

MEDICINE AND SOCIETY

What Are Good Guidelines for Evaluating Uterus Transplantation?

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Abstract

Recent advances in uterus transplantation (UTx) suggest it is on a trajectory toward becoming an accepted clinical practice to treat absolute uterine factor infertility (AUI). Additional uses have been envisioned but not studied. UTx programs thus far have relied largely on ethical frameworks associated with clinical research, surgical innovation, organ transplantation, and assisted reproductive technologies, as reflected in the Revised Montreal Criteria and the Indianapolis Consensus. This article argues that it is time to develop integrated guidelines that incorporate existing evidence, acknowledge and address tensions among the ethical frameworks that have informed judgments of UTx for AUI thus far, identify and address ethical questions on which existing frameworks are silent, and anticipate future ethical issues in UTx research.

Introduction

Recent advances in uterus transplantation (UTx) suggest that it is on a trajectory toward becoming an accepted clinical practice to treat absolute uterine factor infertility (AUI), which Brännström and Díaz-García describe as “infertility that is completely attributable to uterine absence (congenital or surgical) or an abnormality (anatomic or functional) that prevents embryo implantation or completion of pregnancy to term.”¹ UTx is a type of vascularized composite allotransplantation (VCA) for the purpose of assisted reproductive technology (ART), and the uterus is classified as an organ subject to the National Organ Transplant Act.² The goal and desired outcome of UTx are similar to those of ARTs—specifically, gestational surrogacy—yet UTx largely relies on ethical guidelines that are specific to solid organ transplantation (SOT). Translating UTx to the clinical setting requires developing clinical practice guidelines specific to UTx that incorporate existing evidence; acknowledge and address tensions among the ethical frameworks that have informed judgments of UTx for AUI thus far; identify and address ethical questions on which existing frameworks are silent; and anticipate future ethical issues in UTx research, including possible applications other than AUI.

Clinical Practice Guidelines

Clinical practice guidelines are meant to translate reliable evidence into recommendations to improve quality, reduce variation in treatment, constrain costs, empower patients to make decisions, and inform third-party payers' coverage decisions.³ Although the evidence base for the efficacy of UTx for treating AUFIs is limited, it is important to promote quality, consistency, and transparency in UTx clinical programs, recognizing that guidelines will evolve over time.

The revised Montreal Criteria for the Ethical Feasibility of Uterine Transplantation and the Indianapolis Consensus are the most comprehensive recommendations available that are specific to UTx.^{4,5,6} Despite differences among these 2 sets of recommendations for ethical UTx practice—and differences among UTx research program descriptions, which indicate that some programs' practices deviate from these recommendations—both draw on ethical frameworks from clinical research, surgical innovation, SOT, and ARTs, among other fields. For instance, the revised Montreal Criteria call for the recipient to be deemed “likely to take antirejection medication and follow up with the treating team in a responsible manner,”⁵ which mirrors factors measured by SOT eligibility screening tools.⁷ The Indianapolis Consensus recommends that the recipient have AUFIs that has “failed all current gold standard and conservative therapy,”⁵ a criterion that also stems from SOT frameworks.⁸ In addition to these influences, both sets of recommendations suggest, in the words of the revised Montreal Criteria, that a recipient must “not exhibit frank unsuitability for motherhood,”⁵ which is rooted in ART frameworks.⁹ Moreover, the Indianapolis Consensus states that UTx would need to fulfill the criteria for surgical innovation, should require approval by “a duly constituted ethics committee” as recommended or required of any research study or innovative surgery, and should carefully consider risks to living donors and recipients.⁶ UTx's reliance on guidelines from several different fields—and the tensions and ambiguities that could arise from this reliance—call for the development of a set of UTx-specific guidelines.

Developing UTx Guidelines

Because the International Society of Uterus Transplantation (ISUTx) gathers and disseminates information about UTx with a view to developing the field, it could facilitate guideline development. Establishing clinical guidelines for UTx to treat AUFIs will involve consideration of stakeholders; criteria for recipient and donor eligibility, including risks and benefits; data collection; and posttransplantation management.

1. *Stakeholders.* An important first ethical step in developing guidelines for UTx to treat AUFIs is identifying the stakeholders. Who counts as having AUFIs? UTx studies have been limited to genetic females with AUFIs seeking to gestate at least one pregnancy.^{10,11,12} Some have suggested that transwomen also have AUFIs or that all genetic males have AUFIs and should be included.¹³ Deciding whether to include transwomen or men

as stakeholders in this process and the priority to be given their interests involves ethical judgments. In UTx, potential living and deceased donors and their families also have relevant interests.

2. *Eligibility and organ allocation requirements.* Other ethical considerations involve criteria for recipient and donor eligibility and organ allocation. Will recipients be required to have produced their own genetic embryos, as appears to be the case in existing trials,^{10,11,12} or will the use of donor eggs (or the eggs of a female partner) be permissible? Will potential recipients' suitability as parents be assessed and, if so, by whom and how? Must a recipient find adoption and surrogacy unacceptable or is a preference or desire to gestate a child sufficient? If living donors are permissible, will the eligibility requirements differ depending on whether recipients have a willing living donor (LD) or instead rely on a nondirected LD or deceased donor (DD)? How will organs from DD and nondirected LDs be allocated among eligible recipients, and what factors will be considered in prioritizing recipients?
3. *Risks and benefits.* Which risks (eg, hemorrhage, damage to internal organs, general anesthesia)¹⁴ and potential benefits will be considered in establishing eligibility for LDs? How will the significance of these risks be assessed? Will the eligibility requirements for directed and nondirected LDs differ and, if so, how and why? In SOT, paired exchanges—in which an incompatible LD-recipient pair exchanges organs with another LD-recipient pair—are permissible, as are donor chains when incompatible LD-recipient pairs are linked with other pairs to form a donation chain. Would either of these types of exchanges be allowed in UTx? What if the paired exchanges varied in organ type? For example, would a woman be permitted to identify a willing kidney donor who would donate a kidney to someone in exchange for the kidney recipient providing a uterus donor?
4. *Data.* Which data should be gathered and reported as part of the UTx registry maintained by ISUTx,¹⁵ and for how long will LDs, recipients, and future children be followed?
5. *Posttransplantation management.* The expectations of donors and recipients posttransplantation also raise ethical issues. Will recipients be compelled to have the transplanted uterus removed after one or two live births, as currently recommended due to the risks of long-term use of immunosuppressants?⁵ How will this requirement be enforced? What if a woman desires more than 2 children? Which risks and potential benefits will be considered in determining when and how many embryos can be transferred post-UTx? What contact, if any, will be facilitated between LDs or deceased donor families and recipients?

These are among the questions that should be addressed in developing clinical practice guidelines for UTx to treat AUI. The answers to these questions depend not only on medical judgments but also on ethical judgments, which have significant implications for the future of UTx and all potential stakeholders.

Comparison of UTx to SOT and ART

Because 2 UTx clinical trials in progress involve LDs,^{11,12} it is likely that as UTx moves to the clinical setting, it will not be restricted to DDs. Here we discuss how the clinical practice of UTx could draw on guidance on the use of directed and nondirected LDs in SOT and ARTs. Each of these fields has different priorities and norms, which could lead to competing understandings of what is ethically permissible or obligatory in practicing UTx in the clinical setting.

Payment. The strict standards governing living nondirected organ donation limit the authority of donors and recipients, whereas the norms governing ARTs offer more latitude in negotiating the terms of the donor-recipient relationship. The National Organ Transplant Act prohibits organ donors from receiving “valuable consideration” for the organ.¹⁶ Under the act, payment for a uterus donation would be illegal, but coverage of certain donor expenses may be permissible.¹⁷ By contrast, [payments](#) to gamete (sperm and egg) providers and gestational carriers are routine in some jurisdictions.¹⁸ One might argue that donating a uterus is not substantially different from donating an egg or serving as a gestational carrier and that therefore payment to a uterine donor may be acceptable.¹⁸

Recipient characteristics. Organs donated by nondirected LDs are allocated according to the criteria of the Organ Procurement and Transplantation Network (OPTN), which specify that donors may not stipulate recipient characteristics.¹⁹ If SOT guidelines apply to UTx, then nondirected LDs would not be allowed to restrict who might receive their donated uterus. Gestational carriers in the United States, on the other hand, are free to choose with whom they are comfortable entering into a donor-recipient relationship.²⁰ This freedom allows a gestational surrogate to restrict her services based on her preferences; a gestational carrier may decide that she will only carry a child for a gay male couple or that she will not carry a child for single men. If we view UTx for treatment of AUI through the lens of ARTs, we might conclude that a nondirected LD should be permitted to choose among potential recipients or restrict who receives her uterus. These decisions will be more complex if UTx is offered to nongenetic females or for reasons other than pursuing pregnancy.

Future contact with donor. Nondirected LDs and their recipients do not know each other’s identity and receive little information about each other, and future contact must be established through the organ procurement organization.¹⁹ Neither party can set conditions on future contact before the donation, and they can choose to remain anonymous and restrict contact. In the case of uterus donation, this restriction would mean that the donor could not agree to donate

only on the condition that she be informed of the recipient's future pregnancies and their outcomes or receive updates about future children. In gestational surrogacy, however, the parties may not only meet but also become involved in each other's lives, and surrogacy contracts may include provisions for future information about or contact with a child.²¹ If we view UTx through the lens of ARTs, particularly surrogacy, we might conclude that potential donors and recipients should be able to negotiate contract terms rather than be governed by blanket prohibitions typical of SOT.

Ethical issues. UTx also raises ethical questions that are not easily addressed by the SOT and ART frameworks. One question is how to allocate uteri from nondirected LDs and DDs. Uterus allocation could be based on a first-come, first-served basis; motherhood status; child-rearing capacity; likelihood of being able to carry a pregnancy to term; or age.^{22,23,24} Some of the ethical principles that govern the allocation of solid organs do not map neatly onto UTx. To promote the equitable allocation of organs, the OPTN relies heavily on the principle of utility, whereby an action or practice is deemed morally right "if it promotes as much or more aggregate net good than any alternative action or practice."²⁵ Applying the principle of utility to organ allocation involves taking into account all possible goods and harms, including patient survival.²⁵ Unlike many cases of SOT, UTx is not lifesaving or life extending.²⁵ Identifying other factors to be taken into account involves making decisions about the appropriate goals of UTx and ranking those goals. Thus far, the pursuit of pregnancy has been assumed to be the only acceptable primary goal, but another possibility is achieving a sense of bodily integrity or wholeness. This goal could contribute to quality of life, which the OPTN considers part of the utility assessment.²⁵

The allocation framework used for SOT does not map neatly onto UTx for a second reason. The OPTN prohibits consideration of "social aspects of utility" and especially the "social worth or value of individuals."²⁵ Yet assessing the recipient's capacity for child-rearing—which could be seen as resembling social worth assessments—is part of the UTx evaluation recommended by some scholars and practitioners.^{22,24} Someone deemed unworthy of the social role of being a parent would be rejected. Such assessments could be riddled with judgments about what makes a good parent and easily could lead to ranking of potential recipients based on suitability for child-rearing.

Summary. Ad hoc reliance in UTx on ethical frameworks from SOT and ART means that ethical guidance may be applied differently in UTx than it is in SOT or ART and that determinations of legitimate applications of UTx might change over time. For this reason, these 2 frameworks are not sufficient to guide UTx as it moves to the clinical setting. Clinical practice guidelines specific to UTx are needed.

Conclusion

Developing UTx practice guidelines would have a number of benefits. First, guidelines would foster a greater degree of consistency in UTx practice. Variation in UTx practice can arise in criteria for donor and recipient eligibility, time between transplantation and first embryo transfer, the use of living vs deceased donors, the permissibility of using donor gametes, and the number pregnancies or attempted pregnancies permitted. The UTx trials listed on ClinicalTrials.gov reflect this variation. For example, the age requirements for recipients range from 18-45,¹⁰ 20-35,¹¹ and 18-39¹² at time of transplantation. Second, although variability in practice can be reasonable, it also can lead to mistrust, inequitable treatment, and inequitable outcomes.^{23,24} Developing comprehensive guidelines for UTx will thus promote transparency, equity, and trust among those who consider themselves stakeholders in this new procedure. Third, developing practice guidelines also is an important starting point for establishing the future research trajectory of UTx and anticipating the ethical implications of expanded uses of UTx. Just as has been the case with SOT and ART guidelines, UTx guidelines will evolve as more becomes known about the procedure. However, changes to the guidelines should be anticipated and—like the initial guidelines—they should be implemented in an ethically consistent manner.

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