Uterine transplantation

In this issue of *Fertility and Sterility*, Brannstrom et al. (1) report on the first clinical trial of uterus transplantation. Until recently, discussion on this topic was based primarily on nonhuman primate experiments. The time has come to carefully consider the clinical and ethical implications of this approach to family building. As with other transplantation procedures, the decision to donate or receive an organ entails weighing the benefits and risks involved. In the case of uterine transplantation, there are additional issues that must be addressed. The procedure raises some familiar questions about the use of new reproductive technologies. However, looking at the procedure itself is not enough; many complex issues arise after a successful procedure. A thorough analysis must also include follow-up procedures to become pregnant, prenatal care, childbirth, and postpartum care. And in addition to involving the donor and recipient, evaluations must include children born as a result of the procedure. Clearly, some challenging and unique issues emerge when transplant science and reproductive medicine intersect.

Initial considerations take place before the transplantation procedure. As with other major procedures, both donor and recipient must have the support needed to make informed choices about the procedure they will undergo. For the living donor, procedural complications may range from bleeding and infection to pelvic organ injury, requiring further surgical repair. Unlike other living-organ donors, who can expect continued organ system function (e.g., renal or hepatic), the uterine donor loses entirely her ability to have children without the use of assisted reproductive technologies. The implications of this are critical: A woman may change her mind about family building after permanent alteration of her reproductive capacity (2). Therefore, the choice to donate must be fully informed and free of any coercion, because being involved in the transplantation procedure not only puts the donor at surgical risk but also will result in her sterilization.

The recipient must also be equally prepared to make informed decisions about receiving the organ, including the risks of surgery, ongoing immunosuppression, and the possibility of organ rejection. She must also understand the issues that may arise if she becomes pregnant. If the procedure is successful, she will then face many potentially difficult decisions about the pregnancy with only limited information about the impact for her or any future children. Some data do exist, such as those regarding the use of immunosuppressive drugs by pregnant transplant recipients (3). However, many aspects related to maternal and fetal outcomes in this context are not known. Although pregnancies associated with this procedure have been documented (4), there has yet to be a birth by a transplant recipient. Thus, these aspects of the procedure will remain uncertain until such data are obtained.

Additionally, current protocols call for the uterine transplant to be ephemeral. As a result, the organ would be removed after delivery of the first child (or after additional children if desired) to avoid the risk of continued immunosuppression. The fact that the transplant is meant to be temporary raises compelling questions about long-term repercussions for the recipient. Significantly, no other applications of transplant medicine call for an otherwise normally functioning organ to be removed. The removal procedure would place the recipient at additional risk, whether performed as part of a cesarean hysterectomy or some months after delivery. There may be other reasons why the donor may elect against hysterectomy, some of which may not be fully realized until during or after pregnancy. Any plan to remove the uterus as part of the transplantation protocol must be subject to careful ethical analysis.

In the article by Brannstrom et al., we have a report of the immediate postoperative evaluation of nine women who participated in a transplantation procedure, data that bring the realities of this procedure into focus. These procedures are complicated and require the skilled expertise of both gynecologists and transplant surgeons. Specific to the recipient, the article states that the transplant procedure required 4–6 hours to complete. After 6 months, seven of the women still had a functioning uterus. In four women, mild rejection of the graft occurred, as can happen with other organ transplants. The two graft losses were attributed to thrombosis and infection.

This article also indicates that there were relevant issues for the donors. The authors state that it required 10–13 hours to harvest the uterus. The dissection of the deep pelvic veins for anastomosis was noted as an especially challenging part of the procedure. Given the known complications associated with surgery of this length and dissection in this anatomic space, it is critical to obtain further data about the risks faced by the donor. While an approach using the ovarian veins would be more convenient and require less operative time, this would involve removing the ovaries of the donors, thus introducing additional health consequences for premenopausal donors. Additionally, one of the donors experienced a ureteric complication. Although the authors state that these complications are "low risk," we suspect that most of us would challenge this conclusion, given the immediate and long-term implications of such an injury in any context, but particularly in the case of an elective procedure.

Despite the findings presented in the article, important questions remain. Given its complexity, the cost of the transplantation procedures and downstream care for the donor may be quite high. Total cost and breakdown of the financial responsibility have yet to be established. This is just one of the questions that must be addressed as reproductive transplant research moves forward. Several other steps must be taken to ensure that this procedure offers greater benefit than harm to all involved.

First, adequate mechanisms must exist to support the counseling and informed consent processes at all stages in the transplantation procedure. An effective informed consent process will be central to ensuring that the donor and the recipient make informed and voluntary choices at the time of uterine removal and transplantation. These mechanisms must continue into the prenatal period. During this time, the recipient will have to consider her health care choices as they relate not only to the transplant itself, but also to decisions that take place as a standard part of prenatal care.

Safeguards must be in place to ensure that the recipient maintains her ability to make voluntary and informed decisions throughout her pregnancy and that her autonomous decision-making ability is not externally influenced by the risks she has already undergone to become pregnant. And because of the possibility of removal of the transplanted uterus after childbearing is complete, there must be support for women as they consider the risks and benefits of hysterectomy versus ongoing immunosuppression, as well as a mechanism to ensure decisions made at this time are equally informed and voluntary. Because of the nature of uterine transplantation, these mechanisms must directly incorporate the values and preferences of women into the decision-making process. Further research will be needed to help identify what specific support transplantation participants require to make informed choices about this innovative procedure.

It can not be overlooked that uterine transplantation remains experimental. As a result, informed consent discussions should be framed within the context of research and innovative practice. This includes discussions with the participants about the ways in which clinical research departs from proven therapeutic intervention and how ethical conflicts can arise when the same individuals function in the role of physician and researcher. Complete transparency is required on behalf of the team to ensure that the participants understand the implications of being part of an experimental procedure and the potential impact for themselves and the recipient's children.

Furthermore, counseling and informed consent must be grounded in empirical evidence. These data can be obtained only through clinical research. As research in this field expands, it is critical that ethical principles guide all stages of data acquisition, including study design, conduct, data analysis, and interpretation of study findings. Study design should include a clear and ethically justifiable method of defining the thresholds for acceptable levels of risk for all of the involved parties. This is highly relevant, because a growing body of literature calls for careful ethical analysis of the involvement of pregnant women in research (5).

Finally, mechanisms for external oversight must be an ongoing component of the further development of the uterine transplantation procedure. Because uterine transplantation is an experimental procedure, there will be a need for continuing Institutional Review Board involvement to ensure that protections for human subjects are in place for all individuals and at all stages. Multidisciplinary representation will be key to protecting the interests of the donor, recipient, and future offspring.

Uterine transplantation could be an important option for women diagnosed with uterine factor infertility. The authors of this paper are to be commended for their systematic and well developed experimental protocols to investigate the surgical feasibility of the procedure. While this work demonstrates the promise of uterine transplant, it also presents the opportunity to prepare for the ethical challenges inherent in the procedure that will arise for donors, recipients, and children resulting from its success.

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