REVIEW

Uterus transplantation: state of the art in 2021

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Abstract

Purpose To provide a comprehensive review of uterus transplantation in 2021, including a discussion of pregnancy outcomes of all reported births to date, the donor and recipient selection process, the organ procurement and transplant surgeries, reported complications, postoperative monitoring, preimplantation preparation, and ethical considerations.

Methods Literature review and expert commentary.

Results Reports of thirty-one live births following uterus transplantation have been published from both living and deceased donors. The proper selection of donors and recipients is a labor-intensive process that requires advanced planning. A multidisciplinary team is critical. Reported complications in the recipient include thrombosis, infection, vaginal stricture, antenatal complications, and graft failure. Graft rejection is a common occurrence but rarely leads to graft removal. While most embryo transfers are successful, recurrent implantation failures in uterus transplant patients have been reported. Rates of preterm delivery are high but appear to be declining; more data, including long-term outcome data, is needed.

Conclusions Uterus transplantation is an emerging therapy for absolute uterine factor infertility, a condition previously without direct treatment options. It is paramount that reproductive health care providers are familiar with the uterus transplantation process as more patients seek and receive this treatment.

Keywords Uterus transplantation · Reproductive surgery · Uterine factor infertility · Mullerian agenesis

Introduction

Uterus transplantation (UTx) is a burgeoning field of transplant surgery that intersects multiple domains and disciplines. UTx is an emerging therapy that is transitioning from an experimental phase to an established clinical practice, with some centers beginning to perform the procedure outside of clinical trials. While there may be alternate means of family building available to some couples including adoption and gestational surrogacy, these may not be accessible or desired for personal, cultural, or ethical reasons. For those desiring to carry their own child, UTx is the only treatment for absolute uterine factor infertility, which affects an estimated 3–5% women worldwide either by congenital (e.g., mullerian agenesis) or acquired (e.g., obstetrical) causes [1].

Successful uterus transplantation in humans was preceded by extensive work with animal models, including rats, mice, rabbits, pigs, sheep, and primates [2–5]. The first birth from a living donor (LD) took place in Sweden in 2014 [6], with the first birth from a deceased donor (DD) in Brazil in 2016 [7]. As of 2021, there have been more than 31 babies born following this procedure, with an increasing number of research programs being set up around the globe (Table 1). As further evidence of the increasing activity in this field, in October 2020, the American Medical Association approved seven category III Current Procedural Terminology (CPT) codes for uterus transplantation–related procedures to take effect in July 2021[22]. Nonetheless, safety concerns as well as use of health care resources require an objective assessment and further research [1]. We review the preliminary reports from centers with active uterus transplant research programs and forecast the future of this approach to uterine factor infertility.

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Table 1 Reports of live births from uterus transplantation. This table includes all published reports as well as two additional live births from Cleveland Clinic. The true number of live births from UTx is undoubtedly higher, as this table does not include media reports or unpublished data of live births known to have occurred in the Czech Republic, China, Sweden, Italy, India, France, Pennsylvania, and others (publications are still forthcoming)

Running count	Team, publication year	Author	Antenatal complications	Gestational age (weeks)	Birth weight (grams)	Apgar scores
1	Sweden, 2015	Brannstrom et al. [8]	Preeclampsia Single kidney	31 + 5	1775	9-10-10
2–3*	Sweden, 2016	Brannstrom et al. [9]	Intrahepatic cholestasis	34 + 6	2335	9-10-10
4	Sweden, 2017	Castellon et al. [10]	None	35	2700	8-8-8
5–6*	Sweden, 2017	Castellon et al. [10]	Preeclampsia Intrahepatic cholestasis PPROM Single kidney	34 + 5	3074	3-7-10
7	Sweden, 2017	Castellon et al. [10]	Preeclampsia Single kidney	35 + 3	2552	9-10-10
8–19**	Dallas, 2018, 2021	Testa et al. [11] Johannesson et al. [12]	Gestational hypertension (2 pregnancies), preeclampsia (1 pregnancy), gestational diabetes (1 pregnancy)	Median 36+6 (range 30+6 from 38+0)	Median 2890 (range 1770 to 3140)	Median 8–9 (range 4–9 to 9-9)
20	Brazil, 2019	Ejzenberg et al. [13]	Pyelonephritis	35 + 3	2550	9-10-10
21	Sweden, 2019	Jones et al. [14]	None	37	2600	9-10-10
22	Sweden, 2020	Brannstrom et al. [15]	None	36 + 1	2894	9-10-10
23	Cleveland, USA, 2020	Flyckt et al. [16]	Placenta accreta Impaired renal function	34 + 1	1930	8-9
24	Lebanon, 2020	Akouri et al. [17]	Premature contractions, shortened cervix	35 + 1	2620	9-10-10
25	Germany, 2020	Brucker et al. [18]	Preterm rupture of membranes	35 + 1	2180	9-10-10
26	Germany, 2020	Brucker et al. [18]	Oligohydramnios	36 + 3	2500	8-8-8
27	China, 2020	Huang et al. [19]	Subchorionic hematoma	33 + 6	2000	10-10-10
28	Czech Republic, 2020	Fronek et al. [20]	Preterm contractions Gestational diabetes	34 + 6	2376	7-9-9
29	Cleveland, not yet published	Our group, not yet published	Subchorionic hematoma	34 + 6	2600	7-8
30	Cleveland, not yet published	Our group, not yet published	Gestational diabetes, gestational hypertension, PPROM	34 + 2	2480	8-9-9
31	Cleveland, not yet published	Our group, not yet published	None	37 + 1	3022	8-9

*Both of these women have delivered a second child [21]

**One patient in this cohort delivered a second child [12]

Multidisciplinary team and donor selection

UTx requires significant expertise and extensive coordination between multiple specialties including transplant surgery, gynecologic surgery, reproductive endocrinology, psychology, bioethics, and high-risk obstetrics. UTx centers must decide early on to adopt a living donor (LD) model, deceased donor (DD) model, or a hybrid model. In a LD model, donors can be categorized by their relationship to the recipient, either known ("directed") or anonymous ("non-directed"). In the Swedish trial, all were directed donors, with the most common relationship being mother-to-daughter donation [8]. For centers utilizing a DD model, all reported transplants have used brain-dead donors as opposed to Donation After Cardiac Death (DCD) donors. The advantages and shortcomings of each approach have been an area of intense debate [23]. Compared to DDs, LDs allow for a more thorough medical evaluation of the donor and more control in timing of the procedure. However, a LD model involves risks of physical and psychological harm to the donor (see "Complications" below). The

primary disadvantage of the DD is a predicted shortfall of appropriate donors [24]. Comparative success rate between DD and LD models is not known and is an area of ongoing investigation.

Criteria for donor selection vary by institution. There is no consensus regarding age, BMI, and number of living biological children. Given that UTx is a nascent field—and still considered to be experimental by many active centers—donor and recipient selection is by necessity more stringent. A history of infertility, recent cancer diagnosis, and chronic medical conditions that compromise graft survival, recent infections, and fibroids are all criteria cited in protocols to restrict donor selection in a UTx study [8, 16, 25] (Supplemental Table 1). Given the possibility of an undiagnosed uterine factor infertility, a donor with proven childbearing is preferred, though several successful livebirths have resulted from uteri from nulliparous donors [26]. Likewise, premenopausal women are preferred, but again, many transplants from postmenopausal LDs have successfully led to live births, including most of the directed LDs used in Sweden. However, a postmenopausal uterus may present technical challenges due to the smaller vessels supplying/draining the uterus, which led the Swedish group to preoperatively treat these donors with estrogen to improve the quality of the supporting blood vessels. Long-term problems for the recipient or for the offspring born from a donated postmenopausal uterus are not known, but higher rates of preeclampsia, thromboembolism, and preterm delivery with a postmenopausal uterus have been hypothesized [27].

Recipient selection

The early stage of UTx means that criteria for potential recipients must be strict to ensure safety and determine treatment efficacy before expanding the procedure more broadly. For ongoing research trials in the USA where details are available, potential recipients must be women of childbearing age (i.e., prospective recipients at our institution must be 18–45 years old with embryos produced between ages of 21–39) with a patent vaginal canal and absolute uterine factor infertility (AUFI), though it is generally accepted that eventually UTx may be offered to transgender women[28]. Prospective candidates must be willing to undergo rigorous medical and psychosocial evaluation; undergo multiple surgical procedures including IVF, uterine transplant, cesarean section, and eventual hysterectomy; receive high-dose immunosuppressive therapies; receive vaccinations; adhere to strict medication schedules; and be able to provide informed consent. Typical exclusion criteria include tobacco or substance dependence, history of chronic disorders (e.g., hypertension, diabetes, hepatitis, HIV, heart/liver/kidney/CNS disease) or cancer (except for early-stage cervical cancer), active or chronic infections,

high BMI, a low lying pelvic kidney, or medical history that puts them at high risk of surgical complications[16, 29].

Prospective recipients go through an extensive evaluation involving multiple interviews, imaging, and laboratory tests. Prior to the transplant procedure itself, they are required to undergo IVF to cryopreserve a pre-determined number of high-quality blastocysts (i.e., a minimum of 6 is required at our institution [16]). To achieve this, multiple rounds of IVF may be required with or without preimplantation genetic screening for aneuploidy (PGT-A); PGT-A in UTx is not universally performed and is an area of debate: on one hand, most potential recipients are in an age category shown in multiple trials to not benefit from PGT-A[30], while on the other hand, transferring known euploid embryos could potentially shorten time to pregnancy and overall length of immunosuppression exposure [31].

Once a sufficient number of blastocysts are cryopreserved, the prospective recipient is eligible to be added to the transplant list, where they wait to be matched with an eligible donor. ABO status is the primary criteria in matching donors to recipients. CMV status is used by many institutions to match donors and recipients, but this is not universal[16].

Organ procurement

In a LD model, the uterus is procured via open or laparoscopic hysterectomy in a procedure that is similar to or greater than a radical hysterectomy in complexity and morbidity. In a DD model, the uterus is procured through a large cruciate (or modified cruciate incision known as a Tzakis incision [29]) along with life-saving organs. For both DD and LD procurement, obtaining an adequate venous outflow is critical, as one of the most common reasons for graft loss is venous thrombosis [29]. Procurement commences with the tagging the round ligaments, followed by entering and opening the retroperitoneum from the pelvic brim to the vesicouterine peritoneum. The uterine and utero-ovarian veins (also known as the *inferior* and *superior uterine veins*, respectively [32]) are typically isolated for use. DD surgery differs from LD surgery primarily in its greater radicality [7, 33]. Inflow to the graft is achieved via the inferior uterine artery and may require a patch of the internal iliac artery. Vascular reconstruction prior to implantation has been attempted but has largely been unsuccessful due to thrombosis [34, 35].

Venous outflow to the graft is most commonly achieved through anastomosis of the inferior uterine vein to the internal iliac vein. While a non-issue in DD procurement, the dissection of the ureter from the uterine veins is the most time-consuming—and most prone to complications [26]—step in LD procurement, given the close proximity of the ureter [6]. To avoid these challenges and risks, the use of the ovarian and

superior uterine veins has been reported [35–37], though with much controversy regarding the former. Removal of the ovaries in order to utilize the ovarian veins is associated with early menopause and increased all-cause mortality for women under 65[38]. In contrast, utilizing the superior uterine vein proximal to the ovary can spare the ovary [35] and proof of concept studies using baboons demonstrated live births following exclusive use of superior uterine veins, though these vessels are of considerably shorter length [4, 5]. At least two live births in humans have been achieved with this technique [25].

Following uterus procurement, the transplanted organ undergoes a period of ischemia-reperfusion time including warm ischemia time (the time from arrest to cold perfusion) and cold ischemia time (cold storage) [39, 40]. It is of great importance to select appropriate preservation methods to reduce cold ischemia injury such as Euro-Collins solution and University of Wisconsin (UW) solution [34, 41, 42]. Research on the limits of allowable warm ischemia time and how to reduce warm ischemia injury in uterus transplantation is ongoing [43, 44].

Transplant technique

Although the steps in the procurement of the uterus may vary considerably, the steps of the transplant surgery do not. If procurement occurs in the same institution as the transplant (as is typical in the LD setting), then the steps for initiation of the procedure in the recipient are the same. However, if the organ is procured from a deceased donor at a separate site, then coordination with the procurement team to minimize ischemia is critical. In both circumstances, the recipient surgery is not started until the procurement team has confirmed adequate vascular pedicles and no uterine pathology. The LD graft includes the uterus with its entire parametrium, the inferior uterine arteries and veins, the superior uterine vessels along with the round ligaments. The DD uterus graft includes the donor internal iliac arteries and veins, which can be procured in the donor and be used for the anastomosis. The inferior uterine (living donor) or the internal iliac (cadaveric donor) vessels are anastomosed in an end-to-side fashion to the recipient external iliac vessels. The vaginal anastomosis is typically performed following vascular anastomosis. Since impaired venous outflow is thought to contribute significantly to the high vascular complication rate encountered in UTx, several centers have considered augmenting the outflow (or rescuing an impaired one) by anastomosing one (or both sides) of the utero-ovarian veins to the recipient external iliac vein(s). An intraoperative vascular ultrasound is performed to assess arterial and venous intraparenchymal waveforms, which are a very sensitive correlation of tissue perfusion [45].

Complications

Complications can occur in both the recipient and in the LD. Reported complications in the LD include hemorrhage requiring reoperation, vaginal cuff dehiscence, and buttock pain [14, 26, 46]. A 5–14 % frequency of ureteric injury including fistula is the most frequent Clavien-Dindo III complication [14]. There is also an increased risk of mental health–related quality of life issues in women that have donated their uterus to a recipient who did not have a successful outcome from the transplant [47].

In the recipient, the most common reason for graft removal is thrombosis of the artery or vein (overall vascular complication rate is around 20%) [14]. All centers have reported this complication. This is typically an immediate postoperative complication and requires a graft hysterectomy. For this reason, protocol transabdominal ultrasound is performed frequently in the early postoperative phase and on a monthly/bi-monthly basis after the first month. MRI and CT angiograms are performed when concerns on the perfusion of the graft are present. Intraoperatively, systemic heparinization is often utilized in donors and/or recipients to reduce thrombosis.

Most infections are prevented by prophylactic antimicrobial therapy. This typically consists of trimethoprim-sulfamethoxazole (or dapsone if sulfa allergy) for 6 months to prevent *Toxoplasma gondii*, Nocardia, *Pneumocystis jirovecii*, and Listeria; acyclovir/valganciclovir prophylaxis for 3–6 months after transplantation to prevent CMV and other systemic viral illnesses; and antifungal prophylaxis (e.g., *Candida albicans*). Given the possibility of varicella zoster virus reaction, consideration should be given for ongoing acyclovir prophylaxis after the completion of CMV prophylaxis. The main infections to be considered in donor-recipient mismatch are CMV, EBV, HSV, and HPV. A mismatch may have consequences for the recipient in terms of anti-rejection drug levels and graft rejection, infected graft resulting in removal, pregnancy-related complications, and post-transplant lymphoproliferative disorders (PTLD).

Stricture at the vaginal anastomosis site is a common occurrence that may require intervention. At the time of the transplantation procedure, there is often a funneling at the anastomosis because of diameter discrepancy, which can contribute to later vaginal stricturing. Techniques to prevent stricture include stenting the vagina, use of vaginal estrogen and vaginal dilators pre- and postoperatively [48, 49]. An adequate vaginal site is important for menstrual effluent as well as access to the cervix for cervical biopsies to assess rejection and for embryo transfer.

Fixation of the donor uterus to avoid prolapse is accomplished by suturing donor round ligaments and utero-sacral ligaments to the recipient's equivalent structures. Paracervical tissue can also be sutured to the recipient's small uterine remnants.

Monitoring for viability and rejection

While the ultimate measure of success in UTx is the safe delivery of a liveborn child, the US Uterus Transplant Consortium (USUTC) has defined a series of milestones: technical success, menstruation, embryo implantation, pregnancy, delivery, graft removal, and long-term follow-up [32]. Technical success is defined by established outflow and graft viability following surgery. In the months following the transplant, the graft is monitored closely for signs of rejection.

Unlike other abdominal organ grafts—which cannot be easily accessed after transplantation—the uterine cervix can be accessed through a non-invasive gynecologic examination in the office. The cervix of the transplanted uterus is biopsied for evidence of rejection, and biopsies are scored through standardized criteria [50]. In addition, regular ultrasounds are performed to ensure ongoing perfusion to the graft and to measure graft size.

As in other solid organ transplants, immunosuppression in the recipient is essential and is begun with induction therapy at time of transplant (typically thymoglobulin, mycophenolate mofetil [MMF] or azathioprine, methylprednisolone; tacrolimus is begun on postoperative day 1) and transitioned to maintenance therapy (tacrolimus, prednisone). Due to teratogenicity of MMF and need for eventual transition to azathioprine, many programs forgo use MMF entirely for azathioprine.

Graft rejection is a common occurrence in solid organ transplantation and is not considered a complication. The majority of rejection episodes in the literature have been cellular rejection, with just our group reporting the first possible humoral rejection [16]. In reported rejection episodes in the initial Swedish, Czech, and Baylor trials (at least 27 episodes in total[51]), all were treated successfully with complete resolution. Rejection is typically managed with pulse corticosteroids, though in our case of severe rejection, thymoglobulin, plasmapheresis, and IVIG were employed due to the severity and concern for a humoral component. In our case of severe rejection, the rejection was successfully treated and pregnancy was achieved. In the worst case of irreversible rejection, studies of UTx rejection in macaques demonstrate that this is not fatal or life-threatening, even when hysterectomy is not performed [52].

Embryo transfer and implantation failure

In the original Swedish trial, 12 months elapsed post-transplant before proceeding with embryo transfer. In the Baylor trial, embryo transfer was first performed at 6 months; this was later shortened to 3 months for recipients meeting certain criteria, with the justification to reduce total recipient-graft time [51]. Uterine assessment by either saline infusion sonogram or hysteroscopy is performed prior to transfer, as polyp formation is possible in the transplanted uterus following pre-transplant evaluation (typically also by hysteroscopy) of the uterus demonstrating a normal cavity.

Embryo transfer is typically no different in uterus transplant recipients, except in the case of vaginal stricture, which is a common complication which can present technical challenges [48]. Improper use of vaginal dilators can compound the problem by increasing the vaginal length from introitus to point of stricture. In cases of vaginal stricture, exam under anesthesia with manual dilation and/or excision has been performed with success. In addition, use of a vaginal self-expanding stent has been reported in the literature prior to embryo transfer [53].

Published data on IVF outcomes in UTx are scarce [12, 21], and protocols, practice patterns, and pregnancy rates with IVF vary greatly worldwide across geographical areas [54] irrespective of UTx. Of the first 52 UTx recipients worldwide, only 42% patients with a functioning graft ("technically successful transplants") achieved a pregnancy as of April 2020 [21]. However, pregnancy rates for patients with a functioning graft are much higher at both our center (66.7%) and Dallas (79%) as of February 2021 [12]. While all of the pregnancies at our center (which exclusively utilizes DDs) were established after only 1 or 2 embryo transfers, recurrent implantation failure (>3-4 transfers without biochemical pregnancy) has been experienced at our institution, as well as others utilizing LDs, for a subset of patients [12, 49]. Whether or not DD uteri are more at risk of implantation failure than LD, either due to undiagnosed subfertility in the donor, effects of prolonged cold ischemia, or other reasons, cannot be determined at this time. Of note, the Czech trial had no difference in pregnancy rates between LD and DDs [49].

Pregnancy outcomes

While the number of centers performing UTx and subsequent live births continues to grow rapidly, the reported pregnancy outcome data is still relatively limited [21]. Questions regarding antenatal care and optimal timing of delivery remain. It is also unclear if there are any major differences in obstetric outcomes after living vs deceased donor transplantation secondary to the small number of live births reported after deceased donor transplantation.

Currently, antenatal care guidelines are extrapolated from pregnancy in women after other solid organ transplants. Careful monitoring of immunosuppression with serum drug levels, serial surveillance of fetal growth, prevention of maternal infections, and monitoring of blood pressure and kidney function are among the major guiding principles. Tacrolimus, azathioprine, and prednisone are the most commonly used medications. Tacrolimus is not associated with teratogenesis;

however, maternal nephrotoxicity can be seen. Azathioprine is also not considered to be teratogenic in humans but is associated with preterm delivery and low birth weight. The overall rate of fetal malformations with prednisone use is equal to the general population; however, data regarding risk of oral clefting is conflicting [55].

A total of 8 live births have been reported from the initial cohort of the Swedish trial [56]. Preterm preeclampsia was reported in 3 cases with all 3 women having unilateral renal agenesis [10]. Also reported were two cases of intrahepatic cholestasis, an unusually high proportion which has not been seen in other reports. Other complications included pyelonephritis, subchorionic hematoma, and PPROM [14]. In 2019, Jones et al. [14] published a review of the first 45 cases of human uterine transplantation. At that time there were 18 reported live births in the media but only nine with pregnancy outcome data available. One of these followed a deceased donor transplant and the rest were a result of living donor transplants. Overall, the mean gestational age of delivery was 34 + 6 weeks with a range of 31 + 5 to 37 weeks with mean birth weight of 2500 g and range of 1775 to 3074 g. Since that review, many more live births have been reported in the media and the literature and several programs have ongoing pregnancies. Table 1 summarizes reported all reported pregnancies including those reviewed by Jones et al. in 2019; this table does not include media reports or unpublished data of live births known to have occurred in the Czech Republic, China, Sweden, Italy, India, France, the USA, and others.

In all cases of uterus transplantation, delivery is performed via cesarean section [6, 14, 16, 25]. Vaginal delivery is contraindicated. Transplantation does not correct for the appropriate pelvic support of the uterine/vaginal anatomy, there would be risk to vaginal and arterial anastomotic sites during labor, and it is not clear that appropriate labor would result. Animal data after transplantation also point to high risk of stillbirth after vaginal delivery [5].

Long-term outcomes

In current protocols of active centers, hysterectomy is planned after 1–2 deliveries either at the time of cesarean delivery or by interval hysterectomy [12]. During removal of the uterus, which is otherwise performed in typical fashion, the donor vessels are ligated proximal to the uterus. Immunosuppression is immediately stopped. While renal injury has been observed in UTx patients, in our experience, creatinine levels have returned to baseline following cessation of immunosuppression [57].

Given the novelty of the procedure, long-term outcomes of uterus transplantation are not known. Data is needed to assess long-term effects to living donors, recipients with graft failure, recipients with successful pregnancies, families of donors and recipients, and offspring [1]. These data should include not just clinical outcomes but also psychological outcomes for these groups. For example, poor outcomes in the recipient are associated with psychologic and stress in the recipient couple [47, 58].

Ethical considerations

A robust ethical foundation is the core of UTx research [1, 23, 59, 60]. As UTx research takes place, the research team must consider the ethical issues that arise at each stage of the research process, beginning with the initial decision to develop a UTx program to adapting to emerging data about successes, setbacks, and challenges. Ethical considerations must also be woven into the methodological design, recognizing that how outcomes, end points, and adverse events are defined will frame what known risks participant may be exposed to and how those risks may be allocated in the maternal-fetal dyad if pregnancy is achieved. Informed consent is requisite to ensure that women with UFI make informed decisions about participating in UTx and, in doing so, understand that UTx is an experimental procedure for which more data is required to obtain a full picture of its safety and efficacy for family building.

Both informed consent and study design are iterative processes that must be attuned to immediate concerns and future considerations in order to pave the way for clinical implementation of UTx. As new data emerge, research teams have an obligation to revisit approaches to each stage of the UTx process and determine if study procedures must be modified to reduce risks or increase probability of success. While research is underway to define surgical and medical approaches, there is also a need for ongoing studies to understand outcomes, experiences, and preferences of women who participate in a trial so that both the research and translational stages meet the needs of patients, families, and society [61]. For instance, preliminary ethical frameworks of UTx [59] centered on its potential to provide the experience of gestation for women with AUFI. However, growing evidence suggests that these patients' motivations are more nuanced and complex than simply seeking "an experience of pregnancy," which had been an initial framework for the ethics and science of UTx [59–61]. Since then, data about what the "experience of pregnancy" means to women, in addition to understanding women with AUFI's values, needs, and preferences about family and reproductive autonomy, shape how we move forward in this scientific endeavor. Researchers must also critically analyze the data to determine if and when equipoise in the research process has been reached, indicating that one approach to UTx may be superior to another. This may also mark a key stage at

which sufficient data are achieved to consider UTx as a therapeutic option for patients with AUFI. Issues of justice must guide this process to ensure that a ground-breaking approach to AUFI may be available to the patients and communities who would potentially benefit from it. This entails not only long-standing issues of justice related to patients' access to infertility care, but it also includes ensuring that existing health care disparities and social inequalities do not shape how UTx is made available to diverse patient populations.

Conclusion

In summary, UTx requires a team approach with stringent criteria and objective measure of outcomes. The use of DDs removes the risk of complications for a LD; however, there are insufficient ideal candidates for DD [24]. In the LD model, active research is required to simplify the procurement procedure, decrease the operative time, and develop minimally invasive techniques. The use of alternative venous return from the uterus that requires less dissection and morbidity needs investigation. This may require applying techniques commonly used in transplantation such as venous extension grafts. Simplification of the anti-rejection drug protocols may also decrease morbidity without compromising rejection frequency. Recent research in organ perfusion techniques ex vivo may delay ischemia and widen the organ donor radius for each center [62]. Many have advocated that uterus transplantation should no longer be considered experimental, though only a few centers perform uterus transplantation outside of clinical trials. There are significant risks in uterus transplantation that must be addressed within a robust informed consent. Given the preliminary success of uterus transplant programs worldwide and the patient-driven demand for the procedure, uterus transplantation is anticipated to continue to grow rapidly with the intent of developing a safe, efficacious treatment for absolute uterine infertility.

Declarations

Conflict of interest The authors declare no competing interests.

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