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MEETING PROCEEDINGS

Summary of the ISFP congress, Brussels, 10–12 November, 2022

Lara Houeis[1] · Marie-Madeleine Dolmans[1,2]

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Abstract
The 7th International Congress of the ISFP was held in Brussels in November 2022. Hundreds of attendees from all over the world had the rare opportunity to hear the most distinguished leaders discuss and debate the latest advances in the field. Participants were also able to attend workshops under the guidance of skilled practitioners. Numerous topics were considered, including a recap on fertility preservation approaches in cancer and benign pathologies and a section on male factor infertility. Other aspects covered were in vitro maturation and poor responders, the impact of chemotherapy on the ovary, and future perspectives. Participants had the chance to listen to a symposium on fertility preservation techniques, and finally, a keynote lecture on fertility preservation in gynecological cancers brought this prominent and highly influential event to a close.

Keywords Fertility preservation · Ovarian tissue cryopreservation · Ovarian tissue transplantation · Ovarian stem cell therapy · Premature ovarian insufficiency · Uterine transplantation · Adenomyosis · Linzagolix

The 7th World Congress of the International Society for Fertility Preservation took place on November 10–12, 2022, at the Plaza Hotel in Brussels, bringing together hundreds of participants including internationally renowned leaders in the field of fertility preservation. These experts presented important updates on their research in this field of reproduction which has evolved greatly over the past 20 years. Indeed, the first live birth after ovarian tissue cryopreservation (OTC) and subsequent transplantation (OTT) was reported back in 2004 [1].

Thursday 10/11/2022

Thursday was devoted to pre-congress workshops. The first, led by Marie-Madeleine Dolmans (Belgium), focused on OTC, with Claud Yding Andersen (Denmark), Jacques Donnez (Belgium), Marie- Madeleine Dolmans (Belgium), Debra Gook (Australia), and Linn Mamsen (Denmark) outlining indications for ovarian tissue retrieval, freezing, thawing, and transplantation. Participants also had the opportunity to attend practical sessions to learn how to prepare ovarian tissue for slow freezing using bovine ovaries. The other focused on oocyte vitrification, offering some theory followed by hands-on practice, and was overseen by Inge E. Agerholm (Denmark), Martine Nijs (Belgium), Olga DeSilva (Denmark), and Cornelia Meyer (Germany).

Friday 11/11/2022

On Friday, November 11, the current president of the ISFP, Marie-Madeleine Dolmans (Belgium), welcomed the participants and invited Jacques Donnez (Belgium) and Sam Kim (USA), founders of the ISFP to join her on stage. They took us through a retrospective of the past 15 years of the society, from the first meeting in Brussels in 2007 to the present day. They also announced two new members of the board who will replace them: Catherine Poirot (France) and Glenn Schattman (USA).

The opening lecture by Marie-Madeleine Dolmans (Belgium) looked at the results of OTT worldwide, revealing that 300 lives births had so far been reported after the procedure. This is testament not only to the success of the technique, but also its global popularity. In two recent papers, the live birth rate

✉ Marie-Madeleine Dolmans
marie-madeleine.dolmans@uclouvain.be

[1] Gynecology Research Unit, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

[2] Department of Gynecology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

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after OTC and OTT was, respectively, 41% and 30%, proving its effectiveness [2, 3]. Since the first live birth of Tamara in 2004, we have come a long way, but it is time to acknowledge the remaining challenges. The most important of these include how to prevent chemotherapy-induced gonadotoxicity, how to improve results of OTC and OTT, and how to ensure successful *in vitro* growth of immature ovarian follicles and ovaries.

Future research should focus on development of different protectants acting against potential chemotherapy-induced damage like accelerated primordia follicle activation, apoptosis, stromal inflammation, and vascular damage inducing fibrosis.

There are various ways to prevent follicle loss (sphingosine-1-phosphate, tamoxifen, and anti-Müllerian hormone (AMH)), but the best approach without any doubt involves development of effective new chemotherapy drugs able to protect the ovarian reserve. The second key issue is how to enhance follicle outcomes after OTT. Several solutions include shortening hypoxia, boosting revascularization, and/or reducing oxidative stress.

Session one: cancer patients and criteria for fertility preservation

Criteria for fertility preservation were discussed by Richard Anderson (UK). He reaffirmed the robustness of the Edinburgh selection criteria: age under 35 years, no previous chemotherapy or radiotherapy if aged 15 years or over (but mild non-gonadotoxic chemotherapy acceptable if aged under 15 years), a realistic chance of surviving 5 years (> 50%), high risk of premature ovarian insufficiency (POI) (>50%), negative serology for HIV, syphilis and hepatitis B, and not pregnant with no existing children [4]. A number of questions arose, such as the relative difficulty of evaluating the chances of survival and the probability of POI. He also stressed that a partnership with the patient (informed consent, decision aids, etc.) and collaboration between oncologists, pediatricians, and reproductive medicine specialist were of utmost importance.

Glenn Schatmann (USA) then gave us an overview of fertility preservation in the USA, emphasizing the impact of age on the ovarian reserve. He reported that the efficacy of oocyte vitrification decreases significantly after 40 years of age.

Session two: fertility preservation in benign gynecological diseases

Felice Petraglia (Italy) described the endometrial and myometrial mechanisms behind infertility associated with uterine fibroids, adenomyosis, and/or endometriosis. Mechanisms explaining myoma-related infertility are indeed diverse and include uterine cavity distortion, impaired endometrial and myometrial blood supply, increased uterine contractility, paracrine hormone and molecular alterations, defective endometrial receptivity, and impaired expression of genes needed for implantation, such as HOXA10 [5].

Concerning endometriosis and adenomyosis, both are inflammatory diseases that hamper endometrial and myometrial function. Inflammatory factors (particularly TNFa, IL-1, IL-6, prostaglandins, COX-2, MMPs, and reactive oxygen species (ROS)) interfere with implantation and placentation [6]. Petraglia also stressed that endometriomas diminish oocyte quality and deplete the ovarian reserve, leading some women to consider fertility preservation options in case of endometriosis, especially ovarian endometriosis [7].

Jacques Donnez (Belgium) then proceeded on the subject of uterine adenomyosis-related infertility, which according to 2 reviews is real [8, 9]. Indeed, looking at IVF outcomes, the presence of adenomyosis significantly reduces clinical pregnancy and live birth rates and increases the risk of miscarriage. When IVF stimulation protocols are analyzed and compared between adenomyosis and non-adenomyosis subjects, it appears that lowering estradiol levels, with long-term gonadotropin-releasing hormone (GnRH) agonists before controlled ovarian stimulation may reduce the negative association. But what are the current treatment options for adenomyosis-related infertility? Surgical management like the three-flap method for complete adenomyosis resection (according to Osada's technique) presents some disadvantages: surgery is difficult, as is uterine wall repair, and there is a higher incidence of uterine rupture [10]. Among medical therapies, nonsteroidal anti-inflammatory drugs are effective against pain but do not affect fertility, combined oral contraceptives and progestogens show very limited efficacy in reducing uterine volume, while GnRH agonists decrease uterine volume but cause a flare-up effect. Oral GnRH antagonists, on the other hand, bind directly to the receptor and induce immediate gonadotropin suppression, which is dose-dependent and rapidly reversible. One pilot study demonstrated that 200 mg linzagolix for 3 months, without add-back therapy, was able to provoke a significant decrease in uterine size and adenomyotic lesions. In case of severe adenomyosis, oocyte pick-up and vitrification could be proposed prior to medical therapy (GnRH antagonist for 3 months), followed by immediate embryo transfer 2 weeks after the end of therapy [11]. Of course, more large-scale studies are needed to determine the potential of GnRH antagonist in treating adenomyosis-related infertility.

Fertility preservation in endometriosis patients was covered by Ana Cobo (Spain), who discussed results of oocyte vitrification in women with endometriosis compared to cases of elective fertility preservation. In endometriosis patients, despite possibly impaired oocyte quality, the number of oocytes retrieved (prior to any surgery) was almost the same

as in unaffected women, and the live birth rate was similar in both groups [12]. Cobo nevertheless suggested performing surgery on ovarian endometriosis after fertility preservation in young patients, as surgery has detrimental effects on the ovarian reserve, as demonstrated by the smaller number of oocytes retrieved and vitrified after surgery than in the social freezing group [7]. She did stress that the most crucial factor influencing the cumulative live birth rate was age. Significant differences in cumulative live birth rates were observed between patients aged 35 years or less versus patients aged 36 years or more in all groups of fertility preservation by vitrification (elective, oncologic, and endometriotic).

Marie-Madeleine Dolmans (Belgium) then presented a lecture on fertility preservation in Turner patients. These subjects show accelerated follicle apoptosis and atresia, leading to ovarian failure in 80% of cases before or around the time of puberty. OTC is the only fertility option available to prepubertal girls but, Turner girls exhibit lower follicle density and greater drop in follicle numbers after puberty. After xenografting, follicle density also falls dramatically, as observed in normal tissue, so the real question is, with high aneuploidy rates of granulosa cells in small follicles, could OTT be effective? [13].

The most important findings are that aneuploidy rates in granulosa cells declined significantly as follicles developed, and small follicles were able to develop to antral stages after long-term xenografting. In other words, normal folliculogenesis is possible in Turner patients. It is essential to offer OTC to Turner patients before puberty, as the younger the subject at cryopreservation, the greater the chances of finding antral follicles after transplantation. The recommended cut-off is 12 years of age.

Tommaso Falcone (USA) then closed the session on benign gynecological diseases with a very interesting overview of uterine transplantation. The first live birth after uterine transplantation was achieved in 2015 [14], rising to 49 live births by 2022, as reported at a recent congress in Paris.

Uterine factor infertility affects up to 1 in 500 reproductive-age women. The main indications for uterine transplantation are Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome (1/4000 women), acquired uterine factor infertility (post-hysterectomy, adenomyosis, fibroids, and Asherman syndrome), and transgender candidates. Different approaches using living donors and deceased donors were then compared. The living donor technique requires thorough preoperative screening, as the uterine vasculature is the main predictor of success. There are therefore exclusion criteria like major illnesses that could impact vascular function (hypertension, diabetes, and hyperlipidemia), pelvic kidney, gynecological history of anomalies, HPV, and high body mass index [15]. As most donors are postmenopausal, use of preoperative estrogens could yield some benefits, balanced against additional risk of venous thrombotic events.

It is also important to stress that surgery itself is complicated, can take up to 11 hours, and has physical risks for the donor. Compared to deceased donor surgery, it does nevertheless allow additional time for evaluation and convenient scheduling.

On the recipient side of the transplant, there are several preparations to be made. In case of MRKH syndrome, short vaginal length needs to be assessed and use of dilators should be considered prior to surgery to allow cervico (donor)–vaginal (recipient) anastomosis. IVF cycles must also be done before surgery, making at least 6 blastocysts available. After transplantation, immunosuppression has to be maintained with any signs of rejection monitored by cervical biopsies and perfusion control by ultrasound [16]. Embryo transfer can occur 6 months after grafting and, to date, 49 live births have been documented. In a series of 45 uterine transplantations reported by Ayoubi, 23.5% of grafts were removed due to thrombosis, infection, ischemia, and/or hemorrhage [17].

Session three: andrology

The third session of the day focused on andrology with Jan-Bernd Stukenborg (Sweden) opening with a talk on fertility preservation in boys including recent developments, challenges, and new insights. He first presented the most recent clinical advances according to criteria like pubertal stage of the patient (prepubertal or pubertal), immature testicular tissue, mature testis, or semen that can be cryopreserved. He also reminded us that a multidisciplinary team (oncologist, reproductive medicine specialist, and mental health nurses) is there to help patients and their parents [18].

It is important to note that there are more than just oncological indications. Indeed, fertility preservation is also required in boys in case of sickle cell disease, bone marrow failure, immunodeficiency, Klinefelter syndrome (47XXY), and cryptorchidism [18]. There are many challenges remaining in this field, be they clinical or research-related. Protocols must be improved and optimized, everything from patient selection, tissue collection and cryopreservation, transportation, to follow-up.

In research, challenges mainly concern spermatogonial stem cells, from isolation to *in vitro* maturation (IVM).

Rod Mitchell (UK) emphasized the need to understand the damage done to prepubertal testes by gonadotoxic treatments. Thanks to experimental models, we can come up with better patient selection criteria and develop strategies to reduce or prevent gonadotoxicity. Clinical studies (but not experimental studies) suggest that platinum agents used for neuroblastoma and osteosarcoma have an adverse effect on germ cells and spermatogonial stem cells when used in prepuberty [19]. Vincristine chemotherapy, administered in case of acute lymphoblastic leukemia or lymphoma, is considered to have

low gonadotoxicity. In mice, it induces a drop in germ cell count at the end of therapy, even more pronounced than after cyclophosphamide therapy (well known to be highly gonadotoxic) [20] but in clinical studies on human testes, there is no apparent impact on reproductive outcomes

Yoni Baert (Belgium) then presented new perspectives on laboratory-made sperm. Indeed, this futuristic concept is not so far removed. Thanks to testicular organoid techniques, it is possible to enhance *in vitro* spermatogenesis and subsequently create a tailorable and scalable model for each patient. Three-dimensioned bioprinting could help us recreate testicular compartments and control cell deposition [21].

Pasquale Patrizio (USA) spoke about fertility preservation in transgender individuals. He stressed the importance of fertility preservation prior to gender reassignment procedures and talked about the available options. Transfemale (male to female) subjects can undergo sperm freezing, spermatogonial stem cell freezing, or testicular tissue cryopreservation; the latter two options still being experimental [22]. Estrogens administered for hormone transition lower sperm production, so sperm should ideally be harvested before gender transition, according to the American Society for Reproductive Medicine recommendations. For transmale (female to male) subjects, egg retrieval is the main option, and prior use of testosterone does not show any adverse effects in terms of perinatal complications if the eggs are later used [23]. Transgender patients who seek fertility preservation services should nevertheless be informed about the lack of data on long-term outcomes. Financial counseling is essential as assisted reproduction options are expensive and potentially complex. Setting up a specialized transgender health team should be contemplated.

Session four: IVM and poor responders

Michel de Vos (Belgium) gave a lecture on IVM of oocytes. The main advantage of this technique is that no ovulation triggers are needed prior to retrieval. It is actually preferable that oocytes destined for IVM are harvested without any stimulation of ovulation and cultured within the cumulus oocyte complex (COC). IVM requires specific expertise and should only be attempted when oocyte cryopreservation is required but ovarian stimulation is not feasible [24]. This technique is useful in case of polycystic ovaries, to avoid the risk of hyperresponse to gonadotropins and for women with follicle-stimulating hormone (FSH) resistance.

There is now a new application for IVM: fertility preservation in women with cancer. In De Vos's department, around 50 patients have undergone IVM followed by oocyte pick-up for fertility preservation, most of them for breast cancer. Fifty-two IVM cycles were performed, and an average of 8 MII oocytes were cryopreserved after culture. Five patients returned for thawing and implantation, but no live births have been reported to date.

If the patient is over 36 years of age, oocyte quality is often not good enough for IVM. IVM requires a high antral follicle count but presents an alternative when there is no time for stimulation before gonadotoxic treatments. It should be used as a supplementary technique in addition to ovarian cortex cryopreservation.

IVM of the cryopreserved ovarian cortex shows the same maturation rate as after vaginal pick-up (42%) in adult patients, but a much lower rate in prepubertal patients [25]. While IVM of cryopreserved ovarian tissue is a promising technique, especially for patients in whom ovarian grafting is contraindicated, data are limited, and further research must be conducted.

Claud Yding Andersen (Denmark) completed the presentation on IVM by developing the two-for-one concept, namely, freezing ovarian cortical tissue and collecting immature oocytes from the medulla [26]. In the human ovary, there is asynchrony between oocyte and follicle growth, with the final oocyte diameter being reached early on in follicle development. This oocyte diameter is of fundamental importance for meiotic transition: the bigger, the better. However, smaller follicles show lower atresia rates, so small antral follicles might be the best choice for IVM, knowing that their oocyte diameter is the same as that of mature oocytes. Andersen also emphasized the high maturation rate of large COCs (> 50%) versus naked oocytes (12%) [27]. Cumulus cells (and especially large COCs) affect the local milieu during IVM and are likely to have a pronounced effect on the developmental competence of oocytes.

It is important to know that FSH increases expression of luteinizing hormone receptors (LH-R), which is associated with MII transition, and decreases FSH-Rs. FSH-Rs are highly expressed in small follicles, but FSH-R expression is much higher in mural granulosa cells than in cumulus cells in antral follicles [28]. However, high concentrations of FSH (> 70 IU/L) trigger LH-R expression in cumulus cells despite modest expression of FSH-Rs, meaning that COCs act without antral cells in IVM.

The second part of this session focused on poor responders with Stine Gry Kristensen (Denmark) addressing in vitro activation (IVA) of dormant follicles, a method to boost recruitment of quiescent primordial follicles. Different intrafollicular signaling pathways regulate follicle activation, such as the PI3K/AKT pathway and the mTOR pathway. There is a balance between suppressors of follicle activation (like AMH, PTEN, FOXO3a, and p27) and maintainers of dormant follicles (rpS6, PDK1), and follicle activation is induced when change occurs in these molecular pathways [29]. Follicle activation is also regulated by mechanotransduction; the Hippo signaling pathway prevents activation

of primordial follicles but is disrupted by ovarian manipulation [30]. The IVA/drug-free IVA cutting technique has been proposed in women with POI and similar conditions, but contentious issues emerged and success rates are low [31]. IVA cannot yet be considered a viable solution. It is still experimental, there are only limited data available, and it currently requires invasive procedures (at least two laparoscopies) in exchange for relatively low success rates and possible carcinogenic effects of IVA drugs. IVA needs to be thoroughly investigated before contemplating application in a clinical setting [32].

Antonio Pellicer (Italy) gave a very intriguing and hope-giving talk about rejuvenating the ovary through stem cell transplantation, showing promising results in early-menopause patients. Indeed, there are exciting perspectives in this field like the use of platelet-rich plasma (PRP). Platelets contain growth factors, some of which have a positive impact on follicle growth and angiogenesis. According to Cakiroglu et al., women with a poor ovarian response treated with intraovarian injections of autologous PRP showed an improvement in ovarian reserve parameters. However, studies with control patients and continued investigations are needed [33].

The second promising technique is bone marrow stem cell transplantation into ovarian tissue through catheterism. Stem cells secrete growth factors involved in the cell cycle, gene expression, and follicle activation pathways (Hippo and PI3K/AKT). This technique yielded enhanced ovarian function in 81% of poor responders, an increase in AMH and antral follicle count, and retrieval of more follicles and oocytes, resulting in 3 spontaneous pregnancies and 3 IVF pregnancies [34].

The last talk of the day on mitochondrial and nuclear transfer was given by Chii-Ruey Tzeng (Taiwan). Different options were presented including mitochondrial transfer by direct injection, tunneling nanotube transfer, spindle or pronuclear transfer, and polar body transfer. For fertility enhancement or preservation, direct autologous mitochondrial injection from granulosa cells looks promising as a way of rejuvenating the oocyte [35]. These techniques could also be applied to mitochondrial diseases.

Saturday 12/11/2022

Session five: chemotherapy and the ovaries

The second day of the ISFP congress started with a session on chemotherapy and the ovaries. Dror Meirow (Israel) opened the session with a lecture on the mechanisms of ovarian damage resulting from chemotherapy. Chemotherapy triggers an increased apoptosis in growing follicles, but also activation and growth of primordial follicles through direct toxicity or an indirect effect. This leads to over-recruitment due to a drop in growing follicle numbers and causes a global depletion of the follicle pool. Of course, the intensity of these effects depends on the type and dose of chemotherapy, the duration of treatment, and patient age. Chemotherapy also induces stromal damage, such as fibrosis and injuries to blood vessels [36]. Cyclophosphamide exposure results in upregulation of the PI3K-AKT signaling pathway, leading to further activation of primordial follicles and subsequent atresia, described by Meirow's team as the burn-out effect [37]. Thereafter, Oren Kashi (Israel) proposed several options to protect the ovarian reserve during chemotherapy. One of the most exciting, though still experimental, is use of AMH during the initial period of loss following chemotherapy to safeguard the follicle pool

In her lecture, Catherine Poirot (France) drew attention to a very important if contentious issue with the Edinburgh criteria. Indeed, she recommends OTC as a fertility preservation option in women who already received low doses of gonadotoxic treatment or a previous course of chemotherapy. In 2019, she conducted a study on the impact of cancer chemotherapy before OTC and OTT. The study involved 31 patients, 22 of whom were exposed to chemotherapy before OTC, and 9 were not. There was no difference in the characteristics of these two groups at the time of OTC and notably no difference in age. Surprisingly, the percentage of women who gave birth to at least one child was 32% in the group with prior chemotherapy, indicating that chemotherapy is not a contraindication to OTC [38].

In another study investigating only patients with hematological malignancies, the interval between the last chemotherapy session and OTC was considered. Two groups were identified, one with the last chemotherapy far-removed from OTC (> 3 months), and the other with chemotherapy ongoing at the time of OTC. Recovery of ovarian function after OTT was the same in both groups, whether OTC was performed > 3 months after chemotherapy, or during chemotherapy [39]. These results were confirmed in a series of 285 patients, where 44% of women who had had previous chemotherapy prior to OTC gave birth to at least one child, versus only 20.4% in the no-chemotherapy group [3].

One main conclusion that can be drawn from these studies is that previous chemotherapy is no longer a contraindication to OTC and OTT.

Dror Meirow (Israel) reported the Israeli experience in 766 OTCs performed so far 80% of leukemia patients received previous chemotherapy. In 2005, Meirow reported the first live birth after OTT in a leukemia patient, the tissue having been collected during the remission phase [40]. It nevertheless remains crucial to search for minimal residual disease (MRD) in tissue prior to transplantation, as 22% of patients still show signs of MRD in their ovarian tissue.

Isabelle Demeestere (Belgium) then spoke about counteracting gonadotoxicity. She emphasized de-escalation strategies to reduce overall toxicity of treatments, which is a research priority in oncology and should be taken into account in fertility preservation criteria and counseling [41].

Although GnRH analogs represent a pharmacoprotective approach to reducing chemotherapy-induced damage in breast cancer, long-term efficacy remains uncertain, and these drugs should not replace cryopreservation [42]. A number of anti-cancer therapies, immunomodulator agents and inhibitors, like imatinib and rapamycin (mTOR inhibitor) that show potential benefits in ovarian function protection and recovery were also considered. However, there is a lack of clinical data and a risk of potential interaction with cancer treatment [43, 44]. Multitarget strategies using miRNA are also an option that could be contemplated in the future [45].

Symposium: updates on cryopreservation strategies

Michel De Vos (Belgium) opened the symposium with a talk on egg freezing in oncological patients. Oocyte cryopreservation in postmenarchal cancer patients offers hope of recovery and motherhood. It is important to stress that, prior to cancer treatment, these patients can only undergo one cycle of stimulation, but they can undergo further cycles after recovery (then regarded as medical fertility preservation, and not oncofertility treatment). In case of egg freezing for oncological reasons, GnRH antagonist stimulation with a GnRH agonist trigger is the safest, shortest, and most convenient protocol [46]. Random-start stimulation is also possible, even during the luteal phase, as there is no negative impact from high progesterone levels on embryo ploidy. However, patients whose risk of POI is high following their cancer treatment show lower oocyte yields and poorer oocyte quality than their counterparts having less gonadotoxic treatment [47]. Thus far, there is limited utilization of cryopreserved oocytes, and further scrutiny is required.

Elisa Gil Arribas (Spain) then proceeded to speak about egg freezing for social reasons or age-related fertility decline. Indeed, increasing lifespans of populations and new family models have changed global perceptions and concerns about fertility. So far, the only reliable technique to delay fertility decline available is egg freezing, but there are pros and cons. The main advantage is that egg freezing for social reasons empowers women and gives them time to start a family. However, considerable disadvantages include a lack of quality biomarkers, potential late motherhood pregnancy risks, and, above all, high costs [48]. The best success rates are associated with patient age at vitrification (the younger the better), and the number of frozen oocytes.

Marie-Madeleine Dolmans (Belgium) went on to talk about OTC to delay menopause. Women now live without ovarian activity for more than one-third of their lives, and we have come full circle with respect to HRT. When we look at lessons learned from fertility preservation programs, we see encouraging results on ovarian function restoration, which lead us to speculate that OTC at a young age (ideally age 20–25 years), followed by reimplantation at menopause, could be an alternative to HRT in the future. Indeed, some patients are reluctant to receive hormone therapy, but ovarian grafts secrete natural estrogens, unlike synthesized drugs, and heterotopic grafting could allow repeated straightforward procedures to potentially restore hormone levels for more than 15 years [49]. Such elective use of cryopreserved ovarian tissue requires a risk–benefit assessment and further clinical investigations. It may be technically feasible but does that make it ethically acceptable?

Session six: paving the way to the future

Francesca Klinger (Italy) opened the session with a talk on the multiple aspects of the aging ovary in mammals. The ovary is a complex structure in which not only oocytes succumb to age, but also the stromal compartment, including immune cells, the extracellular matrix, and the matrisome. Different strategies are being investigated to extend the ovarian lifespan: (i) bone marrow stem cell transplantation into ovarian tissue, (ii) administration of antioxidants to counteract oxidative stress subsequent to mitochondrial malfunction due to age, (iii) injection of stem cell mitochondria into oocytes at the time of fertilization, and (iv) reactivation of telomerase to maintain the length of telomeres, as we know they shorten with advancing age.

Luciana Cacciottola (Belgium) then reported on how to improve revascularization in ovarian transplants. As ovarian tissue is exposed to ischemic and oxidative stress damage upon grafting, the ovarian follicle pool suffers massive follicle loss shortly after transplantation. Various approaches have been attempted to address this issue in experimental models, including administration of proangiogenic growth factors, hormones, and antioxidants, with controversial results. She developed a strategy to optimize the peritoneal grafting site with adipose tissue-derived stem cells, known for their angiogenic potential. Through their secretome, which shortened the duration of hypoxia and boosted revascularization, follicle loss was mitigated [50, 51].

Evelyn Telfer spoke about *in vitro* culture of ovarian tissue. Knowing that 99.9% of primordial follicles are destined to degenerate, can they be saved and used for fertility preservation by growing them in vitro? Growth of immature oocytes to maturity completely in vitro is a major challenge and there are multiple steps that need to be followed to support oocyte development: (i) optimizing growth from the primordial stage (activation); (ii) supporting development of isolated growing follicles (by maintaining

oocyte–somatic cell interactions); (iii) in the final stages of oocyte development, isolating the oocyte–granulosa cell complex from the rest of the follicle; and (iv) testing function by analyzing meiotic and fertilization potential. With this new method, 30% of oocytes complete the culture process and reach maturity [52]. Since 2008, Telfer has developed and improved the multistep culture system to support human follicle/oocyte development from cryopreserved tissue [53].

The next stages towards clinical application will involve determining the health and developmental competence of in vitro-grown oocytes (by sequencing or studying the epigenome and metabolome) and gaining the approval from the Human Fertilization and Embryology Authority for fertilization of in vitro-grown human oocytes before final embryo testing.

Francesca Duncan (USA) then closed the session with a talk on the ovarian microenvironment and aging. Follicle numbers decrease with age as does the quality of remaining follicles, with increased fibrosis causing tissue dysfunction and stiffer ovaries. Indeed, her results demonstrate that the ovary becomes stiffer with age and that both collagen and hyaluronan matrices serve as mechanisms regulating ovarian biomechanics. Age-associated increases in collagen and decreases in hyaluronan are maintained in the human ovary and may impact follicle development and oocyte quality [54].

Session seven: fertility preservation in breast and pelvic cancer

Four oral communications were preselected for awards. The first was presented by Blandine Courbiere (France), who addressed uterine volume reduction after childhood hematopoietic stem cell transplantation irrespective of conditioning regimen (though much more pronounced in case of total body irradiation). Luciana Cacciottola (Belgium) then proposed apoptosis and autophagy as determinants of ovarian reserve decline from birth to reproductive age in women OTC. Tal Imbar (Israel) showed us that prior exposure to chemotherapy does not reduce the IVM potential of oocytes obtained from ovarian cortex of cancer patients. Finally, Cristina Subiran Adrados (Denmark), who won the award, presented her work on human platelet lysate, which improves growth and survival of isolated human preantral follicles in vitro.

We then had the chance to listen to Catherine Uzan (France), who gave a keynote lecture on conservative surgery in ovarian cancer, borderline ovarian tumors, and cervical cancer. Concerning cervical cancer, Uzan stressed the IB1 stage approach (with negative nodes), reviewing four treatment strategies: simple trachelectomy (or conization), radical trachelectomy by vaginal approach, radical trachelectomy by laparotomy, and radical trachelectomy by laparoscopy. She reported pregnancy rates of respectively 56.3%, 58.7%, 36%, and 46.4%. Recurrence rates, reported in this large series, were respectively 4.1%, 4.7%, 2.4%, and 5.2%. In terms of obstetrical outcomes, the risk of prematurity increased with the height and volume of cervix treated [55]. Regarding the new FIGO IB2 (node negative) stage, French standards require radical hysterectomy or brachytherapy and radical hysterectomy. Options to spare fertility like neoadjuvant chemotherapy should be carefully considered and approved by a multidisciplinary decision.

Uzan's second lecture was devoted to borderline ovarian tumors. Conservative treatment (cystectomy) increases the risk of recurrence, but has no impact on overall survival. Forty percent of women become pregnant after conservative treatment. In women with persistent infertility, IVF might be considered after collegial approval if there are no invasive implants, no residual disease, and no micropapillary patterns. In case of recurrent disease, options like IVF would depend on the ovarian reserve and inherent risk factors related to borderline tumors [56].

Concerning epithelial ovarian cancer, fertility-sparing surgery can be safely offered in case of all stage IA to IC1 low-grade ovarian carcinomas, but there is no place for ovarian preservation in cases above FIGO stage I [57]. Finally, conservative surgery is an option for germ cell tumors, considering that these tumors have high chemosensitivity [58].

Michael Von Wolff (Germany) then spoke about fertility preservation in breast cancer patients, focusing on BRCA mutations. Ten percent of women affected by breast cancer have a BRCA mutation. Those with BRCA 1 show an overall diminished ovarian reserve, but this has little impact in clinical practice.

Having a BRCA mutation does not actually change the algorithms used for fertility preservation. If there is a good chance of survival at 5 years and a high risk of POI (depending on the time frame available), oocyte or ovarian tissue freezing are options. Fertility preservation is not recommended if the chances of surviving 5 years are low or if the risk of POI is small [59].

Finally, Marie-Madeleine Dolmans (Belgium), the outgoing president, led the closing ceremony of the congress, inviting Nao Suzuki (Japan) to the stage to appoint him new president of the ISFP. He announced that the 2024 ISFP congress will be held in Tokyo.

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Declarations

Conflict of interest The authors declare no competing interests.

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