# Importance of patient selection to analyze in vitro fertilization outcome with transplanted cryopreserved ovarian tissue

Meeting the growing demand for fertility preservation remains a challenge. Indeed, with the increasing success of oncological treatments, offering fertility preservation before gonadotoxic treatment should be standard care. Hematological and breast cancers represent the most frequent indications for fertility preservation, especially because they are cancers with the highest prevalence among reproductive-age women. Besides embryo cryopreservation and oocyte vitrification, ovarian tissue cryopreservation (OTC) is often proposed as fertility preservation option in specific indications such as prepubertal girls and women who cannot delay the onset of chemotherapy for ovarian stimulation.

The excellent outcomes of fertility preservation in general and OTC in particular have convinced oncologists to refer their patients to reproductive medicine specialists. Since its first implementation for cancer patients in 1996, followed by the first live birth in a Hodgkin's lymphoma patient in 2004, OTC is now accepted by the American Society for Reproductive Medicine as a fertility preservation option that is not experimental (1).

Ovarian tissue autotransplantation has been performed worldwide. After reimplantation of the frozen-thawed tissue into the pelvic cavity, ovarian activity is restored in over 95% of cases (2). Pregnancies and live births with this technique have started to climb steadily, showing an exponential increase, with the number of live births as of June 2017 exceeding 130 (2) and probably more than 200 in 2020. Analyzing the percentage of transplanted patients in terms of success rates in 2020, three major centers (Sheba Medical Center in Tel Aviv, Cliniques Universitaires Saint Luc in Brussels, and the Infertility Center in St Louis) report a pregnancy rate of 50% and a live birth rate of 41% in a series of 60 patients (3). These results prove the efficacy of the technique and support its use when fertility preservation is needed.

However, the success rates of ovarian tissue transplantation (OTT) are not always reproducible, even within the same IVF units. The article in this issue of *Fertility and Sterility* by Hjorth et al (4) is proof of how important it is to carefully collect and analyze clinical data. Skewed patient selection and incomplete data collection may leave readers with doubts on the efficacy of OTT. Indeed, one clear take-home message from this work is the confirmation that ovarian tissue freezing is a robust option for some patients needing fertility preservation. In fact, the frozen tissue was cryopreserved (even when it was transported for up to 6 hours on ice), thawed, and regrafted successfully in all cases in this cohort of Danish women. However, what needs more caution is the interpretation of the IVF data.

The small number of patients advised to undergo IVF after OTT were highly heterogeneous. Indeed, two (cases 19 and 28) had whole-body radiation requiring peritoneal OTT assuming ovarian atrophy, but there was no mention of a possible impact on the uterus. In addition, some patients had already undergone IVF before the OTT, but these data were not presented, and five patients had elevated FSH levels already at the time of the first ovarian stimulation (therefore they already had a very poor prognosis). Furthermore, nine patients had no ovarian response at their first IVF attempt and four underwent a second OTT before even doing the first IVF cycle. Finally, two of the patients who had the second OTT did not undergo additional IVF cycles, and one wonders if they resumed their ovarian function and perhaps had a spontaneous pregnancy (assuming they were in the group of orthotopic ovarian grafting).

The authors provided no information on the steroid receptor status for 12 of 14 patients with breast cancer, and similarly they had no information about follicular density on the histological samples before cryopreservation. This information may be helpful in anticipating ovarian response and thus IVF outcome. It is unclear why oocyte freezing was not offered to the breast cancer patients. Indeed, oocyte freezing was recommended in these patients by the American Society of Clinical Oncology guidelines of 2006 and later by the American Society for Reproductive Medicine, the European Society of Human Reproduction and Embryology, and the International Society for Fertility Preservation.

It becomes difficult to reconcile the poor IVF results of this study with the data that the same group published extensively on this same topic in previous reports. Nonetheless, it is important to know that for certain selected patients as described here, OTT and subsequent IVF data cannot be extrapolated to the success rates known in the literature. The high rate of pregnancy loss, some even in the second trimester, requires proper patient counseling if confirmed from additional studies.

An interesting observation that certainly merits further study is the 36% empty follicle rate. This specific issue has been previously reported. For example, in a report from Belgium, the empty follicle rate was 29% and the fertilization rate was 50%. These were patients who had not achieved spontaneous pregnancy after 1 year of menstrual cycling.

The possible causes of empty follicle syndrome were previously reported and include: dysfunctional folliculogenesis due to elevated basal FSH concentrations during the early follicular phase; asynchrony between granulosa cell maturation and oocyte maturation; and damage to the oocyte itself by freezing, thawing, and transplantation, leading to a higher rate of empty follicles or oocyte alterations, while granulosa cells may be more resistant.

In a recent systematic review by Andersen et al. (5) on assisted reproductive technology outcomes in women transplanted with cryopreserved ovarian tissue, the empty follicle rate varied between 23% and 35%, the fertilization rate was 57% (in particular, 49% for the Danish cohort), and the live birth rate was 47.5% (19 women out of the 40 transplanted had a baby). Contrasting with the Andersen et al. (5) paper, the fertilization rate reported here by Hjorth et al. (4) was very low (38%). The low live birth rate (18%) was also much lower than the rate reported by the same team in 2015

(31%). The paper by Hjorth et al. (4) documents only one patient who delivered a baby among the 14 breast cancer patients (1/14 = 7%). Among the other 14 patients, four patients delivered at least one baby (4/14 = 29%). In total, only five out of 28 patients gave birth.

In summary, this paper is interesting, but it does not appear to be representative of the current literature on ovarian tissue freezing. The population presented in this manuscript involves patients undergoing IVF on frozen-thawed-grafted tissue, and this situation is known to yield poorer results than IVF on native ovaries in the general population. Colleagues working in fertility preservation should continue to offer ovarian tissue oocyte and/or embryo freezing to give hope of future fertility and childbearing to cancer patients.

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