Ethical Implications of Donor Type for Uterus Transplantation: Why We Should Remain Wary of Using Living Donors

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Over the last few years, research teams have made significant advancements in treating absolute uterine factor infertility through uterus transplantation, culminating in the birth of the first US baby born from a uterus transplant in November 2017. However, studies have differed on the choice of either deceased or living donors, with some centers even exploring both methods. As researchers continue to investigate the medical feasibility of these approaches, it is also important for the medical community to consider how deceased and living uterus donation differ ethically. We argue that if living and deceased donation demonstrate equivalent clinical efficacy and the deceased donor pool is sufficient, living uterus donation should be reevaluated and may no longer be ethically justifiable.

INTRODUCTION

Absolute uterine factor infertility remains the last major type of untreatable female infertility, affecting an estimated 85,000 women in the US and 1.5 million worldwide [1]. Previously, the only options available for these women to achieve motherhood included adoption and gestational surrogacy. However, uterus transplantation provides a new opportunity wherein a woman may be not only a social and genetic mother, but also a gestational mother [2]. After failed attempts in Saudi Arabia in 2000 [3] and in Turkey in 2012 [4], a Swedish team achieved the first live birth after uterus transplantation in 2014 [5] and the first US baby was born from a uterus transplant at Baylor University in November 2017 [6]. Although these initial successes occurred after transplantation from living donors, deceased uterus donation has led to recent live births in Brazil [7] and at the Cleveland Clinic [8]. Uterus transplantation with living and deceased donors is quickly transforming from research to clinical reality.

From a medical perspective, living donors allow for a more thorough donor work-up prior to transplantation, reduced cold ischemia time with donation and transplantation occurring in the same center, and a higher degree of histocompatibility if the donor and recipient are related. On the other hand, deceased donation provides opportunities to obtain organs from younger donors with uteri potentially more suitable for reproduction (e.g. more patent...
uteros in premenopausal hormone levels and decreased rates of vascular disease), to procure the uterus through a simpler procedure taking less time, and to include longer vascular pedicles and all uterine parametria in the organ procurement [9].

Given this ongoing, fast-paced clinical research, the medical community must consider how living and deceased uterus donation differ ethically. The moral implications of both approaches require different protections, procedures, and regulations [1] that must be in place before uterus transplantation transitions from the research phase to clinical practice. Furthermore, although both approaches should continue to be explored currently, if in the future living and deceased donation demonstrate equivalent clinical efficacy and the supply of deceased donor organs is sufficient to meet demand for uterus transplantation, living uterus donation should be reevaluated and may no longer be ethically justifiable [10]. In this paper, we review and explore some of the ethical challenges posed by deceased and living uterus donation individually before addressing this need to proceed with caution.

DECEASED UTERUS DONATION

Deceased uterus donation poses unique ethical and regulatory challenges regarding consent for donation and organ procurement. With respect to the former, autonomy and respect for persons require that organs only be removed when given explicit consent from the deceased or their family. However, the American public remains largely unfamiliar with uterus transplantation, and many women likely were unaware upon donor registration that the uterus may be one of the organs included in the donor registration process in the future. Furthermore, whether women are as willing to donate the uterus given its reproductive rather than life-saving purpose remains unknown [11]. At present, organ donors consent to the donation of the heart, lungs, kidneys, liver, intestines, pancreas, and certain tissues (corneas, tendons, valves, veins, skin, and bones), but not to the donation of vascular composite allografts (VCAs, which include the face, hand, uterus, etc.), the recovery of which “must be specifically authorized” [12]. In the absence of empirical evidence to suggest public awareness and desire to donate such organs, the VCA consent process must remain separate and explicit because these transplants are non-vital and are of a highly personal nature.

However, in the case of uterus donation, the question also persists whether family member consent is appropriate given the organ’s reproductive purpose and the sanctity of individual procreative liberty [13]. Uterus donation may not involve transference of genetic material to offspring, but uncertainty remains regarding the effect of the uterine microenvironment on fetal development [14]. Furthermore, while the 2006 Uniform Anatomical Gift Act prevents family members from overriding the wishes of the deceased if they are expressly known, it does not require that family members consider the deceased individual’s probable intent or wishes when making a decision whether or not to donate. In other words, family members are not held to the same standard of substituted judgment that is well-accepted and commonly utilized in other aspects of surrogate medical decision-making when considering organ donation [15]. Such a policy appears concerning when considering consent for uterus donation given the procedure’s reproductive implications; indeed, even surrogate decision-making bound by the principle of substituted judgment is rarely applied in other aspects of reproductive medicine including assisted reproductive technology and termination of pregnancy. Therefore, it is reasonable to remain cautious of family decision-making for deceased uterus donation. However, as uterus transplantation evolves, additional information regarding the effect of the uterine microenvironment, the public’s attitude toward the procedure, and women’s views of donation in light of their own procreative liberty may add greater nuance to these discussions surrounding consent. Given the misconceptions that persist around solid vital organ donation despite decades of public awareness campaigns, the moral concerns surrounding uterus transplantation are unlikely to ever fully resolve. However, the incorporation of additional insights from potential donors and recipients as well as increasing public knowledge of the procedure may eventually warrant reevaluation of such caution surrounding surrogate-decision making for deceased uterus donation to avoid excessively limiting the deceased donor pool, particularly if a substituted judgment standard is mandated.

Yet another challenge posed by deceased uterus donation is when the uterus should be recovered in relation to the procurement of vital organs [16]. Given the recognition that uterus transplantation is an experimental, non-life-saving procedure, initially procurements almost universally occurred after removal of vital organs to avoid endangering the opportunity for life-saving transplantation by contaminating grafts with the vaginal microbiome, jeopardizing necessary vasculature, and causing hemorrhage leading to donor hemodynamic instability [17-19]. However, some teams have opted to remove the uterus first [20], and a prominent new protocol supports procurement of the uterus prior to procurement of other organs to eliminate difficulty preserving the uterine vasculature post-cross-clamp, minimize ischemia of the uterus graft, and lessen operating room crowding during procurement. Although this approach may help ensure that the vessels and ureters retain sufficient length and quality for pancreas and liver transplantation, donor
hemodynamic instability secondary to blood loss during uterus removal could also threaten the viability of the remaining organs [21].

Beyond these medical considerations, prioritizing uterus dissection carries potential social consequences. Putting uterus removal first may inadvertently suggest that the potential lives of children who could be born from a uterus transplant hold more value than the lives of individuals currently alive and in need of a life-saving transplant [22]. Such prioritization of potential lives over the lives of current members of the state could have concerning implications for reproductive health policies. For example, in today’s sociopolitical climate with highly charged debates over pregnancy termination, prioritizing uterus transplantation over life-saving transplants may unintentionally assign a new ethical importance to potential lives, which could be interpreted as strengthening the moral claims of the fetus against a pregnant woman’s best interests. Prioritizing uterus transplantation may also reinforce the flawed notion that a woman’s value lies in childbearing by promoting a woman’s ability to have children overextending the lives of other women and their male counterparts in need of a vital organ transplant. Sensible public health policy requires prioritizing the lives of current living members of the State [23].

Finally, being the last organ removed may significantly increase ischemia time for the uterus, but in vivo studies suggest that the uterine myometrium is resistant to ischemic effects for at least 6 hours and potentially as many as 24 [24]. Therefore, without evidence to the contrary, uterus procurement and other quality of life transplants should take a backseat to procurement of life-saving organs from deceased donors.

LIVING UTERUS DONATION

Like deceased uterus donation, living uterus donation poses its own unique ethical and regulatory challenges at the intersection between transplantation and reproductive medicine, including issues surrounding consent for donation and donor expectations. By far, the most important ethical challenge lies in justifying the harm living uterus donation causes to previously healthy individuals for the benefit of another, which fundamentally contradicts medicine’s commitment to nonmaleficence. Putting this concern aside for a moment, the informed consent process is complicated by family dynamics and concern for coercion [25], the pressure to gestate in our pronatalist society [26,27], and misunderstandings about the purpose of research.

To protect against these threats to informed consent, additional protections should be included in the living uterus donation process, including a private and confidential donor evaluation performed by a team separate from that of the recipient. Furthermore, an independent living donor advocate should support the potential donor, promoting their autonomy by ensuring that they are fully informed, limiting external pressures to their decision-making, and protecting their right to opt out at any time without sharing their reasoning with the recipient. Although potentially difficult in the setting of close ties between the donor and the recipient, these practices mirror standard practices for living donation of life-saving organs and are essential to ward against pressure to donate upon the donor as well as contingencies of donation upon the recipient.

It is also important to clarify the donor’s rights prior to donation. Donors should understand that they lack any legal rights to the donated uterus and regarding any resulting children. Given the transient nature of uterus transplantation, some donors may feel entitled to the donated uterus after its removal from the recipient, or they may regret ever donating and want to effectively “undo it.” Uterus transplantation is novel and the first form of ephemeral transplant practiced, so donors may have a mistaken understanding of what happens with the organ. Transplant teams should proactively clarify during the consent process that the organ becomes the property of the recipient once donated and medical waste once removed. Furthermore, potential donors should understand that their donation does not imply any parental rights with respect to children born from the transplanted uterus. By clarifying this pre-emptively, uterus transplantation will hopefully avoid the controversy over parental rights that has been evident in surrogacy, gamete donation, etc.

As with other reproductive procedures, potential challenges may also develop from the unique relationship between the living donor, the recipient, and the resulting child. Living uterus donors should not expect a relationship with any children born from the transplanted uterus and all communication from nondirected living donors should go through the resultant child’s parents until the child reaches an age of majority. Furthermore, living uterus donors should respect parents’ rights to choose when, how, and what to share with their children about their genesis. Such issues become even more important in the case of directed living donors (e.g. the recipient’s mother, sisters, aunts, etc.), who might otherwise make their donation contingent upon promises of a future relationship with the resulting child.

CALL FOR CAUTION

Limitations in the Justification for Living Organ Donation

Respect for autonomy provides the most basic argument underlying living organ donation by emphasizing others’ right to develop opinions, make decisions, and
choose action according to individual belief and value systems. However, another moral agent is involved in the donation process – the physician – and respect for autonomy does not annul nonmaleficence, or the principle of “first do no harm.” While organ donors may reap emotional rewards from the altruistic gift (indeed, research demonstrates improved self-esteem, happiness, and quality of life after donation [28-30]) or feel a sense of communitarian responsibility to help fellow members of society, the physical risks of living organ donation require consideration. Indeed, evaluating decision-making capacity and ensuring adequate informed consent for any medical intervention necessitates ensuring that a patient is able to make decisions without undue external pressure and coercion, especially in situations where risks greatly exceed individual benefit to a particular patient. Sole focus on avoiding paternalism and protecting negative rights to autonomy is inappropriate; rather, systems must consider all parties’ moral agency and emphasize shared decision-making [31]. Literature discussing how caregivers can (and even should) refuse exceptional patient requests further demonstrates that physicians are not bound to adhere to every patient request [32].

Thus, medicine places stringent limits on living organ donation. Living organ donation is deemed ethical for life-saving organs only when the overall positive harm-benefit ratio, for both the donor-recipient pairing and the donor themself [33-35], cannot be obtained in a less harmful manner. More specifically, for living donation to be ethical, the organ supply from deceased donors must be insufficient, or the organs transplanted from deceased donors must provide significantly inferior outcomes, because otherwise the same outcome could be achieved with less harm. Only because of the perpetual organ shortage and improved outcomes with living donor transplants does society adopt a utilitarian approach to maximize opportunity for life-saving organ transplantation [36].

Application of This Justification to Living Uterus Donation

Applying these conditions to living uterus donation appears initially problematic because living uterus donation serves a quality-of-life enriching rather than life-saving purpose. However, infertility has significant negative psychological effects – in a study of patients with infertility secondary to cancer or its therapeutics, some patients experienced more distress from their loss of childbearing potential than from the cancer itself [37]. Furthermore, the uterus is a non-vital organ, and assuming the donor is postmenopausal (as has been the case in many clinical trials to date), has served its biological purpose in the donor. Together this implies a lower level of harm to the donor. Nevertheless, this does not imply that the living uterus donation procedure is without harm – even if the uterus is no longer needed in the donor, its removal transforms the donor from a healthy person into a patient for the benefit of another. Thus, living uterus donation requires moral justification in line with that required for living kidney and liver donation described previously.

Despite Grade IIIb Clavien-Dindo complications in four of the first 45 living uterus donor cases (11.1%, including ureteral injuries, uretovaginal fistula, and vaginal cuff dehiscence) [38], thus far the procedure does not appear to cause significant morbidity or mortality, although any long-term consequences remain largely unknown. Considering this, the harm-benefit ratio for donors and recipients currently seems reasonable given that many of the recipients have successfully given birth, which in turn provides an emotional and psychological benefit to the donor, especially should the donor and recipient be related. Although both living and deceased donor transplants have led to successful live births, it is not yet clear whether deceased donor uterus transplantation provides a feasible alternative (in terms of both transplant success rates and organ availability) that causes less harm. Therefore, at least for the time being, living uterus donation is ethically justified.

Importantly, this justification is not without conditions. Surgical teams must take the utmost care to avoid preventable harm to donors. For example, surgical teams should take care to avoid sacrificing the ovarian veins, and if the anatomy or surgical methodology requires use of these vessels in a premenopausal donor, should remain especially wary of performing the procedure. Oophorectomy at the time of hysterectomy in premenopausal women leads to a greatly increased risk of morbidity and mortality and is therefore recommended against as a routine practice by the American College of Obstetricians and Gynecologists for pre-menopausal women [39,40].

WHEN THIS JUSTIFICATION OF LIVING UTERUS DONATION FAILS

Traditionally living donor transplantation provides better long-term outcomes than deceased donor transplantation, but it is unclear whether this status quo will be realized in uterus transplantation given that it is transient with explantation upon conclusion of childbearing. Furthermore, although a large number of women suffer from absolute uterine factor infertility, it is difficult to estimate the demand for transplantation given the procedure’s high cost and the presence of alternatives, including surrogacy and adoption. If future research should prove transplantation with deceased donor uteri to be equal to that with living donor uteri, and an adequate number of uteri may be procured from deceased donors, then living uterus donation should be reevaluated and may no longer be
ethically justified [10]. We argue that even if a potential donor makes the autonomous decision to put themself at risk, if a safer alternative exists with equivalent outcomes and sufficient availability, medicine’s commitment to nonmaleficence as well as safeguarding the health of the community at large requires that it protect them from unnecessary harm. While such an approach may minimize the emotional benefit to the donor of participating in uterus transplant, physicians have the primary responsibility to minimize harm and maximize the health of the public at large; thus, such action is not overly paternalistic. Notably, because this justification requires sufficient availability of deceased donors to meet demand, living donor uterus transplantation may remain acceptable in some regions of the world but not in others.

To inform this ongoing ethical analysis, evaluate transplant success, and address the persistent lack of knowledge about long-term living donor outcomes, an international registry should be developed to monitor the progress of uterus transplantation research trials. The International Society of Uterus Transplantation is already working to establish such a registry, including data about both living and deceased uterus donors as well as their corresponding recipients and their pregnancies. In this manner, the reproductive medicine and transplant communities may continue to evaluate the medical feasibility of both forms of transplantation, which will inform whether living uterus donation is ultimately ethically justifiable in the long-term.

CONCLUSION

As a quality-of-life improving, transient transplant requiring organ removal after childbirth to avoid lifelong immunosuppression, uterus transplantation poses unique challenges unlike all other commonly transplant ed organs. Anticipation of the implementation of uterus transplantation outside of the research phase necessitates that the medical community examine not only how deceased and living uterus donation differ medically, but also ethically. Living uterus donation remains justified currently, but if transplantation with deceased donors is similarly efficacious after further study and the deceased donor pool is sufficient, living uterus donation should be reevaluated and may no longer be ethically appropriate. To better inform this ongoing ethical analysis and track long-term outcomes, transplant teams should continue to actively explore both approaches and share findings in an international registry.

Footnote:

While many uterus donors identify as women, trans men and non-binary persons have been identified as a potential pool of donors.
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