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FERTILITY PRESERVATION

A synopsis of the 2021 International Society of Fertility Preservation bi-annual meeting

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Abstract

On November 19, 2021, the first virtual meeting of the International Society for Fertility Preservation (ISFP) took place. Eight experts in the field of reproductive medicine presented important updates on their research in the field of fertility preservation and reproductive surgery for absolute uterine factor infertility. Presentations included talks on ovarian stem cell therapy for premature ovarian insufficiency, practical aspects of oocyte vitrification, ovarian stimulation for patients with breast cancer, in vitro maturation of oocytes at the time of ovarian tissue harvesting, male fertility preservation, and uterine transplantation. These presentations are summarized below and can be viewed in their entirety at www.isfp-fertility.org

Keywords ovarian stem cell therapy · premature ovarian insufficiency · oocyte vitrification · breast cancer · letrozole · testicular biopsy · sperm · uterine transplantation · fertility preservation

Introduction

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Rejuvenation of the ovary by stem cell therapy

Professor Antonio Pellicer presented an emerging strategy that has been developed in recent years to restore fertility potential in women with premature ovarian insufficiency (POI). Indeed, around 40% of women diagnosed with POI still have quiescent follicles identified microscopically in their ovaries. Autologous stem cell ovarian transplant (ASCOT) with bone marrow-derived stem cells has been shown to rescue these residual dormant follicles and improve ovarian function [1]. In the first pilot study with 20 patients, infusion of stem cells into the ovarian artery resulted in an increase in ovarian reserve markers in 80% of patients and higher numbers of oocytes obtained [1]. Moreover, no difference between the injected and control ovary was observed. The latter finding is of particular importance, not only because it allows a much less invasive clinical approach in further trials, namely stem cell administration by peripheric perfusion instead of catheterizing the ovarian artery for direct infusion, but also because it sheds light on stem cell mechanisms of action. Indeed, stem cell-secreted factors are responsible for promoting follicle development, stromal cell proliferation, and vessel formation in the ovarian tissue of patients with diminished ovarian reserve [2].

Rejuvenating the oocyte by mitochondrial transfer: is it a reality?

Mitochondria are abundant in oocytes and undergo marked microtubule-mediated redistribution after fertilization. Their further transcription and replication occur early in embryonic life, namely at the blastocyst stage, showing an evolving morphology towards the mature state [3]. The mitochondrial mass is of crucial importance in oocytes since its size determines the survival potential of the embryo. Moreover, mitochondrial DNA mutations may lead to genetic diseases in the offspring. For this reason, "mitochondrial medicine" is an emerging branch of reproductive medicine.

Professor Chii-Ruey Tzeng presented the three main mitochondrial transfer techniques: (i) mitochondria transfer by direct injection, (ii) tunneling nanotubal transfer (TNT), and (iii) spindle or pronuclear transfer. The first method consists of the transfer of mitochondria isolated from cumulus granulosa cells to the mature oocyte with a significant benefit on embryo development identified. Indeed, this technique was shown in one small study to increase the percent of top-quality embryos and subsequently pregnancy and live birth rates. This strategy may improve fertility outcomes in those patients who have a decreased quality of mitochondria due to advanced age.

After p53-mediated cell damage, mitochondria transfer from a healthy donor to a recipient injured cell may occur through the formation of tunneling nanotubes, connexin 43-mediated channels in gap junctions, or extracellular vesicles [4]. Investigations on this cell behavior have been leading to development of numerous medical interventions, including those to treat genetic mitochondrial diseases with pediatric onset. Spindle transfer to a healthy ooplasm before fertilization or pronuclear transfer to a healthy zygote may lead to future treatments of mitochondrial genetic diseases [5].

Practical aspects of oocyte vitrification

Oocytes can be successfully cryopreserved by vitrification, which means solidification of aqueous solution in the absence of crystallization, thanks to an extremely fast reduction in temperature and high concentrations of cryoprotectants. Indeed, oocyte survival rates after warming range from 85 to 95% according to patient age (> 40 or < 29 years respectively) [6] and are independent on the presence of morphological abnormalities [7].

Nevertheless, professor Debra Gook presented data about some technical issue that may impact on survival. Among them, the time in vitrification solution appears to impact oocyte survival and spindle formation, while the time in equilibration solution and the volume on cryolock during the cryopreservation procedure do not appear to significantly impact these parameters. Moreover, transient temperature changes during transport time may negatively impact the oocytes, with a significant decline in survival rates if temperatures higher than − 80 °C are reached. Regarding the thawing procedure, some parameters appear to be critical as well for oocyte survival, like the warming time in 1 M sucrose, with an ideal time of 60 s, the rate of the rapid warming, and the specific composition of warming solutions.

Ovarian stimulation in women with breast cancer

Dr. Mitch Rosen did a thorough review of ovarian stimulation in special circumstances for patients with breast cancer. He focused on 3 types of approaches: random start to minimize time from diagnosis to treatment, double stimulation in patients with adequate time to get 2 cycles of stimulation, and increase overall egg yield and post-treatment stimulation while a patient is on adjuvant hormone treatment. He also reviewed the options of treating before and after gonadotoxic treatments.

He focused on random start stimulations which allow for initiating stimulation at any point in a woman's menstrual cycle, even late follicular or luteal phase, and showed that outcomes were similar with all of these approaches. This allows for easier coordination and timing for surgery and subsequent treatments and did not delay initiation of chemotherapy [8]. Breast cancer patients also were found to have similar egg reserves when compared to patients undergoing planned oocyte cryopreservation for delaying fertility as well as similar numbers of oocytes retrieved to these age matched patients [9]. Using letrozole or tamoxifen for estrogen receptor positive (ER+) patients to mitigate the high estradiol levels seen with conventional ovarian stimulation did not affect response or outcomes [10]. Long-term safety was re-assuring and survival and recurrence rates were similar between patients that underwent fertility preservation and those that declined [11].

Double stimulation significantly increased the total egg yield for patients with time to do so. In fact, time to chemotherapy was also no different in patients who underwent 2 cycles of stimulation compared to those who underwent a single cycle only [12].

Lastly, he presented unpublished data about ovarian stimulation post-chemo and while on neo-adjuvant hormone treatment like tamoxifen. While egg yield is lower (as expected after chemotherapy), outcomes with regard to

maturity, fertilization, and embryo cryopreservation were similar to pre-chemotherapy results. Caution was advised to wait at least 6 months post-chemo due to risks to the oocytes from the chemo and potential birth defects.

In vitro maturation of oocytes at the time of ovarian tissue cryopreservation

Although in vitro maturation (IVM) of immature oocytes from 10 to 14 mm follicles have not shown a clear advantage yet in terms of reproductive outcomes in the context of in vitro fertilization (IVF), IVM of oocytes coming from small antral follicles in connection with ovarian tissue cryopreservation (OTC) has gained increasing interest. According to recent publications from the Danish group of the Rigshospitalet in Copenhagen, these immature oocytes derived from antral follicles with a diameter below 3 mm can be successfully retrieved from the surplus medulla of whole ovaries after ovarian cortex preparation for cryopreservation. Professor Claus Y. Andersen presented recently published data about this technique, showing that such immature oocytes are found quite abundantly in young adult patients and, even though maturation rates are still low at around 30%, they can provide for a decent oocyte reserve for future ART procedures [13]. Moreover, these cumulus-oocyte-complexes (COCs) undergoing IVM are characterized by an already stabilized oocyte size of around 115 µm, which is similar to that after IVM. When assessing the optimal follicle-stimulating hormone (FSH) doses for IVM, it appears that high doses of FSH increase maturation rates and resumption of meiosis, by downregulating FSH receptors and upregulating luteinizing hormone (LH) receptor expression [14].

Natural conception versus in vitro fertilization after ovarian tissue transplantation

Professor Marie-Madeleine Dolmans illustrated the most recent published data on fertility outcomes after ovarian tissue transplantation (OTT) [15]. Endocrine restoration is reached in more than 80% of cases after OTT and persists for over 5 years in more than half of transplanted women. Looking at fertility outcomes, pregnancy, and live birth rates are around 40% and 30% respectively with natural conception and 36% and 21% respectively with IVF after transplantation. Reproductive chances appear to be related to the age at cryopreservation, but not to administration of some chemotherapy (CHT) in the months prior to OTC. Indeed, in the series of 285 OTT that was presented, no significant difference is observed in terms of fertility outcomes in subjects with some prior CHT, confirming previously published data in smaller series [16, 17]. These data support the conclusion that OTC is valid and now standard strategy for fertility preservation in women who had already received recent (< 6 months) CHT. On the other hand, data on fertility outcomes after OTT in subjects with previous radiotherapy (RT) show that chances of pregnancy are around 50% in case of low doses of pelvic RT, while they become extremely low (and even zero) in subjects who had received high doses of radiation to the pelvis, with a significant damage of both uterus and potential transplantation sites.

Fertility preservation in the male

Dr. Robert Brannigan gave a stimulating lecture on fertility preservation in the male patient by presenting real world cases. The first was a 39 YO male with colon cancer who had 2 children and was attempting to conceive with his partner when he was diagnosed and not offered sperm banking prior to chemotherapy. The second case was a 32 year old with a history of treatment for Ewing's sarcoma at age 14 who underwent surgery, chemotherapy, and RT, and was also not offered sperm banking prior to treatment. The third case was a 42 year old diagnosed and treated at age 9 for non-Hodgkin's lymphoma. In all these three patients, semen analysis showed azoospermia. With high survival rates of over 75% for these patients, fertility preservation is critical for quality of life after treatment finishes.

Abnormal semen parameters are often present in men with cancer and systemic disease and the effects of different treatments like RT on germ cells was discussed with doses of radiation as low as 2 Gy causing permanent azoospermia [18]. Chemotherapeutic agent effect on germ cell function was discussed with drugs like cyclophosphamide causing significant damage to future sperm production and others like vincristine having less pronounced effects.

Barriers to fertility preservation in men were brought up and the typical excuses were raised: i.e., "not enough time, have to start treatment right away and semen parameters are already poor so not worth freezing." As part of his research, they sent a survey to 1428 pediatric oncologists to gauge their understanding and compliance with current ASCO guidelines [19]. What they found was surprising – 55% were unfamiliar with the guidelines and 44% were not aware of ICSI as a treatment used for poor sperm parameters. Most providers did not follow the guidelines routinely. He presented an outline of how to improve our care for these patients: patient navigators, flexibility with scheduling and a good lab, options for alternative methods

of sperm collection including post-ejaculate urine for retrograde ejaculation (PEU), vibratory or electro-ejaculation (EEJ), and all the way to testicular sperm extraction (TESE) if all other methods fail. In fact, TESE in azoospermic patients yielded an almost 50% rate for recovery of sperm in the TESE sample. A formalized program for fertility preservation significantly improved the percentage of patients who were offered and underwent fertility preservation [20]. Testicular biopsy with cryopreservation of testicular tissue was reviewed as a possibility for pre-pubertal boys and experimental protocols with either autologous transplantation or in vitro maturation were presented [21]. The experimental nature of this procedure should only be done under IRB approval.

Uterine transplantation: where are we in 2021?

Dr. Tommaso Falcone gave a very exciting lecture on the state of the art in uterine transplantation (Fig. 1). Starting with the first birth from a transplanted uterus in 2014, there has been an exponential rise in the number of cases due to varying and uncertain regulations regarding gestational carrier laws throughout the world. More than the surgical aspects of the transplant procedure, a team of people from all aspects of medicine, social work, psychiatry, infectious disease, high risk obstetricians, social work, and patient advocacy are necessary to perform these procedures successfully. The differences between living donor

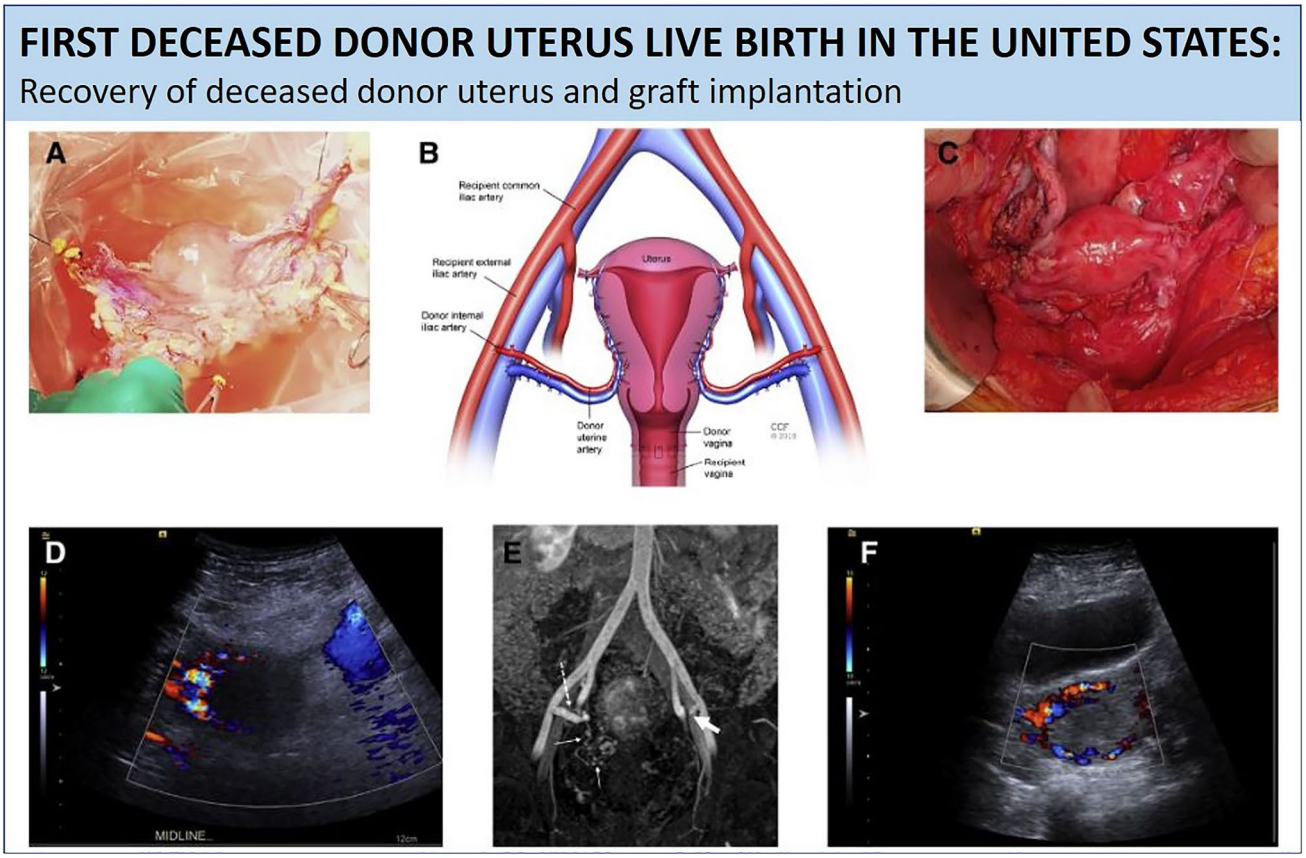

Fig. 1 **A** Image of dissected specimen on the back table. Uterus was isolated and vascular pedicles were skeletonized prior to cross-clamp. In contrast to living donor procurements, a portion of the distal uterus was maintained with the specimen and used as an anatomic landmark to facilitate dissection. **B** Diagram of the vascular and vaginal anastomosis approach used in our uterus transplant protocol. **C** Image of implanted uterus in situ. **D** Transverse midline sonogram of the transplant uterus with color Doppler obtained in the morning after the transplant surgery showing robust vascular flow throughout the right half of the transplant and diminished or absent flow on the left. **E** Coronal T1 postcontrast maximum intensity projection image obtained 2 days after the transplant showing: (i) patent internal iliac segment of the right uterine artery (dashed white arrow), (ii) thinner caliber uterine artery extending towards the lower uterine segment (thin white arrow); (iii) internal iliac segment of the left uterine artery graft truncated (thick white arrow). Left uterine artery is not identified. **F** transverse midline sonogram of the transplant uterus with color Doppler obtained 24 days after the transplant showing improved and more symmetric flow throughout the right and left sides of the transplant uterus (adapted with permission from Flyckt et al., *Am J Obstet and Gynecol 2020* [24])

and deceased donor transplants were reviewed. While living donor transplants are more common, they also carry some risk for the donor. The increased surgical time to procure the uterus from the living donor of ~ 10 h leads to increased risks of surgical complications [22], most of this time is related to dissecting out the uterine veins. The other complication arises from constriction at the site of the vaginal anastomosis and difficulty with embryo transfer procedures. The surgical procedure is slightly complicated in patients with uterine agenesis (MRKH) due to the dissection and limited vaginal length.

Immunosuppressive agents used are similar to renal transplant patients and have been found to be relatively safe in pregnancy. Embryo-transfers have traditionally been performed > 6 months after the transplant is performed to ensure the graft has not been rejected but newer evidence suggests a shorter time interval from transplant to pregnancy as these transplants are not intended for permanent function and will be removed after 2 pregnancies. Cervical biopsies are performed to evaluate for signs of rejection at 1, 2, and 4 weeks and then monthly for a year then every 1–3 months [23].

Worldwide, there have been 31 deliveries to date from uterine transplants and there is a large demand for this procedure. Future research will be focused on overcoming some of the technical challenges with the surgery to procure the uterus from living donors, simplifying the anti-rejection regimen, shorten the time from transplant to pregnancy, and finding alternative approaches to improve the revascularization of the transplanted uterus.

Conclusions

As one can see from the above presentations, the virtual meeting was a huge success. The quality of the presentations was excellent and all who attended learned a great deal. Members may visit the ISFP website at www.isfp-fertility.org to see these presentations in their entirety.

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Declarations

Conflict of interest The authors declare no competing interests.

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