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PEER PERSPECTIVES

#ESHREjc report: Is OTO-IVM the future fertility preservation alternative for urgent cancer patients?

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Fertility preservation for cancer patients (oncofertility) is still a relatively new discipline, given the increase in survival rates of patients undergoing chemotherapy. Ovarian stimulation followed by cryopreservation are the routine techniques recommended for post-pubertal cancer patients (The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020). However, there are many patients who have a contraindication for ovarian stimulation, need an urgent anticancer treatment or are pre-pubertal. Despite the impressive progress in fertility preservation in recent decades, we still lack options with proven safety and efficacy for many of these patients.

The April edition of the ESHRE Journal Club (#ESHREjc) focused on a study describing the experience of a single-centre using *in vitro* matured oocytes collected from ovarian tissue (OTO-IVM) in combination with ovarian tissue cryopreservation (OTC). This technique, applied before gonadotoxic chemotherapy, led to live births after treatment (Segers et al., 2020). Three live births (two from cryopreserved embryos and one from cryopreserved oocytes) resulted from OTO-IVM for 12 patients who returned to the clinic with a desire of pregnancy after successful cancer treatment (from a total of 77 patients). This work shows that OTO-IVM has the potential to be a valuable option for patients with an urgent anticancer treatment, a contraindication for ovarian stimulation or to avoid the risk of reintroducing malignant cells into the body of a patient undergoing ovarian transplantation. Although OTO-IVM is still considered an experimental technique and more data is needed to better define its indications, the Journal Club participants discussed its advantages and future perspectives with a patient-centred care strategy in mind (see Fig. 1).

The #ESHREjc started with a discussion around the ideal population who would benefit from OTO-IVM. Experts and participants agreed that the standard fertility preservation options (i.e. oocytes or embryos cryopreservation after ovarian stimulation) should be used when feasible and according to ESHRE guidelines (The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020). However, it was recognised that patients with very aggressive malignancies (e.g. leukaemia, advanced stage lymphoma or breast cancer) need urgent chemotherapy and cannot always undergo hormonal stimulation. Consequently, alternative techniques should be considered. When asked in a poll, 93% of Journal Club participants preferred OTO-IVM over OTC prior to chemotherapy, specifically to avoid the risk of re-transplanting ovarian tissue with malignant transformation. Another issue discussed was that age and ovarian reserve are predictors of OTO-IVM success (similar to other fertility preservation options), and it was agreed that it should be reasonable to consider similar ovarian reserve indicators used in OTC (age $\leq$ 38 years old and anti-müllerian hormone $\geq$ 0.5 ng/dl) for OTO-IVM patients.

Following the comparison between OTC and OTO-IVM, Journal Club participants discussed possible changes in cryopreservation protocols to improve either of the techniques alone or in combination. In particular, it was agreed that improvements should focus on the optimal preservation of the complex cellular architecture of the ovarian tissue and to reduce the accumulation of cellular by-products during thawing. Such improvements should be supported by industry, research centres and professional societies and must be accompanied by professional development programmes directed to train reproductive medicine specialists. Another concern on the topic was the logistics of ovarian tissue transportation for OTO-IVM from the clinic to laboratories. Data on the effect of long-term ovarian tissue transportation is very limited. Thus, the current recommendation is that transportation

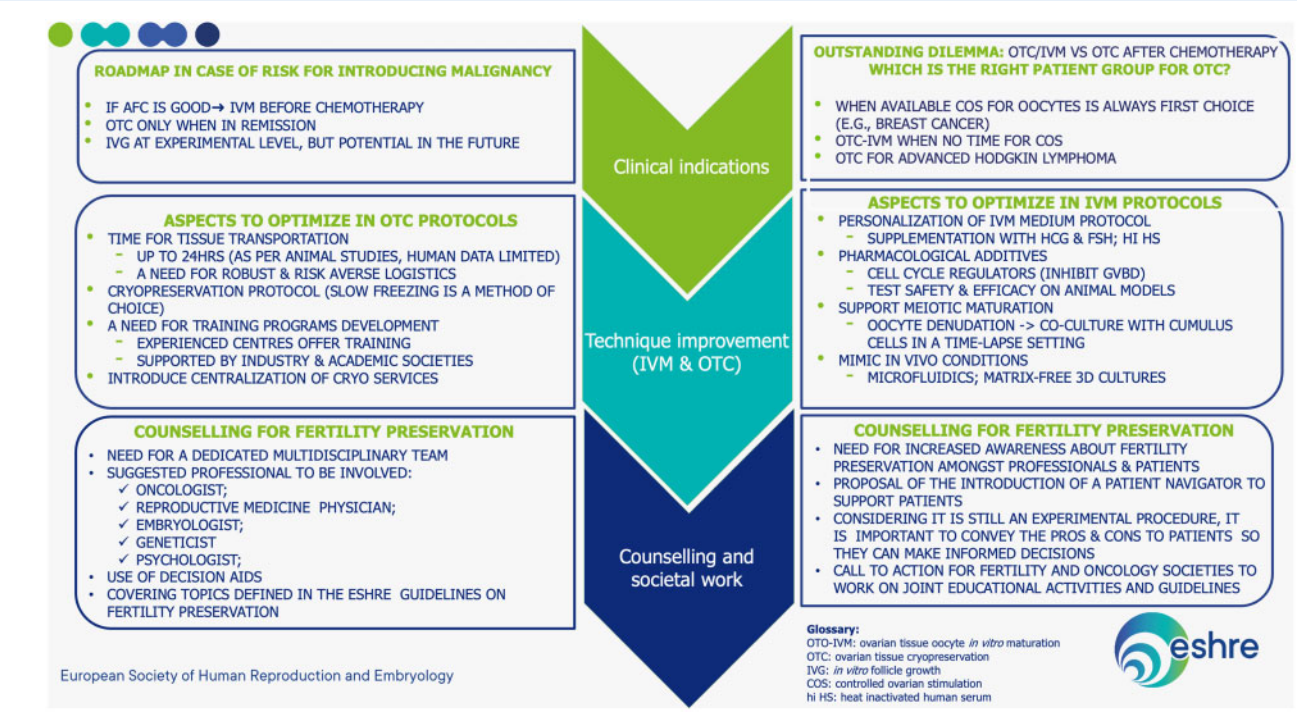

Figure 1. Graphical summary of the April 2021 ESHRE Journal Club: Is OTO-IVM the future fertility preservation alternative for urgent cancer patients?

time should be minimal and the logistics of tissue manipulation should be centralised for each clinic to avoid risks of tissue damage during transportation.

It was evident from the #ESHREjc discussion that clinical outcomes from IVM alone (in the context of fertility preservation) are not yet comparable to standard ovarian stimulation protocols (IVF/ICSI cycles). Expert participants of this month's Journal Club highlighted that, although IVM has been around for decades, there is a lack of standardised protocols resulting in poor professional training in this technique around the world. Journal Club participants agreed that oocyte competence acquired through IVM could vary widely and that the inability to assess the maturation status of oocytes without disturbing the cumulus cell complex are two major roadblocks for successful IVM improvement. In order to improve IVM outcomes, and given the variety of genetic and physiological factors for each patient, Journal Club participants discussed whether personalised IVM protocols could offer an advantage to patients. In particular, the use of a novel biphasic culture system in which the oocyte is arrested at GV stage in a pre-IVM phase, followed by a resumption of meiosis in an IVM phase (Gilchrist et al., 2016), was mentioned as a promising experimental improvement that could be applied to increase the live birth rate of OTO-IVM.

As important as technical development is the proper counselling of patients for fertility preservation before gonadotoxic treatment. This is still a multifaceted and challenging process that needs to be transparent and well balanced. Journal Club participants agreed that a multidisciplinary and cross-functional team of experts should be involved in guiding the oncofertility patient through the whole process. Although when asked in a poll about which professional is the most crucial during the process, most Journal Club participants pointed to the oncologist (50%), followed closely by the psychologist (40%). It was also suggested that reproductive specialists, nurses and embryologists should also be involved. Interestingly, the figure of a Patient Navigator, a professional with wide expertise in oncofertility treatments who counsels and serves the patient as an advocate (Scott-Trainer, 2010) was proposed as a central figure to ensure psychological support, thoughtful decision making and successful follow up after cancer treatment.

When it comes to the type of information that needs to be shared with the patient, participants of the Journal Club concluded that, besides evidence-based information on success rates and risks, costs and economical aids should also be discussed. Fortunately, 84% of the Journal Club participants in another poll were aware of the ESHRE guidelines for fertility preservation (The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020). These guidelines are based on the best evidence currently available to provide clear recommendations on the proper practice of fertility preservation, including information provision and support, pre-assessment, interventions and aftercare treatment.

In summary, Journal Club participants agreed that female cancer patients undergoing gonadotoxic treatment can greatly benefit from OTC-IVM interventions for fertility preservation. However, it was clear that this treatment still remains experimental and Journal Club participants were more inclined to use ovarian stimulation and oocyte cryopreservation as better established protocols for the majority of cancer patients. This is in line with the ESHRE guidelines for fertility preservation stating that both OTC and IVM should be regarded as innovative methods that should only be used in cancer patients when oocyte/embryo cryopreservation is not feasible. In this regard, the work of Segers et al.

(2020), provides strong evidence supporting the further development of OTC-IVM protocols as the method of choice for urgent fertility preservation cases in cancer patients in the near future.

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Conflict of interest

F.K. is an employee of Merck Healthcare KGaA, Darmstadt, Germany. The rest of the authors have no conflict of interest to declare.

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