Ovarian tissue allografts: the next frontier of reproductive transplantation?

At the 2023 American Society for Reproductive Medicine Scientific Congress and Expo, Silber et al. (1) delivered an oral presentation detailing the success of an ovarian tissue allotransplant that was performed between genetically nonidentical siblings using an immunosuppression protocol to prevent rejection. The brevity of this presentation belied the momentousness of the achievement, which has now been published in the August issue of *Fertility and Sterility*, entitled "First successful ovarian cortex allotransplant to a Turner syndrome patient requiring immunosuppression: wide implications." With a successful live birth now documented in this case report, Silber et al. (2) have solidly moved the needle in the field of ovarian tissue transplantation, going beyond the autologous transplantation models of the past to the now feasible transplantation of tissue between 2 genetically distinct individuals. This landmark publication demonstrates clear proof of concept that ovarian tissue can be successfully transplanted between genetically nonidentical siblings using established surgical techniques, leading to graft function, pregnancy, and a healthy live birth. This is a highly innovative method of treating primary ovarian insufficiency, importantly *without the use of assisted reproductive technology*.

Although novel, this next step in ovarian tissue transplantation builds on a long history of national and international ovarian tissue work, beginning with early successes in animal models before its translation into humans. These achievements led to multiple published reports and case series of ovarian tissue cryopreservation and autotransplantation with graft survival and restoration of both endocrine function and fertility; as of 2020, there are more than 200 live births reported in the literature from these techniques (3). In addition to reported live births from autotransplants from multiple groups, Silber et al. (4) previously published a series of allotransplants between identical twins (obviating the need for immunosuppression), again demonstrating restored fertility in women with primary ovarian insufficiency. In light of demonstrated success, ovarian tissue freezing as a method of fertility preservation in woman at risk of primary ovarian insufficiency is no longer considered experimental by the American Society for Reproductive Medicine.

In the August report, Silber et al. (2) describe the case of a 20-year-old patient with nonmosaic 45-XO Turner syndrome, who presented with her 22-year-old 46-XX sister. This sister dyad was human leukocyte antigen compatible but ABO incompatible. The donor sister underwent unilateral oophorectomy with in vitro decortication, yielding one-third of the ovarian cortex for implantation into the recipient alongside a solid organ immunosuppression regimen. The patient's menses returned by day 168 after transplant, and she became spontaneously pregnant 1.5 years postoperatively, successfully delivering a healthy female infant at 40 weeks and 2 days of gestation.

Silber et al. (2) articulate their institutional review board–approved immunosuppression protocol in the manuscript, involving standard immunosuppressive agents from renal transplant medicine. These protocols often involve methylprednisolone and rabbit antithymocyte globulin on the day of surgery, followed by tacrolimus, azathioprine, and prednisone daily for maintenance. A notable feature of this protocol is that patients do not have to be on long-term high-dose corticosteroids, although they did not specify at which point low-dose prednisone is or would be discontinued. According to the publication, the patient had no complications of graft rejection, and the recipient continued immunosuppressants throughout her pregnancy.

Although unconventional in the transplant world, the investigators and patient together elected to proceed with the ovarian tissue transplant despite the ABO group incompatibility. The investigators noted that the patient was counseled and was accepting of the risks of acute tissue rejection, although the extent and nature of this counseling were not described. That aside, it is of particular interest that the investigators did not describe any complications associated with blood type incompatibility. The investigators postulated from this that ovarian tissue survives on diffusion alone, as opposed to neovascularization, and further suggest that revascularization would have led to significant immune reaction and graft rejection in support of this hypothesis. Silber et al. (2) suggests that the initial loss in oocytes is due to a reduction in tissue pressure—a hypothesis supported by the Dynamic Reciprocity theory that claims the rigid extracellular matrix limits follicular expansion and maintains follicles in quiescent state; with removal of this scaffold, follicles mature (5). This theory calls into question long-held beliefs that graft longevity is supported by neovascularization. Although this is an interesting hypothesis and worthy of further exploration, the true mechanism of graft survival in this case is still unknown.

This article is particularly interesting in the context of what is known to every assisted reproductive technology practitioner, which is that in vitro fertilization (IVF) is not for everyone. In addition to costs that may be prohibitive, many patients have personal, philosophical, or religious concerns regarding IVF as well as with the issue of excess embryos and their disposition. The current legal and political climate in the United States threatens standard IVF protocols and processes related to embryos, and patients fear for their current and future ability to make choices regarding embryos. Historically, IVF with oocyte donation was the only option for individuals with primary ovarian insufficiency if they wished to experience gestational motherhood. In this way, the rationale for expanded options feels similar to the expressed wishes of patients with uterine factor infertility who sought uterus transplantation trials to help develop additional reproductive opportunities.

Even more exciting is the idea that ovarian tissue allotransplantation opens a possible window to the future for patients with primary ovarian insufficiency who previously would never have been able to achieve restoration of

endocrine function and potential pregnancy without hormone replacement therapy or use of an egg donor and IVF. Although this publication focused on a patient with Turner syndrome, it is easy to imagine the application of these techniques to any population of patients who historically may have sought egg donation.

There are many lessons learned from the early years of uterus transplantation that can be applied to this content. As additional cases are reported, we will need well-designed clinical trials reporting short- and long-term outcomes data for each attempt at transplantation. We will need to formulate registries of cases to ensure safety for the individuals participating in allotransplantation as well as their offspring. Outcomes with variable human leukocyte antigen matches and ABO groupings should also be assessed, as well as the necessity of long-term or continued immunosuppression. Another critical decision that should be considered is whether to remove the transplanted ovary or not after childbearing is complete to limit exposure to immunosuppression and, if the ovary is not removed, whether immunosuppression can be discontinued safely. This raises the question of eventual tolerance and should be weighed against concerns regarding the risk of rejection with immunosuppression discontinuation.

Very importantly, we should proceed only under institutional review board oversight and with bioethical discussions that occur alongside clinical and technical discussions. The ethical considerations of surgical intervention and the use of potentially nephrotoxic agents should be balanced against the limitations of the current alternative (donor egg IVF with possible resultant excess embryos). However, with evidence of overall well-tolerated temporary exposure to solid organ immunosuppression protocols and successful outcomes both from uterus transplant and this case report, we should also take into consideration patient autonomy and religious practices that may factor into decision-making and why or whether patients will choose to access this option.

CRediT Authorship Contribution Statement

Kathryn Coyne: Writing – original draft, Writing – review & editing. **Isabelle Mason:** Writing – original draft, Writing – review & editing. **Rebecca Flyckt:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Interests

K.C. has nothing to disclose. I.M. has nothing to disclose. R.F. has nothing to disclose.

Kathryn Coyne, M.D.
Isabelle Mason, M.D.
Rebecca Flyckt, M.D.
Division of Reproductive Endocrinology and Infertility, University Hospitals, Cleveland, Ohio

https://doi.org/10.1016/j.fertnstert.2024.11.017

REFERENCES

1. Silber S, Delos Santos RD, Doerhoff RA, Goldsmith S, Brennan DC. First ovary allotransplant to a Turner's syndrome patient: immunosuppression and IVM. Fertil Steril 2023;120:e49.
2. Silber SJ, Goldsmith S, Rubinoff B, Kelly E, Santos RD, Melo A, et al. First successful ovarian cortex allotransplant to a Turner syndrome patient requiring immunosuppression: wide implications. Fertil Steril 2025;123:156–63.
3. Dolmans MM, Falcone T, Patrizio P. Importance of patient selection to analyze in vitro fertilization outcome with transplanted cryopreserved ovarian tissue. Fertil Steril 2020;114:279–80.
4. Silber SJ, Lenahan KM, Levine DJ, Pineda JA, Gorman KS, Friez MJ, et al. Ovarian transplantation between monozygotic twins discordant for premature ovarian failure. N Engl J Med 2005;353:58–63.
5. Thorne JT, Segal TR, Chang S, Jorge S, Segars JH, Leppert PC. Dynamic reciprocity between cells and their microenvironment in reproduction. Biol Reprod 2015;92:25.