(26) 癌症婦女的生育能力保存

Fertility Preservation for Female Cancer Patients

時	間:113年6月22日(星期六)13:20~17:00
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地 點:臺北榮民總醫院 重粒子中心二樓會議室

13:20-13:30	Opening Remarks	陳怡仁教授 Yi-Jen Chen
	座長:洪焕程 副教授 (Huann-Cheng Horng)	
13:30-14:00	面對卵巢老化的治療挑戰:新觀點與方法 Challenges in the Treatment of Ovarian Aging: Exploring New Strategies and Approaches	崔冠濠教授 Kuan-Hao Tsui
14:00-14:30	癌症治療後的孕期照顧 Pregnancy in Cancer Survivors	黃建霈助理教授 Jian-Pei Huang
14:30-15:00	婦科癌症患者的生育能力保存 Fertility Preservation for Gynecological Cancer Patients	何積泓助理教授 Chi-Hong Ho
15:00-15:30	Coffee Break	
	座長:陳怡仁 教授 (Yi-Jen Chen)	
15:30-16:00	子宮頸癌患者在化學放射療法前後之腹腔鏡卵巢轉位手術 Laparoscopic Ovarian Transposition Before and after Chemoradiation in Cervical Cancer	黃寬仁副教授 Kuan-Gen Hung
16:00-16:30	癌症婦女的卵子冷凍保存 Oocyte Cryopreservation for Cancer Patients	陳思原教授 Shee-Uan Chen
16:30-17:00	卵巢組織冷凍保存 Cryopreservation of Ovarian Tissue	易瑜嶠助理教授 Yu-Chiao Yi

Challenges in the treatment of ovarian aging: Exploring new strategies and approaches

面對卵巢老化的治療挑戰:新觀點與方法

Kuan-Hao Tsui

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The aging process in the female ovaries involves a gradual decline in both the quantity and quality of oocytes. When this decline happens prematurely or accelerates, it leads to diminished ovarian reserve and/or ovarian dysfunction, significantly impacting a woman's reproductive and overall health, often resulting in infertility. The majority of clinically infertile patients are of advanced age, and ovarian aging is an irreversible phenomenon. Various factors such as mitochondrial DNA damage, telomere changes, reactive oxygen species, mitochondrial dysfunction, and known genetic mutations associated with primary ovarian insufficiency and reduced ovarian reserve play crucial roles in this process. In our comprehensive assessment of ovarian aging, we adopted a multi-omics strategy, leveraging various cutting-edge techniques. This included single-cell RNA-sequencing to delve into the transcriptomic profile of individual cells, spatial transcriptomics to study gene expression patterns in the context of tissue architecture, genomics to explore the entire set of genes in the genome, metabolomics to analyze the small molecules involved in cellular processes, and nutrigenomics to understand the interaction between nutrition and genes. To delve deeper into the mechanisms, we focused our investigations on target genes. This involved conducting in vitro studies in controlled laboratory environments, utilizing mouse ovaries as a model system, and analyzing germ cells obtained from aging patients. These diverse approaches allowed us to unravel the intricate details of gene expression, regulation, and function during ovarian aging. In clinical trials, we utilized nutrigenomics to identify small molecule drugs and nutritional supplements capable of enhancing energy metabolism and inducing microenvironmental changes in the germ cells of elderly infertile patients. By combining multi-omics with translational medicine, our research seeks to deepen the understanding of the molecular mechanisms underlying ovarian aging. This approach not only advances diagnostic capabilities but also paves the way for innovative treatment strategies.

Pregnancy in cancer survivors

癌症治療後的孕期照顧

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Nowadays, cancer survivors are gradually increasing as improvements in cancer diagnosis and treatment. It is important to recognize the impact of cancer and its treatment, such as operation, chemotherapy, or radiotherapy, on fertility and pregnancy outcomes. Although the fertility rate may be lower in cancer survivors, the pregnancy of them is not uncommon. The impact of previous cancer and its treatment on pregnancy, needs to be assessed and discussed with survivors by a multidiscipline team including oncologist, perinatologist, and associated specialists to support the complex cares for pregnant women after cancer assault.

The evidence of the association between miscarriage or spontaneous abortion and cancer treatment is mixed and varies with different patient cohorts and treatment modality. However, the congenital anomalies rate did not increase if avoid of chemotherapy or radiotherapy during 1st trimester. Although, most of the prenatal care in cancer survivors is the same as other pregnant women. However, there is still some concerns should be addressed. For example, in cervical cancer survivors who received conization, trachelectomy, or pelvic radiation, the incidence of preterm birth may increase. Therefore, the close follow up of preterm birth sign and cervical length may be warranted. Besides, the result of non-invasive prenatal test may be interfered by the cancer cells. Some reports that the incidence of gestational diabetes mellitus and pre-eclampsia going high of cancer survivors. However, the result is not consistent in literatures review. Other adverse pregnancy outcomes, e.g. high cesarean section and operative vaginal delivery rate, preterm birth, small for gestational age fetus, low birth weight newborn, NICU admission rate, and postpartum hemorrhage had been documented in some cancer survivors. The delivery method is major based on obstetric indication. But cesarean section is preferred in cervical cancer survivors after trachelectomy and pelvic irradiation which may cause abnormal birth canal. Breast feeding is not contraindicated in breast cancer survivors, especially feeding by the contralateral breast to avoid mastitis in irradiated breast and could be encouraged in most cancer survivors if they wish.

The effect of pregnancy on cancer outcomes depends on individual condition. Pregnancy could play a protective role or be a worsening factor, even though it doesn't have major effect in most cases. Therefore, either going for contraception or getting pregnancy should be a result of shared decision making by patients, families, and medical professionals.

Fertility preservation for gynecological cancer patients

婦科癌症患者的生育能力保存

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The incidence of gynecological cancers has been increasing in recent years. Due to advances in multimodality treatment, long-term survival is possible for many patients. For young patients who desire future pregnancy, it is necessary to preserve the reproductive organs and their function to prevent loss of fertility. However, for most cases of gynecological cancers, the standard treatment must have these organs removed. Close cooperation between oncologists, reproductive endocrinologists and obstetricians is necessary.

The fertility-sparing surgeries to treat cervical cancer include cervical conization, radical trachelectomy, and ovarian transposition before abdominal and pelvic radiotherapy. Radical trachelectomy is a curative procedure that allows for preservation of the uterine body, ovaries, and fallopian tubes. It is indicated for stage IA2/IB1 cervical cancer and for stage IA1 cervical cancer without vascular invasion.

For patients with endometrial cancer and precancer, fertility preservation should be considered for atypical endometrial hyperplasia and Grade 1 endometroid carcinoma that is localized to the endometrium. Hormone therapy with high-dose progestin is performed as fertility-sparing treatment. However, hormone therapy is not standard therapy for patients with endometrial cancer, and its eligibility must be determined comprehensively.

Fertility-sparing treatment of ovarian cancer can be considered in cases of stage I epithelial and sex cord-stromal ovarian cancer. The basic surgical approach recommended for fertility preservation consists of adnexectomy on the affected side, omentectomy, peritoneal cytology, peritoneal examination, along with pelvic and paraaortic lymph nodes dissection. In cases of germ cell tumor, fertility-sparing surgery is indicated for stage I–IV tumors. The BEP regimen (bleomycin, etoposide, and cisplatin) is very effective for germ cell tumors.

Laparoscopic ovarian transposition before and after chemoradiation in cervical cancer

子宮頸癌患者在化學放射療法前後之腹腔鏡卵巢轉位手術

Kuan-Gen Hung

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Pelvic irradiation almost induces castration and long-term hormone therapy would then be indicated for young women. However, hormone therapy may raise problems of compliance and certain adverse side effects. For young women with invasive cancers need pelvic irradiation, preservation of ovarian function is crucial so that their qualities of life could be improved. Ovarian transposition has been proposed to preserve ovarian function in patients receiving radiation therapy for over forty years already.

Majority of ovarian transposition is requested by patients with fertility consideration or fear of long term exogenous estrogen replacement. Ovarian preservation seems mandatory for premenopausal young patient with non hormone-dependent gynecologic cancers or nongynecologic cancers requiring pelvic irradiation, based on the negligible chance of ovarian metastasis. This high anterolateral transposition of the ovary was not only distant away from the standard irradiated field for gynecologic cancer but also away from the extended radiation field.

We reported a laparoscopic technique for ovarian transposition in patients with invasive cancer before receiving pelvic radiotherapy. We use Lee-Huang point as the first entrance and as a landmark to transpose the ovaries to a high anterolateral position, 3-4 cm above umbilical line. It is a simple and effective procedure for the preservation of ovarian function and it does not complicate the subsequent therapeutic protocol. Although a long-term evaluation and a larger series are necessary, this procedure could be recommended to those premenopausal women who required pelvic irradiation, especially for those less than 40 years old.

Oocyte cryopreservation for cancer patients

癌症婦女的卵子冷凍保存

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Advancements in cancer therapies have achieved much improvement in survival rate of cancer patients. The cancer treatments potentially damage their ovarian function. Therefore, the need for fertility preservation in cancer patients has increased. Appropriate controlled ovarian stimulation (COS) is important for fertility preservation with oocyte cryopreservation in female cancer patients. Most patients have only a single cycle opportunity owing to time constraints before oncologic treatment. Efficient and effective to obtain sufficient good quality oocytes with safety, including decrease of ovarian hyperstimulation syndrome (OHSS). Several protocols of GnRH agonist (long or short), GnRH antagonist, and progestin primed ovarian stimulation (PPOS) had been used. Which protocol is most suitable for cancer patients deserve investigation and discussion. What is the suitable dose for each patient. For the final maturation GnRH agonist trigger, hCG trigger or dual trigger based on follicle number, serum estradiol level, LH levels, and body weight are important.

Determination of the COS protocol and gonadotropin dose for oocyte cryopreservation in cancer patients requires an individualized assessment. To find the appropriate initial dosage of gonadotropin may be according to body weight, AMH, antral follicle count, BMI, and age. Adequate ovarian stimulation and duration (around 10 days) is important to obtain sufficient mature oocytes for fertility preservation. Recently, antagonist protocol or PPOS, feasible for GnRH agonist trigger if risk of OHSS, can decrease OHSS complication. These two protocols are also convenient and time-saving. Earlier counseling or random start can save the time for chemotherapy. Random-start ovarian stimulation for fertility preservation reduces time constraints without compromising oocyte yield and maturity. For estrogen-sensitive cancer, letrozole can be used during ovarian stimulation.

We started the oocyte cryopreservation program for unmarried female cancer patients of medical reasons since 2002. We have performed 115 cases in cancer patients. Breast cancer and hematological cancer were most common reasons. The mean age for freezing oocytes was 32 years. The mean number of oocytes frozen was 15. Ten cases underwent thawing. The usage rate was 8.8%. The mean storage duration was 5.0 years for those who thawed oocytes. The survival rate was 82% and fertilization rate was 76%. Two live births were obtained and one pregnancy got miscarriage. One patient was myelodysplastic syndrome after allogenic peripheral blood stem cell transplantation. The other patient was breast cancer after surgery and chemotherapy. The cumulative live birth per thawed case was 20%. The fertility preservation in cancer patients would be helpful for them to own biological children.

Cryopreservation of ovarian tissue

卵巢組織冷凍保存

Yu-Chiao Yi

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Childhood and adolescent cancer survival has improved greatly these years. However, some of them will eventually have been sterilized by their chemotherapy. Though oocyte and embryo cryopreservation have been widely applied in female cancer victims for fertility preservation, they cannot be applied in adolescence. Ovarian tissue cryopreservation (OTC) is an important development for fertility preservation in girls and young women at risk of premature ovarian insufficiency as a result of treatment for cancer. Unlike traditional method like oocyte or embryo cryopreservation, ovarian tissue cryopreservation involves the removal and freezing of ovarian tissue containing primordial follicles, which can later be thawed and reimplanted or uses for in vitro maturation.

OTC offers several advantages, including the potential for preserving a larger number of primordial follicles compared to oocyte or embryo cryopreservation, making it particularly suitable for prepubertal girls and women with limited time for ovarian stimulation. Moreover, OTC allows for the preservation of hormonal function, which may contribute to better reproductive outcomes and overall quality of life post-treatment.

Despite its potential benefits, OTC presents challenges, including the risk of reintroducing malignant cells in cancer patients, the need for specialized expertise in ovarian tissue handling and cryopreservation techniques, and the uncertain long-term safety of re-implantation.

In conclusion, OTC represents a valuable option for fertility preservation in women facing gonadotoxic treatments. Continued research is needed to optimize the procedure, enhance follicle survival rates, and minimize the risk of reseeding cancer cells. Furthermore, efforts to improve access to OTC and address ethical considerations surrounding its use are essential to ensure equitable fertility preservation options for all women of reproductive age. Collaboration among oncologists, reproductive specialists, and patients is crucial to providing comprehensive care and support throughout the fertility preservation journey.