Fertility preservation in men and women: Where are we in 2021? Are we rising to the challenge?

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Demand for fertility preservation in women for oncologic, nononcologic, and personal reasons has increased dramatically. Meeting that demand is a major challenge, and we are rising to the challenge. Mature oocyte cryopreservation after ovarian stimulation and ovarian tissue cryopreservation are both methods endorsed by the American Society for Reproductive Medicine (formerly The American Fertility Society), and numerous papers confirmed their efficacy. In girls and women with leukemia or cancers who are at a high risk of ovarian metastasis and who may not be eligible for ovarian tissue transplantation, restoration of fertility can only be achieved by in vitro methods. Male fertility preservation has also become a pressing issue and is extensively reviewed in the present journal issue. (Fertil Steril® 2021;115:1089–90. ©2021 by American Society for Reproductive Medicine.)

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In 2017, we published a paper entitled "Fertility preservation in women" in the *New England Journal of Medicine* (1), in which we reported that the demand for fertility preservation for oncologic, nononcologic, and personal reasons had increased dramatically, and that meeting that demand would prove a major challenge in the coming years. Four years on, are we rising to the challenge? According to 4 papers published in the present issue of *Fertility and Sterility*, the answer is clearly yes.

First, it is important to point out that mature oocyte cryopreservation after ovarian stimulation and ovarian tissue cryopreservation (OTC) are both methods endorsed by the American Society for Reproductive Medicine (formerly The American Fertility Society). Further, the papers confirmed the efficacy of both approaches while laying the ground for new perspectives.

In the first review, Cobo et al (2) reported data from one of the most experienced centers in oocyte vitrification. They demonstrated that oocyte vitrification provides the highest yield not only for women with benign diseases or those seeking fertility preservation for personal reasons but also for cancer patients (if, of course, the start of treatment can be postponed). In the largest series published to date, Cobo et al established that of all oocyte vitrification procedures performed within the Instituto Valenciano de Infertilitad network, 2% are done in the context of oncofertility, with a return rate of 7.2% in this group. These authors analyzed outcomes in 3 different groups: oncofertility, endometriosis, and elective (age-related fertility decline) subjects. Endometriosis represented a very large cohort in the Instituto Valenciano de Infertilitad series, and fertility preservation was commonly offered to endometriosis patients in the knowledge that endometriosis per se may be the cause of a low ovarian reserve, whereas surgery for endometriomas may have a further deleterious effect. It should nevertheless be pointed out, as stressed by the authors and also ourselves, that there are uncertainties related to it cost-effectiveness, because systematically offering fertility preservation to patients with endometriosis would have a dramatic impact on public health services. Scrutinizing the outcomes in their 3 large groups, Cobo et al. reached some key conclusions regarding patient age at oocyte retrieval and the number of available oocytes and their effect on live birth rates. They found that having 10–15 oocytes in patients aged <35 years led to reasonable success rates and cumulative live birth rates of 40%–70%, but they clearly stated that oocyte cryostorage is not an insurance policy to secure future motherhood but a means to boost their chances of having a biological child.

In the review by Dolmans et al (3), 5 renowned European teams that included participants from France, Denmark, Germany, Switzerland, Spain, and Belgium with considerable experience (>25

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ovarian tissue transplantations (OTTs) per center) shared their findings on OTT. This was the largest series ever published (285 OTTs) in terms of patient numbers, in which all patient data were available. It is important to note that cancer emerged as the most frequent indication for OTC and OTT. This large series allowed the authors to comprehensively evaluate the results and determine the existing cofactors of success. Ovarian function recovery lasting several years was achieved in almost all transplanted women. The live birth rate was 30% among those conceiving naturally, higher than that in transplanted women undergoing in vitro fertilization (IVF). Indeed, small numbers of oocytes retrieved during IVF and high numbers of empty follicles clearly demonstrated that women grafted with frozen-thawed ovarian tissue should be considered poor responders right from the start. Of course, age at OTC was a determining factor, as evidenced by the fact that women who gave birth in the IVF group were almost 5 years younger at the time of OTC **than those who did not.**

One of the most pertinent points in the paper by Dolmans et al was that chemotherapy at the time of OTC did not impair the chances of success, depending on the type of drugs used (the alkylating agents being the most gonadotoxic) and the total dose administered before OTC. Data from Dolmans et al proved that women undergoing or having undergone several regimens of chemotherapy could still benefit from OTC. Encouraging results in terms of live birth after OTT were observed in this group, particularly in the large series of Poirot, one of the coauthors. Teams dismissing OTT if chemotherapy has already begun should now consider these patients as potential candidates. This is particularly relevant in the case of leukemia, where ovarian tissue should be harvested when patients are in complete remission, thereby eliminating the risk of reimplanting malignant cells at the time of OTT.

In their review, Telfer and Andersen (4) looked to novel approaches to fertility preservation in girls and women with leukemia or cancers at a high risk of ovarian metastasis. In these patients, who may not be eligible for OTT, restoration of fertility can only be achieved by in vitro methods. These authors describe 2 proposed in vitro procedures in detail. First, promoting growth of immature oocytes contained within stored tissue using culture techniques that support complete development and maturation of cryopreserved primordial oocytes into metaphase II oocytes, and second, harvesting immature oocytes from small antral follicles released from ovarian tissue at the time of OTC, followed by in vitro maturation and IVF. Telfer and Andersen (4) also outlined other methods that could be used in combination with transplantation, such as in vitro activation of primordial follicles, which would be beneficial to women with a poor ovarian reserve who only produce a few follicles, even after strong ovarian stimulation. The goal of these new methodologies was to maximize the chances of obtaining mature oocytes from the harvested tissue in order to increase the likelihood of obtaining a pregnancy. As stressed by the authors, these techniques are still experimental, but much progress has been made. Although the potential for fertility preservation is growing all the time, its safety needs to be thoroughly tested.

In their review on fertility preservation in males, Brannigan et al (5) emphasized the high prevalence of cancer, which will affect approximately half of men over the course of their lifetime. Whether because of the disease itself and/or its required therapy, both of which can lead to impaired reproductive health, fertility preservation has become a pressing issue. The manuscript by Brannigan et al provides a state-of-the-art overview of the field of male fertility preservation, including the impact of cancer treatments. Guidelines for fertility preservation are reviewed, and the authors discuss indications and results in terms of outcomes for use of cryopreserved sperm from patients with cancer. They look to emerging stem cell technologies that might well transform the field of reproductive medicine in the future.

Thanks to ongoing research efforts and highly instructive reports, like those of Cobo et al, Dolmans et al, Telfer and Andersen, and Brannigan et al, new information and guidelines on fertility preservation options are now available. We hope this will help health care professionals to provide appropriate counseling to all women and men wishing to protect and preserve their fertility.

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