

Department of Obstetrics and Gynecology

Aikou Okamoto, *Professor*
 Hiroshi Sasaki, *Professor*
 Shigeki Niimi, *Associate Professor*
 Hirokuni Takano, *Associate Professor*
 Osamu Samura, *Associate Professor*
 Kouhei Sugimoto, *Assistant Professor*
 Nozomu Yanaiharu, *Assistant Professor*

Kazuhiko Ochiai, *Professor*
 Seiji Isonishi, *Professor*
 Kuniaki Ohura, *Associate Professor*
 Kyosuke Yamada, *Associate Professor*
 Satoshi Takakura, *Assistant Professor*
 Hiroshi Tanabe, *Assistant Professor*
 Motoaki Saitou, *Assistant Professor*

General Summary

The main research topics of our department are the development of molecularly targeted agents for gynecologic tumors, including ovarian cancer, clarification of the mechanisms of successful pregnancy, and the development of assisted reproductive techniques. These topics were investigated both experimentally and clinically.

Research Activities

Gynecologic oncology

1. Antitumor effects of the interleukin 6/interleukin 6 receptor signaling pathway inhibition in clear cell carcinoma of the ovary

We aimed to clarify whether the interleukin 6 (IL-6)/IL-6 receptor (IL-6R) mediated signaling pathway has clinical relations with clear cell carcinoma of the ovary (CCC) and to evaluate the inhibitory effects of the pathway on CCC carcinogenesis. We found that the IL-6/IL-6R signaling pathway acts on CCC cells to enhance invasion and chemoresistance and that targeting the IL-6/IL-6R mediated signaling pathway could be a promising therapeutic strategy for CCC.

2. Somatic copy number alterations associated with Japanese patients or endometriosis in ovarian CCC

We used high-resolution comparative genomic hybridization to identify somatic copy number alterations associated with the clinical characteristics of CCC. We found that possible associations between CCC and amplification of the zinc finger protein 217 gene (*ZNF217*) among Japanese patients and between endometriosis and amplifications of the epidermal growth factor receptor gene (*EGFR*).

3. The microRNA 21 gene is a candidate driver for 17q23-25 amplification in ovarian CCC

The aim of this study was to investigate the role of the microRNA 21 gene (*miR-21*) in 17q23-25 amplification associated with CCC oncogenesis. We found that *miR-21* is a possible driver gene other than *PPM1D* (protein phosphatase, Mg²⁺/Mn²⁺ dependent 1D gene) for 17q23-25 amplification in CCC. Aberrant expression of *miR-21* by chromosomal amplification might play an important role in CCC carcinogenesis through the regulation of the *PTEN* (phosphatase and tensin homologue) tumor suppressor gene.

4. Dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 2 regulates epithelial-

mesenchymal transition through Snail degradation in ovarian serous adenocarcinoma

The aim of this study was to clarify whether dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 2 (DYRK2) regulates epithelial-mesenchymal transition through Snail degradation in ovarian serous adenocarcinoma. Immunohistochemical analysis demonstrated that DYRK2 expression inversely correlated with Snail expression, and reduced expression of DYRK2 was associated with shorter overall survival in serous adenocarcinoma. DYRK2 may regulate epithelial-mesenchymal transition through Snail degradation in serous adenocarcinoma.

5. Laparoscopic myomectomy with a new suturing-training instrument: 4 case reports

We report 4 cases in which laparoscopic myomectomy was performed after we trained with a suturing box model we developed. We made the model with a stuffed toy that was similar in shape to the uterus and penetrated it longitudinally with wire. Our box model is useful for training in 3-dimensional suturing and the introduction to laparoscopic myomectomy.

6. Clinicopathological examination of AT-rich interactive domain-containing protein 1A expression in stage I ovarian CCC

This study sought to clarify the clinicopathological significance of the loss of AT-rich interaction domain 1A (ARID1A) expression in stage I ovarian CCC. We found that the loss of ARID1A function contributes to the initial stages of carcinogenesis in ovarian CCC and to tumor progression in ovarian CCC derived from endometrial cysts, particularly when tumor cells appear in ascites fluid.

7. Treatment-interval associated effect of irradiation on locoregionally relapsed ovarian cancer

We reviewed clinical records of 61 patients with epithelial ovarian cancer who had received irradiation after chemotherapy was repeated from 1997 through 2006. We showed that irradiation for recurrent ovarian cancer produced a greater survival benefit when applied to chemo-responsive, locoregional recurrent tumor immediately after chemotherapy.

8. Clinical experience of J-VAC drain for skin closure in the laparotomy of obstetrics and gynecology

This study revealed that the subcutaneous J-VAC silicone drain (Ethicon Endo-Surgery Inc., Johnson & Johnson) is useful for closing surgical incisions in gynecology and obstetrics and has no limitations for applicability.

9. Granulosa cell tumors of the ovary: A clinicopathological study of 56 patients

The objective of this study was to investigate the clinicopathological characteristics and the factors related to disease recurrence in ovarian germ cell tumors (OGCTs). This study suggests that OGCTs require long-term follow-up. Because a residual tumor was the risk factor for the recurrence of adult-type OGCTs, it is important to observe the abdominal cavity carefully and achieve complete resection of the tumor during surgery.

10. Ovarian serous borderline tumor: A clinicopathological analysis of 43 cases

The aim of this study was to clarify clinicopathological features associated with malignant potential in ovarian serous borderline tumors (SBTs). Because an SBT with either bilateral occurrence or exophytic growth tends to have extraovarian implantation, these growth patterns may be important as prognostic factors for SBTs. In addition, the activa-

tion of the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS)/B-Raf proto-oncogene, serine/threonine kinase (BRAF) protein kinase pathway in SBTs with micro-papillary pattern could be a possible reason for SBTs to progress toward low-grade serous carcinoma.

11. Innovation of reduced port surgery applying the modified Higuchi's transverse incision

We introduced low single-incision laparoscopic surgery for cystectomy and myomectomy using Higuchi's transverse incision procedure. Low single-incision laparoscopic surgery was suggested to be effective for the treatment of large tumors and to be as safe as conventional procedures.

Perinatology

1. Establishing possible connections among antenatal stress, anxiety, and postpartum depression using human herpesvirus 6 and 7 or antibodies

The Department of Virology of The Jikei University School of Medicine has identified human herpesvirus (HHV) 6 and HHV-7 as potentially effective ways to measure levels of stress and fatigue. The purpose of this study was to establish possible connections among antenatal stress, anxiety, and postpartum depression using HHV-6 and HHV-7 or antibodies found in maternal blood and sputum for evaluation on a depression scale. As of July 2015, we have succeeded in enrolling 139 pregnant women and are now in the process of analyzing the received data.

2. The importance of prenatal genetic counseling

We performed tests to detect aneuploidy in high-risk pregnant women with adequate genetic counseling in Japan. The clinical data, test results, and pregnancy outcomes were recorded. Our study describes the findings of a nationwide demonstration project in Japan aiming to introduce noninvasive prenatal testing for fetal aneuploidies using maternal plasma, based on the historical background of the prenatal diagnosis. We expect our data to stimulate a debate regarding prenatal genetic testing and hopefully lead to improvements in the perinatal care system with respect to genetic counseling in Japan.

3. Immunohistochemical localization of bilirubin oxidation in human placenta

Bilirubin is an intrinsic antioxidant, produced from heme through biliverdin, which is catalyzed by heme oxygenase 1 (HO-1) and generates oxidative metabolites called biopyrins as a result of the reaction with reactive oxygen species. To find a new biomarker of pathological pregnancy, in this study we investigated the expression of these enzymes in the human placenta. Placental tissues from 10 patients with pre-eclampsia and 7 patients with uncomplicated preterm deliveries were examined immunohistochemically with monoclonal antibodies against bilirubin (24G7) and HO-1 (EP1391Y). Although staining for HO-1 did not differ significantly between the groups, staining for bilirubin was more diffuse and more intense in cases of pre-eclampsia than in uncomplicated cases. This results suggest that biopyrins will be a useful biomarker to predict pathological pregnancy relating to oxidative stress.

Reproductive endocrinology

1. Agenda for starting clinical practice of Oncofertility

Fertility preservation for cancer survivors is emphasized with advancing of both cancer treatment and reproductive medicine. We researched the actual circumstance and agenda of oncofertility by examining the patients preserving their sperms or embryos. The results showed the patients after receiving chemotherapy are decreasing, and the unmarried patients who preserve their sperms are increasing. It indicated that the issue of oncofertility was being recognized gradually after Japan Society for Fertility Preservation was established in 2012. Cancer treatment should be taken on top priority in Oncofertility. We should provide information and take care of patients fully by multidisciplinary support team when examining immediately fertility preservation. We consider it important that we should construct the fully coordinating system between each facilities or each professional.

2. The Impact of Word “Oocyte Aging” on Infertility Patients

The expression “oocyte aging” was used in a special news report which made a big impact on society. The impact of “oocyte aging” also influenced the content of infertility counseling. The number of infertility counseling sessions associated with the key words of “termination of treatment” and, “infertility in aging women” markedly increased. Now, we need to discuss female fertility decline with advancing age. In the future, we should consider when and how to provide information about female fertility decline with advancing age. Public education about female fertility decline with advancing age need to decrease the number of aging infertile women desiring children, and must be effective at reversing the decline in the nation’s birth rate.

Publications

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