (IDS), which was similar in twTC patients. Regarding as toxicity, grade 3/4 anemia (20% vs. 56%), thrombocytopenia (0% vs. 61%), over grade 2 neuropathy (0% vs. 33%), and treatment delay over 14 days (0% vs. 38.9%) were significantly high incidences in twTC patients. There were no statistical differences in progression free survival and overall survival. [Conclusion] Weekly administration of paclitaxel and carboplatin had less hematological and non-hematological toxicities while having equal efficacy compared with conventional twTC. NACT with wTC might be a treatment option for poor PS patients with ovarian cancer.

ISP-39-12 A prospective study on the safety on chemotherapy combined with bevacizumab in Japanese patients with recurrent ovarian cancer

Keio University
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[Objective] Recent overseas phase III clinical trials revealed that adding bevacizumab (Bev) to chemotherapy (CT) improved progression-free survival in patients with ovarian cancer (OC). The aim of this study was to assess the safety of CT with Bev in Japanese patients with recurrent OC. [Methods] In this study, 16 recurrent OC patients selected to receive CT with Bev were enrolled. Patients in poor general condition were excluded. After the institutional review board approval and written consent were obtained, each patient was monitored prospectively for adverse events (AEs). Treatment was continued until intolerable AEs or disease progression. [Results] Paclitaxel plus carboplatin with Bev was performed for 12 platinum-sensitive recurrence patients (median cycle ; 7.5), while topotecan with Bev for 4 platinum-resistant recurrence patients (median cycle ; 5.5). Serious AEs (>CTCAE Grade 2) occurred in 13 patients, including hematological toxicity required blood transfusion, hypertension, allergic reaction, diarrhea, and sepsis. Grade 2 hypertension, proteinuria, and venous thrombosis occurred in 7 patients, which were thought to be associated with Bev. None of the patients experienced GI perforation. [Conclusion] CT with Bev was tolerated by Japanese patients with recurrent OC. Our results suggest that CT with Bev can be performed safely under careful management.

ISP-39-13 The adequate distance of suture ligature in the laparoscopic surgery

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[Objective] In a previous study, we described that the best direction was zero degree against foot direction and the best angle was 65–77° between ground and a needle-holder to suture ligature at a diamond trocars position in laparoscopic surgery. In the present study, we investigated the adequate distance to suture ligature. [Methods] We fixed the direction and degree with previous study results. We set up equally-spaced 10 points between 6cm and 24cm from a center trocar. We sutured 10 times and measured these times. [Results] The average time and S.D. of each 6cm- 24 cm point were 51.4 ± 7.0, 40.8 ± 1.9, 37.4 ± 4.4, 33.5 ± 2.1, 31.4 ± 2.9, 32.3 ± 3.7, 33.2 ± 2.9, 36.5 ± 3.3, 40.2 ± 4.0, 42.7 ± 4.9. The point of 6cm required significantly more time than the other points. 8cm point did than 12cm-18cm points. 22 cm point did than 14cm-16cm points. 24 cm point did than 12-18cm points. [Conclusion] We revealed that it takes longer time to suture at short and long distance points. At short distances, a narrow work-space, trocars obstruction, the bigger motion need for pulling a string might be associated. At long distances, each other forceps obstruction, difficulty of a circle motion for ligature, difficulty of fine motion due to long distance might be associated. Therefore, we will apply this result in a clinical setting by modifying trocar position and uterine manipulator motion etc.

ISP-40-1 Accuracy and limitation of image diagnosis of lymph node metastasis in uterine cervical cancer

Kinki University
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[Objective] Precise evaluation of lymph node (LN) metastasis in uterine cervical cancer before treatment is important to determine therapeutic strategy. The aim of this study is to investigate accuracy and limitation of image diagnosis of LN metastasis in cervical cancer. [Methods] We reviewed 124 patients of cervical cancer performed pelvic LN dissection from January 2009 to June 2015. Preoperative diagnosis of LN metastasis by MRI, CT, and PET-CT was compared to the pathological diagnosis. We analyzed other factors than LN size whether they contribute to diagnostic accuracy or not. [Results] When LN metastasis was defined as over 10mm short-axis diameter, sensitivity, specificity, positive predictive value, negative predictive value, and correct diagnostic rate were 59% (95%CI : 41-76%), 92% (85-97%), 73% (52-88%), 87% (78-93%), and 84% (76-90%). Sensitivity was 38% when pathological metastasis was 1-3 in number, while it was 88% (p=0.009) when metastasis exceeds 4, suggesting diagnostic difficulty when metastasis is small in number. Sensitivity of low stage (IA1-IB1) cases vs advanced cases was 38% vs 74% (p=0.07), indicating metastasis is easily missed in low stage cases. [Conclusion] Image diagnosis of LN metastasis in cervical cancer is not so accurate, especially when metastasis is small in number and in low stage cases. Developing a new method to make accurate diagnosis is needed.

ISP-40-2 Patient's characteristics and reproductive outcomes of radical trachelectomy

Tohoku University
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[Objective] Radical abdominal trachelectomy (RAT) is a treatment option for early stage uterine cervical cancer patients who desire to preserve their fertility. In this report, we present here, characteristics and obstetric outcomes of patients who underwent RAT in our hospital. This study was approved by the Ethical Committee of our hospital, and written informed consent was obtained from the patients. [Methods] This is a retrospective follow-up study. Patient's characteristics, reproductive and obstetric outcomes of 24 patients who underwent RAT during 11 years of 2002-2013 were investigated. [Results] Patients' median age was 32 years. Nine out of 24 underwent infertility treatment. The median period until they started infertility treatment was 24.4 (9-60) months. Three out of 24 patients became pregnant. Two and one patients conceived naturally and IVF, respectively. A patient who conceived naturally had induced abortion. Two patients underwent planned cesarean section at 36 weeks of gestation, and got healthy babies. [Conclusion] Reproductive outcome was relatively poor after RAT. This probably attributed to delay on fertility intervention, albeit with a ban on conception is lifted at 6 months after RAT in our facility. An appropriate counseling involving information of reproductive and perinatal prognosis related to RAT, should actively be provided by reproductive specialist.

ISP-40-3 Expressions of TUBB3 and Bcl-2 effect paclitaxel sensitivity in ovarian cancer cell

Iwate Medical University
Ikue Ishikawa, Fumiharu Miura, Atsumi Kojima-Chiba, Hiroaki Itamochi, Chihaya Maesawa, Toru Sugiyama

[Objective] Chemotherapeutic resistance is one of the most crucial topics for ovarian cancer treatment. Some studies have investigated that the association between expression of TUBB3 and paclitaxel resistance. And it is already known that MCL1 (Bcl-2 family) regulated sensitivity to antitubulin chemotherapeutic. We investigated how these proteins involve paclitaxel resistance in ovarian cancer. [Methods] We used ovarian cancer cell lines obtained from Riken Cell Bank. Expressions of TBB3, Bcl-2, Bcl-XL, MCL1 and FBW7 in ovarian cancer cell lines were investigated by Westernblotting and real-time RT-PCR. ATPase assay was performed with siRNA (TUBB3) and ABT-737 (Bcl-2 inhibitor). [Results] Expression of TUBB3 associated with paclitaxel resistance. But there were no association between expression of MCL1/Bcl-2 (Bcl-2 family) and paclitaxel sensitivity. However paclitaxel sensitivity was increased in ovarian cancer cell line when the combination of siRNA for TUBB3 and ABT-737 was used. [Conclusion] This study suggested that Bcl-2 expression associated with paclitaxel sensitivity not only TUBB3 and MCL1. It is needed to investigate that the effect paclitaxel sensitivity by the other Bcl-2 family protein, Bcl-XL and FBW7.

ISP-40-4 Predictive factors for oocyte retrieval failure in controlled ovarian hyperstimulation with GnRH agonist or antagonist protocols

Yamagata University
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[Objective] To elucidate analyzed the predictive factors for oocyte retrieval failure following controlled ovarian hyperstimulation (COH) with GnRH agonist and GnRH antagonist protocols in ART programs. [Methods] This study was a retrospective cohort observational study and approved by the ethical committee. In total, 744 cycles from 361 patients who underwent COH with GnRH agonist long or antagonist protocol were examined. Treatment cycles with oocyte retrieval failure and with one or more oocytes retrieved were compared to determine predictive factors for oocyte retrieval failure. [Results] Oocyte retrieval failure occurred in 38 cycles (5.1%). Cycles with GnRH antagonist protocol (OR 3.06, 95% CI 1.05-8.96), LH level on the day of hCG injection (OR 1.19, 95% CI 1.06-1.33), and estradiol level on the day of hCG injection (OR 0.997, 95% CI 0.996-0.998) were independent predictive factors for oocyte retrieval failure, on multivariate logistic analysis. In all cycles, the areas under the curve (AUCs) for estradiol and LH were 0.84 and 0.63 ; 0.84 and 0.52, respectively, for cycles with GnRH agonist long protocol ; and 0.81 and 0.82, respectively, for cycles with GnRH antagonist protocol. [Conclusion] Our results suggest that in cycles with GnRH antagonist protocol, the levels of estradiol and LH on the day of hCG injection might be predictive factors for oocyte retrieval failure.

ISP-40-5 Significant clinical response of glypican-3-derived peptide vaccine therapy for progressive recurrent ovarian clear cell carcinoma

Nagoya University
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[Objective] Glypican-3 (GPC3) is carcinoembryonic antigen and it's not expressed normal cell. Vaccine immunotherapy that targeted human leukocyte antigen (HLA)/GPC3 peptide complex was reported the clinical response of advanced hepatocellular carcinoma. In previous study, we showed that 40% of ovarian clear cell carcinoma (CCC) express GPC3, so we prepared the clinical trial. We performed phase 2trial to evaluate the clinical outcome of ovarian CCC patients treated with a GPC3-derived peptide vaccine. [Method] One of the subjects this study is the recurrent CCC of chemotherapeutic agent resistance. We screened the HLA type and the patients of HLA-A2 or A24 participated in this study. [Case report] Case1. A 42y patient with advanced recurrent ovarian CCC with liver and retroperitoneal lymph node metastases, received the HLA-A24-restricted GPC3 peptide vaccine. CT at week 10 revealed a partial response (PR). Case2. A 67y female with multiple lymph node metastases. She was injected with the HLA-A2-restricted GPC3 peptide vaccine. PR was achieved at week 37. Case3. A 65y patient with peritoneal dissemination. She was treated with HLA-A24-restricted GPC3 peptide vaccine, and kept PR for 9 months. [Conclusion] This study reveals the clinical response of GPC3 peptide vaccine for the patients of CCC. In a few cases, the effectiveness of GPC3-peptide vaccine was showed, and it may improve the overall survival of CCC patient.