Evolving Ethical Challenges After a Decade of Uterus Transplantation: Recommendations From the International Society of Uterus Transplantation Ethics Committee

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Abstract. Uterus transplantation (UTx) became a clinical reality with the birth of the first baby in 2014. Following increased success, the procedure has now transitioned to clinical practice in many institutions throughout the world. With a rising number of donors, recipients, and babies born from this procedure, and with more institutions offering UTx, ethical challenges have evolved while novel aspects gained prominence. Here, the Ethics Committees of the International Uterus Transplantation Society, a section of The Transplantation Society, summarize current and future ethical challenges in UTx and provide recommendations for addressing these challenges. Ethical considerations covered here span (i) donor and recipient selection, (ii) living versus deceased donation, (iii) use of assisted reproductive technologies, (iv) informed consent, (v) clinical provision of UTx, and (vi) research protocols for further studies of UTx. For each topic considered, ethical analysis and recommendations are offered to ensure the practice of UTx remains within an acceptable foundational ethical framework that balances respect for autonomy, beneficence, and justice.

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INTRODUCTION

Uterus transplantation (UTx) is the only curative treatment for women with absolute uterine factor infertility (AUFI) who want to experience pregnancy and give birth to a baby. The procedure became a clinical reality in 2014 when the first baby was born following a live donor UTx performed in Gothenburg, Sweden.[1] UTx is now offered at approximately 20 centers worldwide. Based on personal information and data collected by the registry of the International Society of Uterus Transplantation, UTx has been performed at 25 centers in 20 countries.[2]

UTx is a unique treatment, characterized as a non–life-saving yet life-giving temporary transplant. Immunosuppression and antimicrobial treatment are largely comparable to that of other solid organ transplants with the graft monitored by transvaginal ultrasound, color Doppler by abdominal ultrasound, and cervical biopsies to detect rejection.[3,4] From an immunological perspective, the typical UTx situation presents as an allogeneic transplant involving an embryo that is allogeneic to the uterus but semiallogeneic to the pregnant mother.

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Ten years after its first successful achievement, UTx now represents an established clinical procedure that is covered by health insurance in a few countries.[5,6] Not only has the clinical practice of UTx evolved, but the ethical challenges with this procedure have advanced from questions of whether UTx should be performed at all, to questions of how to ensure that it is performed in the most ethically appropriate manner.[7,8] The success of UTx has thus raised questions on how to expand the field, starting new programs, and transitioned from research into clinical practice, all of which bring up additional ethical challenges not considered at the inception of UTx.

In general, the ethical justification for UTx is based on the ethical principles of beneficence and respect for autonomy. First, the procedure is justified on grounds of beneficence as the fulfillment of a morally significant need or reproductive preference: specifically, the potential achievement of what are alleged to be lifelong improvements to psycho-emotional quality of life, despite the ephemeral or short-term nature of the transplant.[9] From this perspective, the risk-benefit ratio of UTx might arguably be comparable to that of other transplant techniques, even though UTx is not intended to preserve life. The second justification centers on the respect for autonomy, which may be construed as either reproductive autonomy (in the case of recipients) or rights of bodily autonomy (in the case of donors).[9,10] This article identifies and discusses the contemporary ethical challenges with UTx and provides recommendations for navigating these challenges (Table 1). Notably, we address UTx for reproductive purposes rather than gender affirmation, based on the current international guidance formulated in the Montreal Criteria.[11] The justification for this distinction is that the desire for pregnancy and childbirth is a first-order desire while that of UTx to fulfill identity is a second-order desire. Second-order desires can be addressed with psychological therapy, which may better serve patients as opposed to surgery and lifelong immunosuppression.[11]

DONOR AND RECIPIENT SELECTION

The first challenge considered here concerns selection criteria. There is variability among UTx programs in the inclusion and exclusion criteria for UTx recipients and donors.[12-14] According to the first report of the International Society of Uterus Transplantation, the inclusion criteria for recipients at most centers include AUFI, age of fertility (<39 y old), body mass index <28, and the absence of overt systemic or psychiatric illness. For living donors (LDs), the report suggests an upper age limit of 50 y old with no other inclusion or exclusion criteria.[2] However, beyond these general criteria, each center has additional factors that they consider for inclusion and exclusion. Some of these factors are psychosocial criteria and require ethical rather than scientific evaluation and justification.

TABLE 1.

Recommendations for addressing ethical challenges in uterus transplantation

Recommendation 1: The availability of an appropriate social support system is a recognized and necessary condition for UTx recipients, but social support assessment should not automatically rule out or give priority to potential UTx recipients who are not married or partnered.

Recommendation 2: Animal research is needed to determine the feasibility of UTx in, and uterus donation from, transgender patients and UTx in cisgender males who want to experience pregnancy. If medically and surgically acceptable, gender identity and reproductive status should not be exclusionary factors for uterus donation or transplantation.

Recommendation 3: Potential UTx recipients with prior children should not be excluded from UTx listing. Centers should have clear eligibility criteria based on donor and recipient reproductive status and those that do not offer UTx for women based on prior healthy live births or donation based on nulliparity should offer transfer to a center offering this opportunity.

Recommendation 4: Research should continue into DD UTx, to optimize outcomes and to understand the consequences of uterine injury resulting from ischemia/reperfusion. Further ethical research is needed to determine the validity of donor, family, and recipient anonymity and to ensure resulting children's rights and interests are duly protected. Ethical analysis should also continue in relation to managing equity in recipient selection and allocation of deceased donor and nondirected living donor uteri. Guidelines for LD UTx acceptability based on ethical foundations and vulnerability analysis should be established.

Recommendation 5: UTx recipients should be treated as those undergoing IVF with options to use their own oocytes or when indicated, donor oocytes. When using their own oocytes, the retrieval should be performed before the UTx.

Recommendation 6: UTx recipients should ideally identify a sperm donor before the oocyte retrieval so that at least some embryos are created from fresh, rather than cryopreserved oocytes. If gamete or embryo donation is used, centers should follow available guidelines from professional societies and government regulations. The UTx recipient together with the medical team should discuss the number of oocytes or embryos to cryopreserve by considering family-forming wishes, and the center's experience and policies.

Recommendation 7: Where PGT-A is offered, counseling to perform this technology should be individualized and include considerations of costs in addition to known risks and benefits.

Recommendation 8: UTx recipients should have the same independence and protection to decide on an abortion as any pregnant woman.

Recommendation 9: Informed consent for UTx should describe the entire process rather than just the procedure, disclosing both the known risks as well as the unknown longer-term risks of UTx. Multiple discussions regarding the necessity for and timing of graft hysterectomy may be needed throughout the course of UTx.

Recommendation 10: Clinical provision of UTx is acceptable in established centers or those being proctored by centers/key personnel with experience. All programs engaged in UTx should submit data to relevant national or international registries.

Recommendation 11: Advocacy for public and private coverage of the costs of UTx as well as other infertility treatments is necessary.

Recommendation 12: Research protocols for UTx should be considered when there is a novelty in the application, population, program, or protocol.

DD, deceased donor; IVF, in vitro fertilization; LD, living donor; PGT-A, preimplantation genetic testing for aneuploidy; UTx, uterus transplantation.

Three key psychosocial criteria have generated recent ethical debate and contention, and we suggest there are grounds for their ethical re-evaluation and potential revision:[15,16]

- Relationship status (recipients)
- Gender identity status (recipients and donors)
- Reproductive status (donors and recipients).

Relationship Status: Recipients

Many currently approved research protocols recommend that recipients be partnered or married. Previous studies have shown some psychological advantages for recipients who have been in a stable relationship for at least 2 y.[17,18] However, such requirements exclude single women who desire UTx and as such raise questions about equity as well as potential discrepancies with prevailing community attitudes and values in many countries in which UTx is (or will be) available.

The underpinning rationale for a requirement that recipients be partnered or married is most justifiably a concern to ensure that a recipient has adequate social support throughout the considerable demands of UTx surgery, recovery, embryo transfer(s) (ETs), pregnancy, and birth.[19] In solid organ transplantation, social support has been associated with medication adherence, indicating its value for the complex management of post-transplant patients.[20] Social support is recommended in the inclusion criteria for UTx by the American Society of Reproductive Medicine, while the revised Montreal Criteria recommend only that the recipient does not have "frank unsuitability" for motherhood.[11,21] The availability of adequate social and emotional support systems—and hence access to UTx—should not be assumed to be dependent upon a recipient's current romantic or marital status, and may be provided by other social networks or even transplant programs. Rather, psychological and social screening protocols need to assess and confirm the availability of adequate emotional and practical support for a recipient, irrespective of whether such support will be provided in the context of a romantic or marital partnership. Single women—and, of course, nonheterosexual couples who may not have access to legal marriage—should not be treated as exceptions and excluded.

Recommendation 1: The availability of an appropriate social support system is a recognized and necessary condition for UTx recipients, but social support assessment should not automatically rule out or give priority to potential UTx recipients who are not married or partnered.

Gender Identity Status: Recipients

To date, UTx has only been performed on genetic females but its application to transgender women has been strongly debated. Moreover, there may be a role for UTx in cisgender men with a desire to experience pregnancy.[22-26] Further research is needed in animal models to establish the clinical safety and feasibility of UTx in both transgender women who have undergone appropriate hormonal treatment to support their transition from male to female, and cisgender men who are willing to undergo temporary hormonal treatment to support pregnancy.[27] It is known that at least some transgender women desire to experience pregnancy, childbirth, and parenthood, and are likely to seek UTx using either their own, donor gametes, or donor embryos.[28-31] If medical safety and feasibility are established and surgical challenges carefully assessed, principles of nondiscrimination support potential recipients and donors not being automatically excluded from UTx solely on any nonmedical grounds relating to gender identity.

Gender Identity Status: Donors

Similarly, for transgender men undergoing hormonally supported transition from female to male, principles of nondiscrimination support the inclusion of these individuals in living uterus donation eligibility, provided that safety and efficacy have been established.[32] The impact of long-term androgen treatment on the quality of uterine vessels and uterine tissue in these potential donors has not yet been studied. Research is needed to determine whether graft quality is compromised in this potential donor cohort. However, if such research establishes appropriate graft quality, there is no sound ethical justification for treating this class of potential donors differently from female donors, provided voluntary informed consent requirements are fulfilled.

Recommendation 2: Animal research is needed to determine the feasibility of UTx in, and uterus donation from, transgender patients and UTx in cisgender males who want to experience pregnancy. If medically and surgically acceptable, gender identity and reproductive status should not be exclusionary factors for uterus donation or transplantation.

Reproductive Status: Donors and Recipients

Nonparity has historically served as a relative or absolute contraindication for living and deceased uterus donation.[31] However, additional principles of inclusivity and nondiscrimination pertaining to opportunities for parenthood may warrant expansion of eligibility criteria in support of nonparous donors.[33] The need to avoid gendered and pronatalist assumptions tying sex/gender to reproductive function and motherhood applies to potential transgender donors for whom goals of gestation, childbirth, and motherhood may never have figured in their plans, or as in cisgender donors who never had a desire for motherhood. However, there may be a higher risk of graft nonfunction in UTx from nulliparous donors as uterus-related infertility would not have been identified before donation.

From a recipient standpoint, some centers consider the recipient's reproductive status in deciding whether to offer UTx.[18] For example, some consider potential recipients who already have a healthy child (eg, underwent hysterectomy for postpartum hemorrhage) to have a contraindication to UTx.[19] The rationale is that a complication resulting in the death of the recipient would be a harm to the existing child who would lose a parent. However, given the current outcomes of UTx, with no related deaths at this time, the concern about maternal death is not based on

empirical evidence that UTx pregnancies carry more risk than other pregnancies.

Others consider prior children versus no children to be a justice issue in that the opportunity to undergo UTx should favor those women who have not already had a child. Because reproductive decisions and family desires are highly personal, potential UTx recipients with prior children may have equally strong desires for UTx and subsequent children as those who do not have children. However, other centers do not consider the reproductive status of a recipient in eligibility as the desire for a subsequent child or children as strong as for a first child. Nevertheless, women who want to proceed with UTx after having their own child or children should be allowed if they meet medical and psychosocial criteria for UTx. At this time, UTx is a limited resource, and centers may need to have criteria to help determine prioritization for listing or transplantation based on factors such as reproductive status. If they consider prior children as lower priority, this needs to be disclosed to potential recipients who should be given the opportunity to seek care at a different center.

Recommendation 3: Potential UTx recipients with prior children should not be excluded from UTx listing. Centers should have clear eligibility criteria based on donor and recipient reproductive status and those that do not offer UTx for women based on prior healthy live births or donation based on nulliparity should offer transfer to a center offering this opportunity.

LIVING VERSUS DECEASED DONATION

Considerations of both short supply of deceased donor (DD) organs versus harm minimization in the setting of living donation provide support for research to continue in DD UTx, alongside further development of the LD model of UTx (LD UTx).[34] Historically, the majority of UTx procedures internationally have involved living donation (75%) as opposed to deceased donation (25%). Importantly, DD UTx incurs no physical risk, financial burden, or inconvenience to the donor.[35] Of further note concerning the principle of beneficence are the potential benefits that might be incurred by a DD family, for whom the opportunity to provide a uterus for transplantation may be morally significant. DD UTx also carries the benefit of providing longer vessels and vaginal cuff, which decreases technical difficulty. Although the international number of successful DD transplants is currently much lower than that of the LD model, existing evidence suggests that the procedure from a DD can be both safe and effective.[36]

Key ethical questions in DD UTx include the distinct challenges to be resolved around authorization for deceased uterus donation. Appropriate protocols need to be established, with a range of authorization pathways possible, from inclusion on standard donation authorization registers to nonregistered surrogate authorization mechanisms. As a nonvital, as well as reproductive organ, community and stakeholder views are mixed as to whether it is an organ with special significance as compared with the other transplantable organs.[37,38] There is no settled view yet regarding the best mechanisms for donation authorization, hence the need for further research and consultation on this topic.

DD UTx also raises distinct ethical questions relating to resource use, allocation and management, and equity. There is a general ethical consensus that, as a nonvital organ, the uterus should be retrieved only after the retrieval of vital organs, or without disruption of vital organ retrieval when done prior.[39,40] Available research findings on cold and warm ischemic times support the ability to maintain graft viability even if scheduled for retrieval only after all vital organs have been retrieved.[41,42]

A further set of ethical questions raised by DD UTx concerns the possible psychological and familial challenges that it may pose. Further ethical inquiry is needed into the interests of the children resulting from deceased donation UTx. Questions include whether a UTx child might have interests in or rights to knowledge of the DD, and to a potential connection with the donor family, and whether donor families might assert rights claims like those of children born from donor gametes and embryos, or through adoption and surrogacy. Donor families may want to meet the UTx recipient and children who were born from the transplanted uterus. As with other solid organ transplants from DDs, donor and recipient privacy and confidentiality should be protected, and communications or meetings between recipients and donor families should be arranged through the same mechanisms, requiring mutual agreement to identity disclosure. Moreover, recipients and donors should only meet when this is mutually agreed upon and must be protected from demands for social and economic compensation.

Although these ethical questions are not yet resolved, there are important differences between potential claims that might arise in DD UTx cases and those that arise in cases of gamete/embryo donation and adoption. This is because, while life-sustaining and biologically important, the uterus does not make the same kind of contribution to the constitution of a child as is made by gametes in the case of donor conception and adoption. Given the lack of genetic contribution made by the uterus, donor and donor family anonymity might be justifiable in the case of DD UTx. Especially in countries with an opt-out system, anonymity may be considered a proportional instrument for balancing the protection of donor's rights. However, this does not account for societies that have different conceptualizations of kinship, which may be related to the origin of the uterus, so in these cases, anonymity would need to be determined before UTx. If anonymity is accepted, any resulting interests or rights claims relating to donor families, recipients, and/or resulting children should be effectively managed via approved consenting and counseling protocols and mechanisms.

In LD UTx, there are still debates about appropriate risk thresholds for living donation based on both donor and recipient outcomes.[10,35,43] The use of an individual framework with the LD as a patient, and combining research ethics principles together with a vulnerability analysis, provides a robust methodology for the determination of donor acceptability in LD UTx.[43] Additional ethical challenges with LD UTx center around appropriate informed consent practices that minimize the risks of coercion or undue manipulation for donation, claims relating to knowing or having a relationship with the offspring of

UTx recipients, and the appropriate allocation of nondirected LD grafts.

Recommendation 4: Research should continue into DD UTx, to optimize outcomes and to understand the consequences of uterine injury resulting from ischemia/reperfusion. Further ethical research is needed to determine the validity of donor, family, and recipient anonymity and to ensure resulting children's rights and interests are duly protected. Ethical analysis should also continue in relation to managing equity in recipient selection and allocation of deceased donor and non-directed living donor uteri. Guidelines for LD UTx acceptability based on ethical foundations and vulnerability analysis should be established.

UTILIZATION OF ASSISTED REPRODUCTIVE TECHNOLOGIES

- Gamete and embryo donation

Although guidance documents on good practice for the evaluation, screening, and testing of potential gamete and embryo donors have been issued by both the European Society of Human Reproduction and Embryology[1] and the American Society for Reproductive Medicine,[2] they each stress that local and national guidance legislations should also be considered. To our knowledge, there are no publications regarding the existence of distinct ethical issues associated with the use of donor games or embryos in UTx. Although this may be the subject of future research, we here assume that the ethical issues mirror those recognized to exist with gamete and embryo donation generally.

One ethical question is which patients should consider gamete or embryo donation given that women with AUFI often have functional ovaries from which oocytes can be procured. Recipients without ovaries or with very poor ovarian reserve would require oocyte donation and those with partners who have severe male factor infertility or without male partners would need donor sperm. For UTx recipients who need both oocyte and sperm donation, they may elect double gamete donation or embryo donation. In terms of risk assessment for gamete or embryo donation, donors should undergo thorough medical and psychosocial evaluation, provide voluntary, informed consent, and agree to undergo genetic screening for any relevant diseases or disorders. They may also be asked to undergo expanded genetic testing based on family history or age. Gamete donor informed consents must be signed by the donor and include relinquishing all rights of the donor to any child that may result from the donation, as well as details regarding whether and when the donor's identifiable data can be obtained by future offspring.

For UTx recipients using their own oocytes, the first consideration is the timing of oocyte retrieval. In terms of minimizing risk, the recommendation is that oocyte retrieval should be performed before UTx because the risk of ovarian hyperstimulation syndrome during or after gonadotropin stimulation and immunosuppression may increase the risk of pelvic infection after oocyte retrieval.

Recommendation 5: UTx recipients should be treated as those undergoing IVF with options to use their own oocytes or when indicated, donor oocytes. When using their own oocytes, the retrieval should be performed before the UTx.

CRYOPRESERVATION

After retrieval, there are 2 options for the management of oocytes: they can be cryopreserved as unfertilized oocytes or used fresh to create embryos by conventional insemination and or intracytoplasmic sperm injection in an in vitro fertilization (IVF) cycle. Oocyte freezing is applicable in women who do not have an identified sperm donor or partner to provide sperm for IVF. Moreover, oocyte rather than embryo cryopreservation will be advantageous for the recipient in cases where separation from the partner occurs after UTx but before ET. However, the implantation rate of embryos from frozen oocytes is lower than from those that undergo fresh IVF, so the recommendation is for potential UTx recipients to identify a sperm donor or partner to provide sperm before oocyte retrieval, so cryopreservation of at least some embryos can occur in an IVF cycle before UTx.

The number of embryos or oocytes to freeze is also a question that centers need to decide. For oocyte cryopreservation, some algorithms help guide physicians and patients on the optimal number based on maternal age, ovarian reserve, and family-building wishes.[44,45] For embryo cryopreservation, the number of children that the UTx recipient desires, along with the stage and quality of cryopreserved embryos, need to be considered. Each center will have to determine the number of embryos required for UTx recipients based on these considerations.

Recommendation 6: UTx recipients should ideally identify a sperm donor before the oocyte retrieval so that at least some embryos are created from fresh, rather than cryopreserved oocytes. If gamete or embryo donation is used, centers should follow available guidelines from professional societies and government regulations. The UTx recipient together with the medical team should discuss the number of oocytes or embryos to cryopreserve by considering family-forming wishes, and the center's experience and policies.

PREIMPLANTATION GENETIC TESTING

Preimplantation genetic testing for aneuploidy (PGT-A) has been a topic of debate in the UTx community because uterus recipients are typically young without a high risk of oocyte aneuploidy, so in the absence of UTx, PGT-A would not be uniformly recommended in similar cohorts.[46] There are both ethical and medical dimensions to the debate. From an ethics standpoint, the risks and benefits of PGT-A must be weighed in making center- and patient-level decisions about its value. The potential benefits of PGT-A include reduced risk of miscarriage, shorter time to pregnancy, and a potential reduction in the cost of IVF if the number of IVF stimulations and ETs can be kept low.

The potential risks include increased risk of intrauterine growth restriction, questionable efficacy (particularly in women under 35 y of age), and possible need for additional ovarian stimulation and oocyte retrievals because of failure of suitable embryos for biopsy or no euploid embryos for transfer.[47] All of these outcomes would be associated with higher costs. On the contrary side, waiting to make a diagnosis with prenatal screening may result in extended graft recipient time, increasing the time of exposure to immunosuppression, if a condition incompatible with life is diagnosed and the UTx recipient decides end the current pregnancy and restart the process of embryo creation or transfer. As noted by Brannstrom et al,[48] "The nuances associated with these opposing arguments indicate that adequate counseling is paramount and the decision to proceed with PGT-A should be individualized."[48] Use of PGT-A will also depend on variations in costs and national regulations with some countries including Sweden, prohibiting PGT-A testing in the clinical setting.

Recommendation 7: Where PGT-A is offered, counseling to perform this technology should be individualized and include considerations of costs in addition to known risks and benefits.

ABORTION AFTER UTX

To the best of the authors' knowledge, no UTx recipient has undergone an abortion but this will, in all likelihood occur. Even though a pregnancy after UTx is carefully planned, the psychosocial situation for the woman and/or the couple may change resulting in a desire to end the pregnancy. Other reasons for an abortion could include the detection of fetal abnormalities or severe illness in the UTx recipient. Pregnant women after UTx must have the same independence and protection to decide on abortion as any pregnant woman. Notably, it is beyond the scope of this analysis to provide recommendations on appropriate legal approaches to abortion. The specific goal is rather to advocate that UTx recipients have the same access to abortion as their nontransplant counterparts.

Recommendation 8: UTx recipients should have the same independence and protection to decide on an abortion as any pregnant woman.

INFORMED CONSENT FOR UTX

In parallel to UTx transitioning to a clinical procedure in experienced centers, the consent process has also undergone a transition from a research protocol to clinical consent. The goal of informed consent is to allow patients to exercise their autonomous right to make medical decisions that are consistent with their goals and values. The requirements for informed consent are understanding, voluntariness, and agreement. Although UTx should follow the same guidance as other surgical procedures, there are unique aspects of UTx that require additional disclosure during informed consent discussions, namely the explicit purpose of UTx and the expected course of pregnancy as well as indications for graft hysterectomy (GH).

The goal of UTx is to allow the uterus transplant recipient to experience pregnancy and childbirth, and, in many cases, to have a genetically related child (particularly in areas where surrogacy is not allowed, so a UTx is the only path to having a genetically related child). To achieve this goal, the uterus transplant is just the start of several procedures and months to years of medical care. In a study of UTx recipients from the Dallas uterus transplant study (DUETS), participants were overall happy with the information provided to them for informed consent about the procedure. This information was presented in written form and verbal communication with the transplant team.[9]

A second important element in the informed consent process is a discussion about the necessity and timing of GH. Once the goal of UTx—1 or more successful, healthy live births—is achieved, or once it becomes clear that it will not be achieved, the graft should be removed to limit exposure to immunosuppression and related long-term complications of continuing these medications. The DUETS trial set a limit on graft recipient time to 5 y and the trial in Sweden planned uterus removal after 1 or 2 successful pregnancies.[49,50] Discussions about indications and timing of GH should occur from the beginning of the informed consent process for UTx and be revisited frequently throughout the process so that recipients can make decisions about GH timing that are consistent with their goals and values, with transplant teams helping to guide those decisions based on best medical care.

Recommendation 9: Informed consent for UTx should describe the entire process rather than just the procedure, disclosing both the known risks as well as unknown longer-term risks of UTx. Multiple discussions regarding the necessity for and timing of graft hysterectomy may be needed throughout the course of UTx.

CLINICAL PROVISION OF UTX

With experience, some centers have transitioned to UTx as a clinical procedure, outside of a research protocol. University Hospital Tuebingen was the first transplantation center worldwide to implement UTx as a government-paid procedure after the completion of 4 UTx and done in communication with all stakeholders (ethical, legal, medical, and political). Baylor University Medical Center completed a clinical trial of 20 uterus transplants before offering this procedure under a self-pay model. Moreover, Sahlgrenska University Hospital in Sweden has received authorization to start publicly funded UTx procedures following their completion of 20 cases (2012–2019) within 3 separate trials.[51] Although 2 of 3 centers used 20 cases as a point of experience to move into clinical applications, there is no empirically defined number of cases necessary for experience in UTx or other new procedures. The term "experienced centers" is used in the Society of American Gastrointestinal and Endoscopic Surgery (SAGES) Guidelines for the Introduction of New Technology and Techniques, but a concrete number of cases or a set of criteria to define experience is not provided.[52] The United Network for Organ Sharing guidelines for membership as a uterus transplant program does not have a specific number of cases required for establishment but does require that the primary surgeon has 1 of 5 qualifications: Accreditation Council for

Graduate Medical Education-approved gynecologic oncology fellowship, other gynecologic oncology fellowship that meets criteria, abdominal organ transplant fellowship, clinical experience with uterus transplants, or clinical experience with radical hysterectomies.

As more programs start up, there must be standard program requirements. For centers that do not have an established research program, they will need to learn the procedure from experienced centers, attain proctoring for early cases, or hire team members with experience in UTx. The number of cases that should be observed and proctored should be determined by the regulatory bodies of each country and be comparable to the requirements for starting other solid organ transplant programs. According to SAGES guidelines, "while a defined number of proctored cases is frequently suggested or required, such recommendations are usually arbitrary and not based on solid evidence of effectiveness."[52] Therefore, we do not have recommendations for a specific number of proctored cases for new centers.

Beyond developing technical competence, the essential staff required for the conduct of UTx should be defined. We recommend that, at minimum, a transplant surgeon and ob-gyn should partner in program leadership.[53] Additional support staff should include coordinators, reproductive medicine, maternal-fetal medicine, neonatal intensive care, and a social worker/psychologist. The program should be at a hospital with the capacity to provide care for high-risk pregnancies and deliveries. Protocols should be developed in conjunction with proctoring centers.

In addition to requirements for program set-up, there should also be either national or international reporting requirements. As per the IDEAL recommendations for surgical innovations, there are strong recommendations for prospective research databases during the exploration phase of development after the mechanical technical aspects have been worked out. In the absence of randomized control studies, robust databases can provide the power necessary for propensity matching to ascertain outcomes based on different inputs. For example, such databases could be used to determine the safest and most efficacious immunosuppressive regimens initiated for the uterine transplant. Another example would be to determine outcomes from LD versus DD models of UTx.[54] For programs that have national registries for transplant patients (eg, the United States), reporting requirements can be fulfilled through this mechanism. For programs in countries without such registries, the International Uterus Transplant Registry[2] should be used. In addition, programs that have mandatory national registries are encouraged to voluntarily contribute to the international registry so that comprehensive data can be stored in 1 location.

Recommendation 10: Clinical provision of UTx is acceptable in established centers or those being proctored by centers/key personnel with experience. All programs engaged in UTx should submit data to relevant national or international registries.

FINANCIAL AND LOGISTICAL IMPLICATIONS OF UTX

Another area of ethical inquiry is the financial and logistical implications of UTx. With the clinical provision of UTx, reimbursement will have to come through insurance, government payments, or personal payments. During the inception of a uterus transplant program, hospitals may cover costs for a given number of patients until the program is established. At this time, there is no international standard for how uterus transplants should be paid for. Government programs cover UTx in Germany and Sweden, but it is unclear if that is the case in any other country. Private insurance may cover some amount for infertility treatment but may not yet cover the entire amount. Out-of-pocket payment for UTx has been estimated to be as high as USD 250 000, putting UTx out of reach for most patients. Programs not supported by governmental or private insurance should be allowed to offer UTx as a fee-for-service intervention that patients can privately finance. However, advocacy for the coverage of UTx as well as other infertility treatments is essential to eventually gain wider and more equitable coverage of these interventions. Moreover, the impact of expanding coverage for UTx on other health goods and services needs to be monitored as well as the impact of UTx volume on other hospital services. At this time, the volume of UTx is so low that its impact is likely minimal but it could be more sizeable with program growth.

Recommendation 11: Advocacy for public and private coverage of the costs of UTx as well as other infertility treatments is necessary.

RESEARCH PROTOCOLS FOR UTX

As UTx moves into clinical practice, there is a question of when uterus transplant procedures should be conducted under research trials versus as clinical care. The Belmont report distinguishes between research and clinical care based on the goals of the intervention.[55] Clinical practice refers to interventions that are designed to "enhance the well-being of an individual patient and have a reasonable expectation of success."[55] Research designates an activity that is "designed to test a hypothesis, obtain conclusions, and contribute to generalizable knowledge."[55] A report on UTx from 2021 noted that UTx has been performed in at least 10 countries around the world, with >80 procedures done and 40 live births in uterus transplant recipients.[56] Detailed reports from experienced centers show that UTx is safe, successful, and reproducible.[57–59] At this time, given clinical success with both DD and LD UTx in multiple centers, the need for more clinical trials on standard UTx is unlikely.

However, there are indications for clinical trials that address novelties in UTx, which should be directed by local, national, and international guidelines. In novel situations, reasonable expectations of success cannot be guaranteed, and therefore, research protocols to address hypothesis testing and create generalizable knowledge should be implemented. Novelty can be conceptualized as application, population, center, or protocol-specific. An example of the novelty of application would be if UTx is applied to a "novel" patient population such as transgender patients. A novel population may also relate to the first time UTx is performed in a country or geographical region. Center-specific novelty refers to

the first time UTx is attempted in a center. For example, while there are several centers in the United States that have performed UTx, a new center may elect to start under an institutional review board–overseen protocol to have additional research oversight. Although institutional review board oversight should not be used alone to address inexperience, it is 1 of the options recommended by the SAGES for monitoring the introduction of new technology or techniques into surgical practice. Others include the individual surgeon, institutional credentialing committee, new technology committee, and specialty society.[52] Finally, research protocols may be used to evaluate substantive changes to clinical care protocols, such as comparing different immunosuppression regimens or prolonging the amount of time a graft can stay in or the number of pregnancies allowed with a transplanted uterus. As UTx grows in prevalence, the community must closely consider when changes to different aspects of the procedure are sufficiently novel to warrant research protocols. These considerations should be guided by the distinguishing factors laid out in the Belmont Report.

Recommendation 12: Research protocols for UTx should be considered when there is a novelty in the application, population, program, or protocol.

CONCLUSION

UTx has evolved from a research endeavor to a clinical procedure over the past decade. While early ethical challenges centered around questions of whether we should pursue UTx, new challenges revolve around how to most ethically manage donation, fertility treatments, and data collection for quality assurance and research. The recommendations offered here are intended to help guide the field in identifying and responding to the new ethical challenges that will arise as UTx matures.

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