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Letter from the Editors

Inside This Issue

Every woman deserves the chance.

Dear Colleagues:

In this Newsletter of the ISFP, one is the report of "Young Scientists Congress in Brussels", an international conference on fertility preservation which was held by DOLMANS and DONNEZ earlier this year and it was recorded by Michelle SOARES. This was a unique opportunity for young scientists from different centers and continents to meet, to present their research, and to have fruitful discussions both with young and leading researchers in the field of fertility preservation.

Another report is the Summary of "Update on Fertility Preservation For Girls and Young Women With Cancer" by Professor Hamish Wallace from Royal Hospital for Sick Children, University of Edinburgh. Last year we discussed the issue of ovarian tissue transplantation with cancer recurrence. In spite of this uncertain risk, ovarian tissue cryopreservation with orthotopic transplantation seems to be the only option available for restoring those cancer patients' fertility. At the congress entitled "Freezing of oocytes, embryos and ovarian tissue: focus on fertility management and fertility preservation" in Brussels held in January 2015, experts gave their views on this important issue.

The second report from Wallace, et al. has first accurately picked out vulnerable young female cancer patients with the Edinburgh selection criteria, as candidates for this fertility preservation option. With growing numbers in live births after frozen-thawed ovarian tissue transplantation, this procedure seems feasible and practical nowadays. Keeping follicle survival in the grafts to improve its efficiency is an ensuing challenge.

Chii-Ruey Tzeng, M.D., M.P.H.
Dror Meirow, M.D.
Co-Editors of ISFP Newletter

Young Scientists Congress In Brussels

By Michelle Soares
on behalf of Professors Marie-Madeleine Dolmans and Jacques Donnez
Congress Organizers

On January 16-17, 2015, in a cozy conference room at The Hotel in Brussels, participants gathered for an international conference on fertility preservation, endorsed by the ISFP. This congress, entitled “Freezing of Oocytes, Embryos and Ovarian Tissue: Focus On Fertility Management and Fertility Preservation” was organized by Professor Marie-Madeleine Dolmans and Professor Jacques Donnez, experts in the field.

These two days saw the world’s leading pioneers in the field of cryopreservation and fertility preservation present their views and engage in debates on key issues in this area. Apart from 12 keynote plenary lectures, providing insight into specialized and truly challenging aspects of this field, the innovative element of this congress was the featuring of oral presentations by selected young scientists (under 40 years of age), who, in between the keynote lectures, shared results of their fascinating research and latest findings. Hence, the congress was very much focused on the work of young upcoming scientists, which also gave the gathering its dynamic and captivating character. Twenty abstracts were selected from among more than 50 submitted, and these young presenters received free registration to the congress, as well as a travel grant and two paid nights at the conference venue.

On Friday morning, a warm welcome by the organizers was followed by an instructive session on the oocyte, with an exciting opening lecture by Professor D.F. Albertini (USA), illustrating the complexity of this unique and largest cell of the human body. The next session saw two experts in the field, Dr. C.A. Amorim (Belgium) and Dr. M.B. Zelinski (USA), present updates on their research into the transplantable artificial ovary and in vitro maturation of follicles respectively.

Later that morning, we had the opportunity to listen to Professor A. Hsueh (USA) explain the role of Akt and Hippo signaling pathways and their impact on follicular activation in ovarian tissue. He demonstrated how, by combining Hippo signalling disruption (ovarian fragmentation) with Akt stimulation (treatment with PTEN inhibitors and PI3 kinase stimulators), they were able to achieve growth of secondary follicles to the preovulatory stage, achieving two live births after ovarian tissue transplantation in patients suffering from premature ovarian failure.

The last keynote lecture of the morning was given by Professor D. Meirow (Israel) on how to prevent follicular damage due to chemotherapy. This captivating talk reviewed the known mechanisms of activation and growth of the dormant follicle pool induced by chemotherapy, and provided insights into the

latest pharmacological agents, like PI3K pathway inhibitors and AMH, that could potentially prevent this damage.

The sessions after lunch were dedicated to oocytes and embryos. Dr. Laura Rienzi (Italy), internationally recognized authority in the field of human clinical embryology and research, shared her expertise on oocyte vitrification. She showed us how, thanks to high oocyte survival, embryo development, clinical pregnancy and live birth rates, oocyte vitrification had become a real alternative to embryo freezing in IVF programs, constituting a legitimate option for fertility preservation in cancer patients. She also touched on the topic of oocyte vitrification for social reasons. This compelling lecture gave way to yet another: embryo selection to improve IVF outcomes. Dr. Carmen Rubio Lluesa from Valencia presented the results of the first RCT to validate the strategy of culture and selection of embryos in an integrated time-lapse monitoring system demonstrating an improvement in reproductive outcome. She also shared more than 3 years of clinical experience with aCGH arrays for aneuploidy screening of cleavage-stage and blastocyst biopsies as a co-adjuvant technique to improve reproductive outcome in IVF patients at high risk of aneuploidy. The last keynote lecture of the day was by Professor W.B. Schoolcraft from the USA. In this engaging lecture, he presented several prospective RCTs showing the clear benefits of blastocyst-stage biopsy with comprehensive chromosomal screening (CCS) and frozen embryo transfer, compared to 3-day embryo biopsy, as expounded in the previous lecture.

On Saturday, January 17, Professor C.Y. Andersen (Denmark) opened the meeting with his objective review of the question, “Ovarian Tissue Vitrification Versus Slow Freezing: Where Are We In 2015?”. The important take-home message from this lecture was that for the moment, there is not enough proof of the superiority of vitrification to change our practice in a clinical setting. Professor M-M. Dolmans from Belgium then gave us a comprehensive overview of the results and risks of ovarian tissue transplantation, and shared the findings of a very recent large-scale experimental study using sensitive PCR techniques proving the absence of malignant cells in ovarian tissue from sarcoma patients.

The next session saw two preeminent experts in the field, Professor H. Wallace (UK) and Professor J. Donnez (Belgium), tackle the specific issues of prepubertal ovarian tissue. Professor Wallace spoke of ovarian tissue cryopreservation in children and adolescents as an experimental procedure at present, and defended use of the Edinburgh selection criteria for ovarian tissue cryopreservation in girls and young women with cancer, based on follow-up of ovarian status in their series. Professor J. Donnez, on the other hand, argued that ovarian tissue cryopreservation is no longer experimental in prepubertal girls, and stressed a number of histological differences, explaining that an extensive primordial follicle pool persists in prepubertal tissue after 6 months of xenografting, in contrast to adult tissue, where massive activation of follicles occurs.

In the last session on stem cells, Professor Evelyn Telfer (UK) presented an objective review of ovarian stem cells. According to the latest research by her team, a population of cells isolated from the ovary is able to develop into follicle-like structures when cultured in bovine ovary, but the true nature of these structures is yet to be determined. In the final keynote lecture, Professor G.P. Schatten (USA) wrapped up the proceedings with a humoristic review lecture on pluripotent stem cells (PSCs) and their capacity to differentiate into spermatozoa.

All 20 presentations by the selected young scientists delivered in between the keynote lectures were of a high scientific level, and touched upon the different topics presented by the experts. Worthy of note was the announcement of the first clinical pregnancy following in vitro maturation of ex vivo-harvested harvested oocytes at UZ Brussel.

During this second day, Professor D.F. Albertini, Editor-in-Chief of the Journal of Assisted Reproduction and Genetics (JARG), announced his intention to publish the proceedings of the congress in this journal, and invited all the young scientists to submit their article or communication with a view to publication after peer review. Thus, very soon, these exciting and innovative findings and ideas presented during the congress will be available to a much larger audience.

All-in-all, this Congress was an outright success, generating thought-provoking and lively debate on the hottest topics by leading authorities in the field of cryopreservation and fertility preservation, and offering young scientists a unique experience that they will never forget.

Update on Fertility Preservation For Girls and Young Women With Cancer

Professor Hamish Wallace, Royal Hospital for Sick Children, University of Edinburgh, Edinburgh, UK

For prepubertal girls and young women with cancer who are unwilling to delay the start of chemotherapy, cryopreservation of ovarian tissue is the only fertility preservation option available. So far, at least 30 live births have been reported after reimplantation of cryopreserved ovarian tissue in adult women: none have been reported using ovarian tissue from prepubertal girls. The procedure is invasive and the success rate unknown. The majority of girls and young women treated for cancer will retain a window of opportunity for fertility in the future. The assessment of which patients are at highest risk of loss of fertility thus justifying invasive experimental approaches is critical.

In our population based study cryopreservation of ovarian tissue has been selectively offered to girls and young women with cancer who met the Edinburgh

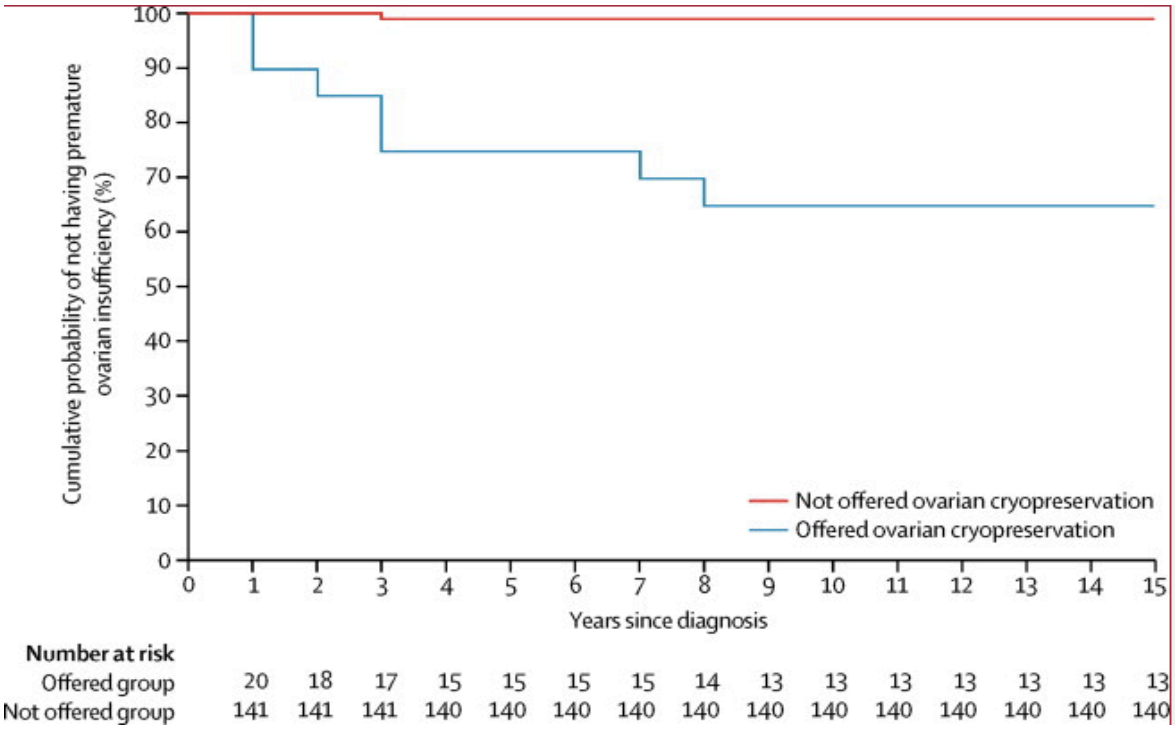
selection criteria since 1996 (Panel 1). Between Jan 1, 1996, and June 30, 2012, 410 female patients younger than 18 years at diagnosis were treated for cancer (including leukaemia and brain tumours) at the Edinburgh Children's Cancer Centre. We determined the ovarian status of these patients from review of clinical records and classified them as having premature ovarian insufficiency (POI) or not, or as unable to be determined.

34 (8%) of the 410 patients met the Edinburgh selection criteria and were offered ovarian tissue cryopreservation before starting cancer treatment. 13 patients declined the procedure and 21 consented, and the procedure was completed successfully in 20 patients. The cumulative probability of developing POI after treatment was completed was significantly higher for patients who met the criteria for ovarian tissue cryopreservation than for those who did not (15-year probability 35% [95% CI 10–53] vs1% [0–2]; p<0·0001; hazard ratio 56·8 [95% CI 6·2–521·6] at 10 years) see Figure.

In our study we have shown that the Edinburgh Selection Criteria predict which young female patients with cancer are more likely to develop premature ovarian insufficiency (POI) and therefore are most likely to benefit from ovarian tissue cryopreservation. The procedure is invasive requiring surgery and the success rate in terms of future live births remains unknown. It is important to acknowledge that a minority of young females with cancer is at high risk of POI and, as this approach remains experimental, to limit ovarian tissue cryopreservation to those patients at highest risk of POI. Future research and funding should focus on the development of this new and experimental service for young females with cancer who are at highest risk of POI but who have a realistic chance of survival.

The Edinburgh selection criteria

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years
- A realistic chance of surviving for 5 years
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (from parents and, where possible, patient)
- Negative serology results for HIV, syphilis, and hepatitis B
- Not pregnant and no existing children



References:

1. W Hamish B Wallace, Alice Grove Smith, Thomas W Kelsey, Angela E Edgar, Richard A Anderson. Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation. Lancet Oncol 2014; 15:1129-36.
2. Sabine Sarnacki. Ovarian tissue cryopreservation in children with cancer. Lancet Oncol 2014; 15: 1049-50.

Newsletter Submissions

Instructions for submissions
Deadline for Submissions : The 1st of the month prior to the next issue: (December 1, March 1, June 1 and September 1).
Submissions: ≤ 6 pages, double-spaced; consist of a concise summary of new findings and future directions; avoid extensive review of past literature; include relevant peer-reviewed references. Submissions will be reviewed by the President of the ISFP and the Editor for content and accuracy.
Editorials: ≤ 2 pages, double-spaced; clear statement of position and sources to support this position; employ insight, diplomacy and respect; inflammatory statements will not be allowed.
Send to: Norma Turner at nturner@kumc.edu

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