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Reproductive Technology Considerations in Uterus Transplant

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Abstract: Uterus transplantation (UTx) provides a new pathway to parenthood for patients with absolute uterine factor infertility. The application of reproductive technologies, such as in vitro fertilization, embryo cryopreservation, and frozen embryo transfers, for this unique population, is particularly nuanced and continually evolving. There are important pretransplant and posttransplant reproductive considerations for physicians and patients anticipating UTx. As with any rapidly evolving medical innovation, efforts to consolidate experiences and knowledge by centers offering UTx is paramount.
Key words: uterus transplant, Mayer-Rokitansky-Kuster-Hauser, MRKH, uterine factor infertility

Uterus transplantation (UTx) has expanded family-building options for patients with absolute uterine factor infertility (AUFI). There are many unique considerations about the application of reproductive technologies with this experimental treatment. This review will discuss the current framework and evolving practices of reproductive care for patients considering and pursuing UTx.

Unlike the vast majority of organ transplants, UTx is not lifesaving, but life-enhancing, akin to face or limb transplants. In addition, uterus transplants are temporary; they remain in place through one or multiple live births and are removed to obviate the need for lifelong immunosuppression. UTx has, to this point, been conducted as investigational, performed under strict inclusion criteria. At the time of preparation of this publication, UTx has only been performed in cisgender women with AUFI. AUFI is infertility from uterine absence secondary to congenital or acquired disease (eg, hysterectomy for postpartum

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hemorrhage or malignancy), or a nonfunctional uterus (eg, secondary to leiomyomas or Asherman syndrome).[1] The true prevalence of AUFI is difficult to determine. Given the incidence of congenital absence of the uterus or Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome is 1:4500[2] and estimates of the women 18 to 49 years of age in the United States from census data, we estimate 15,000 reproductive aged women in the United States have congenital AUFI. In addition, fragmented reviews of US hysterectomy data estimate 9.5 million reproductive age women have acquired AUFI.[3]

Pretransplant Considerations

PATIENT SELECTION

Appropriate candidate selection is the first critical consideration when reviewing the role of UTx. Despite the broad range of AUFI etiologies, nearly 90% of UTx occurred in patients with MRKH syndrome.[4] Patients with Asherman syndrome and hysterectomy after obstetrical hemorrhage and sarcoma, have also received UTx. Clinical trials expanding the indications for UTx including, complete androgen insensitivity syndrome (karyotype 46, XY) and transgender individuals, are currently unavailable. Observational studies of potential recipients, demonstrate the diversity of patients considering UTx. Although many centers restrict enrollment to nulliparous patients, ecological studies indicate strong interest among parous patients. Among respondents, 17% had a least 1 biological child.[5] Acceptable medical and nonmedical exclusions require constant re-evaluation. We will discuss current rationale for more stringent inclusion criteria adopted by most UTx trials (Table 1).

MRKH syndrome is a congenital disorder with uterine and upper vaginal agenesis or aplasia, normal secondary sexual characteristics, and 46, XX karyotype.[6] There is a genetic predisposition, but the patterns remain incompletely understood. Some cases appear sporadic, though emerging familial studies, discordant twin pairs, and comprehensive next-generation gene sequencing suggest an autosomal dominant inheritance pattern with incomplete penetrance.[7]

MRKH syndrome is classified as type I or type II.[8] Type I MRKH patients account for 50% to 70% of cases and have isolated uterine and vaginal aplasia.[8] Patients with type II MRKH have additional manifestations including skeletal, cardiac abnormalities, sensorineural, and conductive hearing loss.[6,8] Renal anomalies, the most common extragenital abnormalities, occur in 30% to 40% of all MRKH patients. Unilateral renal agenesis (~50%), pelvic kidney, duplex kidney, and horseshoe kidney have been observed. Renal abnormalities are important because UTx patients, like all donor organ recipients, require immunosuppression to prevent graft rejection. Tacrolimus, a commonly used immunosuppressant, is renally cleared. Given the potential for calcineurin-inhibitor related renal damage, some protocols exclude patients with renal anomalies. However, there have been at least 4 UTx recipients with renal malformations, including single and unilateral pelvic kidney.[4,9] There was a disproportionately higher rate of pre-eclampsia after UTx in patients with single kidneys necessitating preterm delivery (~75%), compared with those without renal abnormalities, although given the small number it is unclear if this is a significant increase.[10]

CREATION OF THE NEOVAGINA

For recipients with a congenitally absent or aplastic vagina, a well-developed vagina prior to UTx is essential. The recipient vagina is required to create the vaginal-vaginal anastomosis during transplantation and anastomosis patency is needed to access the grafted cervix for biopsies to monitor for rejection, and to perform

TABLE 1. Recipient Requirements by Selection of Clinical Trials

Clinical Trial and Location	Year Clinical Trial Established	Minimum Number of Cryopreserved Embryos	PGT-A Required	Renal Pathology Excluded	Age
Baylor University Medical Center Dallas, Texas	November 2015	At least 2 d 5–6 euploid blastocysts of satisfactory quality, increased to 4 good-quality euploid blastocysts midway through study	Yes	Exclude individuals with renal malformations (not including single kidney)	20-35 at the time of IVF
Cleveland Clinic Cleveland, Ohio	October 2015	6	No	Exclude individuals with presence of low-lying pelvic kidney(s)	21-45 (embryos produced between age 21-39)
Institute for Clinical and Experimental Medicine Prague, Czechia	October 2015	10	No	Not specified	18-40
Hammersmith Hospital, Imperial College NHS Trust London, UK	February 2019	≥ 10 embryos	Not specified	Exclude individuals with renal pathology	24-38 (or 40 if eggs frozen <38)
University of Pennsylvania, Philadelphia, Pennsylvania	November 2017	≥ 2 high quality blastocysts	No	Exclude individuals with renal abnormalities (including single kidney or pelvic kidneys)	21-40

IVF indicates in vitro fertilization; PGT-A, preimplantation genetic testing for aneuploidy.

embryo transfers (ETs). Recommendations for an adequate neovagina include: dimensions of 6 cm by 2 cm, tissue elasticity, functional vaginal epithelium, and natural anatomical axis between the bladder and rectum.[11] Approaches to establishing a neovagina range from nonsurgical (self-dilation) to surgical methods using intra-abdominal traction (Vecchietti procedure) or transplanted tissue (eg, intestinal, skin flaps).[11] UTx has been performed in recipients with vaginas present from birth and neovaginas created by self-dilation, laparoscopic Vecchietti procedures,[4,12] surgically dilated vaginas,[9] skin-graft,[9] and intestinal neovaginas.[11] There is no consensus about the optimal method to achieve a successful graft and avoid postoperative vaginal stenosis. The American College of Obstetricians and Gynecologists (ACOG) recommends self-dilation as a cost-effective first-line treatment with high success rates (75% to 95%) and no surgical morbidity. Long-term dilation or regular penetrative vaginal intercourse is required to maintain patency.[13,14] The Vecchietti procedure uses progressive transabdominal traction on sutures below the peritoneum attached to a plastic olive at the vaginal dimple. It offers low complication rates and high anatomic success rates without the need for intercourse or self-dilation to sustain

patency.[15] Surgical vaginal reconstruction using skin or intestinal tissue is an exclusion criterion in some trials given high death rates after uterovaginal anastomosis in grafted vaginas of patients with Mullerian anomalies.[16] A recent review concluded self-dilation or surgically created neovaginas with nontransplanted tissues (either via a Vecchietti procedure or Wharton-Sheares-George vaginoplasty whereby a neovagina is created by dissecting the vesicorectal space) are likely the most appropriate methods for neovaginal creation in UTx patients, though more longitudinal research is warranted.[11]

ASSESSMENT OF REPRODUCTIVE POTENTIAL

Given the goal of UTx is for individuals with UFI to carry and deliver a live-born child, candidates must have adequate reproductive potential. At present, UTx grafts the donor uterus, cervix, and upper vagina. Importantly, fallopian tubes are not transplanted and pregnancy following UTx requires assisted reproduction with in vitro fertilization (IVF). Age is the most significant predictor of female fertility, driving both the quantity, quality, and aneuploidy-risk of embryos. Consequently, existing trials have age limits, with the maximum age being 40 years, often paired with the requirement that untested cryopreserved embryos are created before the age of 38, though older euploid embryos may still be eligible for transfer.

Patients listed for UTx have already undergone ovarian stimulation with exogenous gonadotropins, oocyte retrieval, and embryo cryopreservation to ensure an adequate number of embryos are available for transfer after transplant. Cryopreservation of embryos before UTx has been a fundamental prerequisite for trial eligibility to avoid posttransplant ovarian stimulation and retrieval that could affect and prolong immunosuppressive regimens or disrupt the vaginal or vascular anastomoses of the grafted organ. All ETs after UTx, used autologous, or a patient's genetic embryos. Donor embryos have not been transferred, though use of donor oocytes and sperm are permitted and may expand the pool of acceptable recipients.

Data regarding the reproductive potential MRKH patients, though limited and retrospective, are reassuring. They have spontaneous ovulation and normal ovarian reserve.[17] Ovarian anomalies are rare, and include unilateral agenesis, ectopic location, polycystic or streak morphology. The ovaries are occasionally displaced cranially and laterally to the external iliac arteries,[2,6] though most reported oocyte retrievals are performed transvaginally.

Embryo banking in UTx candidates has proven to be largely efficient and straightforward. Most cycles used antagonist protocols with an average of 2 retrievals before transplantation to bank sufficient embryos.[4,18,19] Experience from the first 9 patients in the Czech trial reported an average of 1.9 oocyte retrievals to amass a minimum of 10 blastocysts.[4] Cleveland Clinic investigators reported data from 10 cycles completed by 8 patients enrolled in their clinical trial. Of the 10 retrievals, 8 were completed transvaginally—one required a transabdominal and the other a transvesical approach. An average of 14 oocytes were retrieved per cycle, yielding an average of 8 blastocysts.[19] Of the 20 recipients in Baylor's trial, 17 met banking criteria of 2 to 4 euploid embryos after a single retrieval.[20]

Although ideally avoided, there have been successful post-UTx oocyte retrievals. Two recipients in the German trial required additional cycles. Patients underwent antagonist protocols and uncomplicated transvaginal oocyte retrieval despite ovariopexy performed during UTx to lateralize the ovaries. A fresh single blastocyst was transferred with 600 mg of vaginal micronized progesterone supplementation, leading to

successful live births in both patients.[18] Baylor also reported 2 patients cumulatively requiring 6 post-UTx retrievals after multiple failed transfers.[20]

There is no consensus on the minimum number of embryos that should be cryopreserved before UTx. Clinical trials require a broad range of 2 to 10 embryos (Table 1). This heterogeneity reflects variable laboratory practices, outcomes, and legal restrictions dictating what stages of embryos can be cryopreserved. Although the rationale for quotas are well-intentioned (to avoid a posttransplant oocyte retrieval for its potential negative implications on the graft, infection risk, and immunosuppressive regimen), they may produce an undue financial burden to undergo UTx.

A recent review summarizing proposed recipient criteria, suggested recipients cryopreserve more than "8 normal embryos."[21] If we interpret this to mean euploid, it is important to underscore there is no formal recommendation for the exclusive transfer of preimplantation genetic testing for aneuploidy (PGT-A)-tested embryos after UTx. Universal versus targeted PGT-A remains controversial and highly variable even in routine fertility treatment and there is similarly no convention for UTx trials.[22] Adopting PGT-A in UTx patients is rooted in an effort to utilize all available tools to maximize pregnancy and live birth and minimize a recipient's time on immunosuppression.[20] However, PGT-A has a false-negative rate of 1% to 3%. Furthermore, euploid embryos can fail to implant and do not prevent miscarriage. PGT-A may reduce the sequelae of transferring an aneuploid embryo (eg, implantation failure, pregnancy loss), however, this should be balanced with the age-specific risk of aneuploidy. If embryo banking is performed at a relatively young age, PGT-A is arguably less useful. The greatest benefit of PGT-A has been demonstrated in women older than 38 and most UTx clinical trials recommend banking before this age.[22] Universal PGT-A may unethically restrict access given additional costs. PGT-A use is best tailored to age at embryo banking, patient preference, cost, and clinic-specific performance.

It is worth noting in our experience, the efficacy of noninvasive prenatal genetic testing (NIPT) with cell-free DNA (cfDNA) has been variable after UTx. Our first recipient successfully conceived after transfer of a euploid embryo by PGT-A. Her cfDNA result was "high risk" because of low fetal fraction (1.8%). This was partially attributed to concomitant use of therapeutic enoxaparin for a thrombosis —a known risk factor for low fetal fraction.[23] However, our second recipient had similar findings. NIPT at 16 weeks' gestation was "no call" given insufficient fetal fraction (2.8%). Both patients had reassuring sequential screening, nuchal scans, and healthy live births. NIPT has been found to be unreliable after other solid organ transplants as grafted organs contribute significantly to cfDNA.[24] To our knowledge, failure of cfDNA after UTx has not previously been described. If others experience similarly unreliable NIPT results, counseling patients about limitations of prenatal genetic testing and alternatives, given ACOG's and the Society for Maternal Fetal Medicine's recent affirmation of cfDNA as the most sensitive and specific screening option regardless of baseline risk or maternal age, would be imperative.

Transplant Considerations

DONOR SELECTION

UTx has successfully occurred from both deceased donors (DD) and living donors (LD), though >75% of all transplants utilized LD. Although the total number of UTx worldwide is small, some suggest superior outcomes with LD. LD, based on other solid organ transplants experience, yield superior long-term outcomes because of detrimental inflammation incurred during brainstem death.[25] However, the expected lifespan of UTx is much shorter (typically

less than 10 y) than other, life-sustaining grafts, so this benefit may be of lesser consequence. Deceased donation can avoid potential LD morbidity; major surgical complications after procurement are estimated at 12%,[21] and include infection, ureteral injuries, uretero-vaginal fistula, hemorrhage, and vaginal cuff dehiscence.

Donor selection must be balanced with the unfortunate reality of long delays awaiting a match. Evaluation of a single large US organ procurement organization, demonstrated with liberal inclusion criteria (reproductive age with uterus and no active infections), only 5% of DD had a uterus suitable for transplant. Stricter criteria (prior parity, no gynecological disease, nonsmoker) left fewer than 1% eligible.[26] LD have more relaxed age criteria and are significantly older than DD (46 compared with 36-y old, respectively).[21] Of note, live births following UTx have even been achieved using postmenopausal LD. Before transplant in these cases, short 1- to 3-month courses of hormonal supplementation are used to ensure the endometrial lining appropriately responds to exogenous treatments.[21] However, even if a postmenopausal uterus can generate an adequate endometrium, age is an independent risk factor for arterial calcification and stiffness, which may compromise vascular anastomoses. Abortion of a transplant after graft procurement in a 61-year-old woman with multiple cardiovascular risk factors occurred after inability to flush the graft's vessels due to atherosclerotic disease.[12]

More experience is critical to better characterize the benefits of LD versus DD. However, both approaches are valuable given scarcity of available grafts. The number of UTx required to address the noninferiority of DD versus LD in a methodologically rigorous manner is unachievable. Success rates after attempted UTx are inconsistently published, and a highly complex and multidisciplinary surgical intervention, like a solid organ transplant, is subject to an institutional learning curve. Centers have performed anywhere from 1 to > 20 transplants and to use cumulative success rates based on counts across sites with a wide range of experience may provide an inaccurate estimate. For example, Baylor University recently published its cumulative live birth rate of 55% based on the largest single center cohort of live births after 20 UTx.[27] Notably, the surgical success rates were 50% and 90% in the first and second set of 10 UTx performed which highlights the steep learning curve observed at this and other centers performing UTx. However, if we combine published experience from multiple sources, the best estimate of cumulative live birth rate after LD UTx (accounting for graft failure) is roughly 40%.[28] Experience with DD is more challenging to assess given that fewer UTx from DD have been performed and not all experience is published. If we assume DD have a cumulative live birth rate of 36% based on best estimates from individually published center experiences and personal communications, then 241 patients per arm (482 total) would be required to test for a noninferiority margin of 15% with 80% power.[28,29] Given the unlikely feasibility of achieving a study of this size, trials with both LD and DD remain essential.

Posttransplant Considerations

IMMUNOSUPPRESSION

Immunosuppression is required to prevent graft rejection after UTx and is complicated by an anticipated pregnancy. Induction with polyclonal antibody antithymocyte globulin is most common, followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil (MMF).[21] Given the teratogenicity of MMF, some centers have adopted maintenance regimens of

tacrolimus and azathioprine instead, or simply discontinue MMF 3 months before ET and continue tacrolimus alone.

VAGINAL STENOSIS

Posttransplant vaginal stenosis has been reported at numerous centers in patients with both surgically created and self-dilated neovaginas. Stenosis has been attributed to postoperative healing and discordance in size and plasticity between the donor cervix and recipient vagina. Treatment is required for cervical access to obtain routine biopsies assessing for organ rejection and perform the ET. Surgical repair of vaginal stenosis at the uterine-vaginal anastomosis in the first Czech recipient lead to bladder injury and vesicovaginal fistula.[4] We have experienced posttransplant vaginal stenosis in 2 of the 3 recipients in University of Pennsylvania's clinical trial. These stenoses resolved with in-office and home self-dilation before ET. Notably, one recipient had recurrence of the stenosis following delivery of her first child, 6 weeks after discontinuing vaginal dilation. To our knowledge this is the first report of recurrent postpartum vaginal stenosis after UTx. Stenosis was corrected with resumption of vaginal dilation in anticipation of her attempt at a second pregnancy.

ET

The first ET after UTx has occurred between 6 to 18 months post-transplant. The uterine lining is prepared with several weeks of exogenous estrogen and typically five days of progesterone in a programmed frozen embryo transfer (FET). Alternatively, the patient's own ovulatory cycle is used and endogenous production of estrogen from a growing ovarian follicle prepares the lining in a so-called natural cycle and the corpus luteum provides progesterone, often supplemented with vaginal progesterone. Spontaneous menstruation occurred in most patients within 1 to 5 months of UTx, which is necessary for a natural cycle ET.[4,27] Once the endometrium is prepared, a cryopreserved embryo is thawed and transferred via the vagina to the uterus by a catheter under ultrasound guidance. Both cleavage stage and blastocyst embryos have been transferred and resulted in live births.[21]

There is no universal recommendation for optimal endometrium preparation, with live births resulting from programmed and natural cycles FETs, and fresh ETs. Anecdotal reports of increased rejection rates during programmed FETs are likely related to supraphysiologic estrogen levels. Even small doses of exogenous estrogen lower tacrolimus metabolism through inhibition of hepatic and intestinal CYP450 3A.[30] Vigilant monitoring of tacrolimus levels and renal function are essential with programmed ETs and pregnancy. Endometrial receptivity assays have been performed after UTx to attempt a personalized approach to timing of the ET after multiple failed transfers, although this is not routine.[20] It is recommended a single blastocyst be transferred to prevent the maternal and fetal morbidity of multiple gestations.

Conclusion

UTx has profoundly changed the treatment landscape of AUFI. There are numerous unique considerations in the application of reproductive technology for UTx recipients. As the treatment continues to evolve it is critical that experiences in trials are efficiently published to build a comprehensive, dynamic, and accessible shared body of knowledge about best practices and outcomes.

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