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Egg freezing and the clinical application

Egg/oocyte freezing is a method using assisted reproductive technology to retrieve and freeze oocytes in order to preserve the gametes at a younger age. The development of cryopreservation technique, as well as promotion by social media, has encouraged many women to embrace the idea of deferring childbearing. According to previous evidence, this procedure has brought about biological babies for them with a fairly good success rate (Cobo, et al., 2018). However, the actual benefit and risk imposed on women is still under evaluation.

Oocyte cryopreservation was started in the late 20th century, followed by the first human birth from the frozen egg in 1986. Ever since vitrification was introduced (Kuleshova, et al., 1999) and replaced slow freezing technique, the efficiency of freezing oocytes improved and largely advanced. Being an effective method, gamete cryopreservation was firstly proposed for cancer patients, who were planned for gonadotoxic treatment (Practice Committee of the American Society for Reproductive Medicine, 2019). This technique was later proposed to single women for age-related fertility loss and the experimental label was further removed (ESHRE Guideline Group on Female Fertility Preservation, et al., 2020, Ethics Committee of the American Society for Reproductive Medicine, 2018).

The reasons for elective/planned oocyte freezing were mostly due to lack of a suitable partner or incomplete self-accomplishment (Nasab, et al., 2020, Platts, et al., 2021). Since the number of cases seeking for oocyte freezing has exponentially risen in the past ten years (Yang, et al., 2022), the success rate (i.e. live birth rate) is the most concerned issue. Prediction tool was developed for counseling women the live birth rate based on age at oocyte freezing and number of frozen mature oocytes (Goldman, et al., 2017). As expected, freezing the oocytes at a younger age and accumulation of more mature oocytes resulted in a better success rate of live birth was also proven in other observational studies (Cobo, et al., 2018).

However, in the actual situation, we faced enormous questions lying in the usage rate of these frozen eggs and the related cost-effectiveness analysis. For women below 35 years old, the cumulative live birth rate was high. However, it would be more cost-effective only if the return rate approached 49-61% for those who froze oocytes before 35 or 38 years old according to prior models (Devine, et al., 2015, van Loendersloot, et al., 2011). In reality, the usage rate is very low in current evidence (Blakemore, et al., 2021, Cobo, et al., 2018, Yang, et al., 2022); and the legislation in different countries might influence the women' s willingness and opportunities to thaw oocytes (ESHRE Guideline Group on Female Fertility Preservation, et al., 2020). On the other hand, the cost might considerably raise for those who came for oocyte freezing at older age with a comparably low success rate (Yang, et al., 2022). Thus, the value of oocyte freezing is still debatable.

In conclusion, oocyte freezing for medical or non-medical reasons are both ethically permissible. While oocyte cryopreservation is a reasonable option for unmarried women to delay motherhood, the costs, the risks and the likelihood of success and usage should be reasonably disclosed to the patients. The psychological and behavioral changes after oocyte freezing should be foreseen. It should also be discussed that the pregnancy-related complications due to older maternal age cannot be overcome by oocyte freezing. More data is needed for decision-making for public health policy and consultation for women willing to preserve fertility.

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Hysterosalpingography-OSCM from A to Z as an initial diagnostic exam for infertility

One of the major causes of female infertility is a tubal factor. Hysterosalpingography (HSG) is recognized as the only reliable and reproducible diagnostic examination. HSG involves an X-ray procedure called fluoroscopy to view and evaluate whether the fallopian tubes are patent and if the shape of the uterus is normal. HSG is an outpatient procedure that usually takes less than 10 minutes to perform, it is usually done after the menstrual period ends but before ovulation. HSG has been considered as the most basic, primary, simple, or easy but important diagnostic examination, however, every detail of each step of HSG has not been well described comprehensively. In this presentation, the importance of Fallopian tubes on human reproduction and the practical method of HSG based on scientific evidence regarding the following points will be explained in detail.

Hysterosalpingography procedure. In the gynecologic exam room, the gynecologist places a balloon catheter into the uterine cavity through uterine cervix, which is then inflated with saline to fix its position. How to place the catheter in the uterus? Should oil-soluble (OSCM) or water-soluble contrast media (WSCM) be used for fluoroscopy? We use OSCM depending on their characteristics of easy handling and accurate interpretation of their images. Once moved to a radiology exam room, the patient is laid down on a radiographic table where x-ray machine and a detector suspended over the table. X-ray imagers can monitor the contrast movement and take pictures or movies during the procedures. OSCM is slowly administered to fill the uterine cavity and flow through the Fallopian tubes. As the contrast enters the tubes, it opacifies the length and highlights the statis, such as patent, stenotic or occluded, of the tubes and spills out their ends if they are open. The balloon catheter will be removed from the uterus following a specific manner.

Thus, clinicians should thoroughly understand the limitations and potential pitfalls of HSG as well as the appropriate follow-up steps based on the result.

In conclusion, as over the past several decades, HSG continue to play an important role in the evaluation of Fallopian tubes and is an essential diagnostic procedure during fertility assessment. Meticulous procedures, an accurate interpretation of the results, and complication management are crucial in optimizing patient treatment outcomes. I hope this presentation will improve your HSG performance to some extent.

Keywords: HSG, hysterosalpingography, OSCM, Tubal factor, Infertility

Highlights

- The importance of HSG with meticulous manner before starting infertility treatment.
- Characteristics of OSCM HSG regarding beneficial, therapeutic and adverse effects.
- Special attention to handling of OSCM before and after HSG procedure.

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高齡夫或妻接受試管嬰兒療程的臨床議題

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The trend toward delayed child-bearing in Taiwan is evident. According to statistics published by the Ministry of the Interior, the average age of fathers has risen from 33.2 years old in 2008 to 34.7 years old in 2020. Like-wise, the age of mothers has risen from an average of 29.3 years old in 2008 to 31.7 years old in 2020. Although lacking a strict definition for advanced maternal or paternal age, most studies and health organizations have employed a range between 35 to 40 years old. The characterization of this effect is vital, as delayed child-bearing is progressively becoming the societal norm.

Besides having demographical and societal consequences, there is mounting evidence that advanced maternal and paternal ages have detrimental health effects on the offspring. The effects of age on fertility, and its effect on the occurrence of health complications in the offspring, such as aneurploidy, have been better characterized in advanced age women. Less well-known, however, is the effects of age on male-related issues, including fertility and the health impacts in the offspring. This information has only started to be recognized in the last 10 to 15 years.

This session summarizes some of the more recent findings on age-related effects from the perspective of male and female fertility, and offspring health. It is hoped that by the end of the session, clinicians may have a better understand of the potential risks associated with delayed childbearing, and provide adequate consultation for prospective parents.

Keywords: Advanced maternal age, Advanced paternal age, Offspring health

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Pharmaconutrition: Vitamin D in ART

維生素 D 的「活性代謝物」可直接調控人類細胞核內數千個基因轉錄（DNA Transcription），因為這些基因皆有維生素 D 的反應區（Vitamin D Response Element, VDRE），包括: AMH（Anti-Mullerian Hormone）、HOXA10、TFAM（Mitochondrial Transcription Factor A, Mitochondrial Biogenesis Gene）…等基因。統合分析顯示: 接受 ART 治療的婦女，若體內維生素 D 足夠，則活產率（Live Birth Rate)相對增加 33%；補充維生素 D，則臨床懷孕率（Clinical Pregnancy Rate）相對增加 70%。

脂溶性維生素 D 不會蓄積在體內，因它在細胞內會被代謝成水溶性的不活性代謝物 Calcitroic Acid，進而從糞便、尿液、汗液等排出。此外，補充巨量維生素 D 會促進脂肪細胞崩解，故已被用於輔助治療減肥。維生素 D 是不活性，不具藥理作用及毒性。故補充維生素 D 的臨床效益與其劑量沒有直接的關聯性，而是與其活性代謝物在血中及細胞內的濃度具有緊密的關聯性。它的活性代謝物包括骨化二醇（Calcidiol，25(OH)D）或骨化三醇（Calcitriol，1α ,25$(OH)_2$D）。Calcidiol 和 Calcitriol 皆可與細胞內的維生素 D 受體結合並結合在基因的 VDRE 上，進而調控基因轉錄。血中 Calcidiol 濃度已被認定為體內維生素 D 足夠與否的指標，其數值在 200 – 700 ng/mL 仍未誘發高血鈣症。依據基因學研究，血中 Calcidiol 濃度約在 60 - 90 ng/mL 可調控高達 1,289 個基因。依據 IVF 研究，相對於濾泡內 Calcidiol 濃度較低的不孕症婦女，濃度約在 43 ng/mL（相當於血中 Calcidiol 濃度約在 70 ng/mL）的不孕症婦女有相對較高的臨床懷孕率和著床率。

包括維生素 D_2（Ergocalciferol）和維生素 D_3（Cholecalciferol），維生素 D 商品的臨床應用有三種觀念：

一、維持生理功能（Nutrition Support）：依據「國人膳食營養素參考攝取量」之建議，成人每日攝取 200 – 400 IU，建議攝取的耐受性上限(Tolerable Upper Intake Levels)為 2,000 IU，此劑量非毒性上限。此劑量的應用常見於營養配方商品，例如: 糖尿病或腎臟病患者的營養配方商品。

二、藥品（Pharmacotherapy）: 自 1941 年至今，美國 FDA 核准維生素 D_2 藥品 Drisdol，每顆膠囊 5 萬 IU，其處方適應症包括: 用於維生素 D 抗性的佝僂病（Vitamin D-resistant Rickets），每日劑量是 1.2 萬– 50 萬 IU；用於副甲狀腺功能低下，每日劑量是 5 萬– 20 萬 IU。

三、藥理性營養治療（Pharmaconutrition）: 患者補充巨量維生素 D 來矯正體內維生素 D 缺乏症，以預防或輔助治療疾病。在短時間內補充巨量（10 萬~60 萬 IU），以快速地提昇患者體內 Calcidiol 濃度，稱為沖擊療法（Stoss Therapy）。維生素 D 的藥理性營養治療已超過 80 年之久。例如: 在 1930 年代，歐洲各國為了防治佝僂病，患者可單次補充 60 萬 IU。在 1955 年至 1980 年代，東德實行「新生兒在 1 歲半之前，必須補充 6 次，每次 60 萬 IU，以預防佝僂病」之國家政策。

國人維生素 D 狀態的調查顯示: 大多數女性呈現維生素 D 缺乏 (< 20 ng/mL)。由於維生素 D 指標數值與婦女的生殖功能呈現相關性，故建議: 檢測不孕症婦女的血中 Calcidiol 數值、以 Stoss Therapy 快速地矯正維生素 D 缺乏、在 ART 治療及懷孕期間，維持血中 Calcidiol 數值約在 60 - 90 ng/mL。

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Aromatase inhibitors (Letrozole) for ovulation induction

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Letrozole is a 3rd generation aromatase inhibitor, exerting significant estradiol suppression after 2– 3 days of commencement and with a half-life of 45 h. Letrozole can inhibit the growth of non-dominant follicles, promotes single-follicle development. Its direct effects are limited to the treatment cycle, hence eliminating the issues of accumulation between cycles associated with anti-estrogenic medications such as clomiphene citrate. The first reported use of Letrozole in assisted reproduction was in 2001, wherein letrozole was effective for ovulation induction in anovulatory infertility and for increased follicle recruitment in ovulatory infertility. A meta-analysis showed that letrozole was better than clomiphene, the previous first-line agent, for ovulation rate per patient, pregnancy rate per patient, and live birth rate per patient. Also, letrozole resistance rates and multiple pregnancy rates appear lower with letrozole versus clomiphene. From evidence of ART, letrozole-induced reduction in follicular phase E2 serum levels may improve endometrial receptivity and embryo implantation. However, the degree of E2 suppression by letrozole is variable among patients, and some research showed that low E2 levels might be associated with a significantly higher miscarriage rate and lower live birth rate.

Usually, the starting dose of letrozole is 2.5 mg/day for 5 days (usually starting on day 3 of the cycle). The dose of letrozole should be increased to 5 mg and then 7.5 mg/day in subsequent cycles in cases of absent ovarian response. Patients who ovulated with a higher dosage of letrozole would take longer to conceive and their compliance would be affected, especially for women of advanced age.

The speech aims at the updated evidences including:
1. Overview of letrozole
2. Whether the pre-treatment characteristics reflecting the reproductive ability of PCOS patients had the predictive value for their ovarian response to the minimal ovulation doses of letrozole
3. Whether extending letrozole treatment duration could induce ovulation in women with PCOS who previously failed to ovulate after a 5-day regimen of 5 mg letrozole daily for at least 1 ovulation induction cycle, defined as “Letrozole resistance”.
4. Ovulation induction using letrozole combined with other agents (metformin/clomiphene/dexamethasone/gonadotropin)
5. Letrozole versus laparoscopic ovarian drilling in clomiphene citrate-resistant PCOS women

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Mosaic embryo transfer: how to select and monitor after pregnancy

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Chromosomal mosaicism (defined as a state in which there is more than one karyotypically distinct cell population arising from a single embryo is an inherent biological phenomenon in human preimplantation embryos. Following the implementation of PGT-A (Preimplantation genetic testing for aneuploidy), usually based on next-generation sequencing (NGS) of trophectoderm (TE) biopsies, the detection of intermediate copy number on chromosomal analysis (indicating chromosomal mosaicism among the biopsied cells) has become more frequent.

After the first report showing that the transfer of embryos with a chromosomal mosaic result on PGT-A can yield healthy babies(1), a growing series of studies has been published on this topic, with the largest dataset of 1000 embryos described in 2021. (2) These data suggested that the transfer of embryos with putative mosaic PGT-A results yielded lower implantation rates and higher miscarriage rates when compared with euploid embryo transfer.

Recent challenges have been made to prioritize different characteristics of mosaic PGT-A results to assist with embryo selection decisions as well as to counsel about potential success rates, risks, and outcomes. Prenatal test recommendations after mosaic embryo transfer are another area in which evidence-based guidance is lacking. Most best practice statements in this area uniformly recommend prenatal diagnosis by amniocentesis as the gold standard follow-up test(3).In this session, current prenatal tests after mosaic embryo transfer will be reviewed with emerging data.

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