Ovarian tissue cryopreservation: still experimental?

It has been nearly 10 years since the Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology reviewed the evidence surrounding "Ovarian tissue and oocyte cryopreservation" and declared both techniques "experimental" and to be offered only under Institutional Review Board (IRB)–approved protocol (1). Much has changed in the intervening decade—the experimental label was dropped from oocyte cryopreservation after the delivery of more than 900 babies and reassuring data from several randomized controlled trials (mostly involving oocyte donors, not oncology patients) (2). Despite accruing clinical experience, ovarian tissue cryopreservation is still considered experimental, but are we ready as a field to change that designation?

In the current issue of *Fertility and Sterility*, Diaz-Garcia et al. from the IVI group in Spain report on a large experience of 800 ovarian tissue cryopreservation procedures and compare them favorably to outcomes from the more accepted technique of oocyte vitrification (3). They cite several clinical scenarios in which freezing ovarian tissue may be preferable to freezing oocytes. For example, some oncology patients have limited time to undergo ovarian stimulation before the start of their treatment. However, with random start protocols for fertility preservation, this occurs less often, and those women who cannot be cleared to delay chemotherapy by a couple of weeks likely are not candidates for surgical fertility preservation unless they are undergoing a concomitant surgery. Ovarian tissue cryopreservation provides a viable, albeit invasive, option for prepubertal girls and holds the potential to restore long-term hormonal function and improve the quality of life after cure from cancer. It also provides the potential for multiple rounds of ovarian stimulation after transplantation, rather than having all of one's eggs in one basket, so to speak, from a single cycle of oocyte cryopreservation.

But are we ready to remove the "experimental" label? Some would argue yes, but they practice at the centers with the most experience using these techniques (4). The most recent consensus opinion from the Barcelona International Society for Fertility Preservation ESHRE-ASRM 2015 expert meeting still considered the technique of whole ovary cryopreservation and transplantation experimental (5).

While the data are compelling and very reassuring, more experience is required before this technique can be routinely offered to women as a method of fertility preservation. There are several differences between oocyte and ovarian tissue cryopreservation. The technique of vitrification has become fairly standardized, even automated, with commercially available vitrification and warming media and cryopreservation devices. Most laboratories accrued experience with embryo vitrification and warming in clinical assisted reproductive technology (ART) before offering oocyte cryopreservation for cancer. In addition, these techniques could be tested and refined on immature and discarded oocytes. With ovarian tissue there are a variety of techniques and options, such as cortical strips versus whole ovary transplantation, orthotopic versus heterotopic transplantation, and debate whether slow freezing or vitrification is preferred. Most ART laboratories do not have experience with freezing and thawing tissue.

Most of the published experience with ovarian tissue cryopreservation is limited to a few large centers such as the reported experience in this issue. In this paper alone, three different techniques were employed: subcortical pouches, microsurgical stitches, and subperitoneal pouches. It would be challenging for a center to introduce tissue cryopreservation, and it would be reasonable for them to review their own experience in an IRB-approved protocol.

The studies on tissue cryopreservation also suffer from a lack of a control group. While it would be unethical to perform a randomized controlled trial, it would be informative to explore the reproductive outcomes in women who declined surgical fertility preservation. It is possible that some of the pregnancies resulted from the native ovarian tissue and that the surgical removal of ovarian cortex or a whole ovary may increase a woman's risk for postchemotherapy infertility and amenorrhea. Also, it appears that ovarian tissue cryopreservation may not yield favorable results in women with lower ovarian reserve, and the authors no longer recommend this technique in women >35 years old unless there is very good ovarian reserve.

Finally, the use of both cryopreserved oocytes and ovarian tissue appears to be very low. While it is well documented that offering and undergoing fertility preservation provides hope and allows women to better cope with their cancer diagnosis, prospective patients should be counseled on the low use. In this study, 800 surgeries were performed and only 50 women came back for transplantation (44 seeking pregnancy) after a mean follow-up time of 5.5 years. Although complications are not reported here, even a safe procedure like laparoscopy or minilaparatomy will result in some serious complications, especially when performed by less-experienced surgeons offering a new technique.

These are exciting times, and women facing gonadotoxic therapies will ultimately benefit from having more validated fertility-preservation options. These techniques should be transferred from pioneering centers to other ART programs affiliated with cancer centers in a responsible way so patients achieve the best possible outcomes before cancer treatment.

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