Trials and tribulations of in vitro fertilization after ovarian tissue transplantation

In their systematic review of ovarian stimulation and assisted reproductive technology (ART) outcomes in women who have undergone ovarian tissue transplantation (OTT) (1), Andersen et al. attempt to provide a consistent overview of the current state of play, which is no easy task given the heterogeneous and often discrepant data available on the subject. Indeed, questions raised in this article concerning issues of oocyte quality, poor ovarian reserve, empty follicle syndrome, and unfavorable in vitro fertilization (IVF) outcomes have not significantly changed since we first sought to address them more than 10 years ago, when we evaluated the quality of oocytes and embryos derived from frozen-thawed transplanted ovarian tissue in a series of women who had not conceived after 12 months of spontaneous cycles after OTT (2). In that study, the empty follicle rate per oocyte retrieval was 29% and the percentage of abnormal oocytes (immature or degenerated) was 38%. Three hypotheses were proposed: 1) possible dysfunctional folliculogenesis due to elevated basal follicle-stimulating hormone concentrations during the early follicular phase (whereby early oocyte atresia occurs with an apparently normal hormonal response); 2) asynchrony between granulosa cell maturation and oocyte maturation (which could be the result of premature follicular cell activation induced by ischemia after OTT); and 3) possible damage to the oocyte itself induced by freezing, thawing, and transplantation. It is true that some ultrastructural alterations observed in these oocytes (2) may be attributed to cryopreservation procedures. Indeed, transmission electron microscopy analysis in our series revealed anomalies of the zona pellucida and microvilli, increased vacuolization, and the presence of rounded smooth endoplasmic reticulum vesicles forming aggregates with mitochondria. We were able to identify multiple changes to the granulosa cell–oocyte complex, but clear answers to the remaining questions still elude us.

In Andersen et al.'s review (1), the stated pregnancy rate of 14.4% per cycle may appear to be extremely low compared with the general population, but this figure can be misleading. The take-home baby rate in these women after ovarian tissue cryopreservation, cancer remission, and OTT is actually almost 50% (19/40) in this review, which is limited to ART cycles only (1). This effectively means that approximately one-half of cancer survivors who would otherwise have been menopausal are able to fulfill their dream of having their own child thanks to transplantation of their frozen-thawed tissue (3, 4). What we must not forget is that these patients constitute a particular population, having undergone chemo- and/or radiotherapy that may well have impaired the quality of their endometrium by damaging blood vessels and altering cytokine expression, thereby interfering with embryo implantation. From this review (1) as well as the publication by Meirow's team (3), we may conclude that previous chemotherapy is not a contraindication to ovarian tissue cryopreservation and that these patients should not expect poorer outcomes than other cancer survivors (3).

ARE COMPARISONS ACCURATE?

Stimulation Protocols

ART in women with transplanted ovarian tissue is much more challenging than in the general population and cannot be implemented using the same stimulation protocols, because the results will inevitably be disappointing. These patients should be treated as poor responders (1–3), and although Andersen et al. found no statistical difference between modified natural cycles and antagonist protocols (probably because of a lack of power), antagonists do yield slightly better outcomes (1). This may therefore be worth considering in individuals willing to do anything to maximize their chances of success. However, in the absence of confirmation of superiority, modified natural cycles remain an excellent option in terms of patient comfort and cost-effectiveness.

Timing of IVF

It is impossible to make accurate comparisons when the approach of different teams varies so broadly and there is no consensus on if, when, and how to proceed. Some prefer to give their patients the possibility of natural conception before resorting to ART (2), whereas others (3) prefer to press on with ART as soon as adequate hormone levels are reached after OTT. There are pros and cons with both strategies. The sooner ART is performed after transplantation, the more follicles are available and the higher the pregnancy rates. Conversely, spontaneous multiple follicle development is not rare in the months after OTT (4). Whether these follicles are of sufficient quality is another question. On the other hand, ART performed as soon as possible after OTT robs patients of the chance to conceive naturally. As reported in this article, this is something that happens not infrequently in patients referred for immediate IVF, as demonstrated by the five spontaneous pregnancies achieved in patients after a considerable delay (1). It does, however, highlight an obvious selection bias, hampering the interpretation of overall results.

All this serves to illustrate the undeniable difficulty of investigating ART outcomes in women with transplanted ovarian tissue in a clear and unequivocal way. There are so many different parameters and protocols to take into account, and we still do not fully understand what happens to follicles and oocytes in ovarian grafts. As can be seen from this review (1), a large percentage of them do not undergo the correct maturation process and appear to present with a range of abnormalities. These anomalies were described in 2009 (2), but even after all these years, we have not managed to find a clear explanation for the impaired oocyte quality encountered after freezing, thawing, and transplantation, also reflected in lower fertilization rates (1). Andersen et al.'s table summarizing published ART protocols and reproductive outcomes underscores this irrefutable fact, with its multitude of heterogeneous results and scarcity of coherent data. However, this apparent confusion in the presentation of results actually mirrors the reality of the current situation in the field, and so paints an essentially accurate picture.

There is no doubt that after OTT, patients should be regarded as poor responders. Despite resumption of the menstrual cycle and increased estradiol concentrations after

transplantation, follicle-stimulating hormone levels tend to stay relatively high and antimüllerian hormone (AMH) remains low or undetectable in most cases (5). This suggests not only a diminished ovarian reserve, but also a probable absence of dialog between follicles at different stages. Low or undetectable AMH concentrations were indeed found in all women in the study by Janse et al. (5), regardless of the interval since OTT. Use of AMH in patients with transplanted ovarian tissue is therefore very limited, because AMH levels do not appear to be associated with the duration of ovarian graft function or the likelihood of achieving a pregnancy (5).

At the end of their paper (1), Andersen et al. cite a meta-analysis by Shi et al. (Sci Rep 2017;7:8538) suggesting that vitrification causes less follicular DNA damage and allows better preservation of stromal cells. I would like to stress that very few pregnancies have been reported after OTT of vitrified-warmed tissue (4). Moreover, recently published experimental studies in baboons by Amorim et al. (Hum Reprod 2019;34:323–34) ascertained recovery of ovarian function, but failed to demonstrate restoration of fertility, indicating possible damage to the structure of the oocyte itself.

Finally, as pointed out by the authors themselves (1), unsuccessful fertility treatment is highly likely to be underreported. However, there is a pressing need to report positive as well as negative results from large series in order to evaluate reproductive outcomes and the efficacy of different ART protocols after OTT.

Marie-Madeleine Dolmans, M.D., Ph.D.
Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, and Gynecology Department, Cliniques Universitaires Saint Luc, Brussels, Belgium

https://doi.org/10.1016/j.fertnstert.2019.07.1347

REFERENCES

1. Andersen ST, Pors SE, Poulsen L, Colmorn LB, Macklon KT, Ernst E, et al. Ovarian stimulation and ART in women transplanted with cryopreserved ovarian tissue: a systematic review. Fertil Steril 2019;112:908–21.
2. Dolmans MM, Donnez J, Camboni A, Demylle D, Amorim C, van Langendonckt A, et al. IVF outcome in patients with orthotopically transplanted ovarian tissue. Hum Reprod 2009;24:2778–87.
3. Meirow D, Ra'anani H, Shapira M, Brenghausen M, Derech Chaim S, Aviel-Ronen S, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril 2016;106:467–74.
4. Donnez J, Dolmans MM. Fertility preservation in women. N Engl J Med 2017;377:1657–65.
5. Janse F, Donnez J, Anckaert E, de Jong FH, Fauser BC, Dolmans MM. Limited value of ovarian function markers following orthotopic transplantation of ovarian tissue after gonadotoxic treatment. J Clin Endocrinol Metab 2011;96:1136–44.