CLINICAL OBSTETRICS AND GYNECOLOGY
Volume 65, Number 1, 4–14

Uterine Transplantation in 2021: Recent Developments and the Future

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B.P.J. and L.K.: the article was conceived and written. M.C.: helped write the manuscript and revised the final draft. S.V., S.S., T.B.M., M.Y.T., J.N., C.D.-G., I.Q., J.Y., and J.R.S.: reviewed and contributed expertise to the manuscript.

The authors declare that they have nothing to disclose.

Abstract: Uterine transplantation has evolved rapidly over the last decade. As the number of cases performed increases exponentially worldwide, emerging evidence continues to improve collective knowledge and understanding of the procedure, with the aim of improving both surgical and reproductive outcomes. Although currently restricted to women with absolute uterine factor infertility, increasing awareness as a method of fertility restoration has resulted in a demand for the procedure to be undertaken in transgender women. This manuscript summarizes the recent advances in uterine transplantation, and elaborates further upon the key novel avenues research within the field will focus on over the coming years.

Key words: gynecology, infertility, absolute uterine factor infertility, transplantation, uterus, tissue engineering

Introduction

Over the last 2 decades, uterine transplantation (UTx) has evolved from an experimental procedure to a realistic method of fertility restoration in women with absolute uterine factor infertility which is now being performed globally.[1,2] The objective of UTx is to restore reproductive anatomy and functionality of women with absolute uterine factor infertility, so they have the opportunity to gestate biologically related offspring in order to meet their reproductive aspirations. UTx differs from conventional solid organ transplantation, in that the aim of the graft is to function for a finite number of years until the woman has completed her family. Subsequently, the graft is then removed, thereby reducing the overall cumulative immunosuppression exposure and associated risk. By 2020, 54 living donor (LD) and 19 deceased donor UTx procedures had been performed worldwide.[3] A recent review of reproductive outcomes reported that 23 confirmed livebirths had been achieved following UTx,[4] exemplifying further that it is now unquestionably feasible.

Progress within the field of UTx has evolved rapidly in recent years, with multiple centers establishing UTx programmes globally. In particular, recent developments include utilizing minimally invasive retrieval techniques, changes to the vascular venous drainage, and methods to expand the pool of eligible donors. Moreover, as evidence supporting the efficacy and success of UTx escalates, novel changes to not only the way surgery is performed, but also the application of UTx to other infertile populations, such as transgender women, now requires further focus. Furthermore, with advancement in technology, research into the possibilities of a bioengineered uterus in the future is also rapidly emerging.

The aim of this manuscript is to reflect upon the evolution in practice of UTx, through discussion of key research themes and to consider how the field may develop further in the future.

Refinement of Surgical Protocol

The traditional technique utilized for uterine retrieval involves excision of the graft, including the uterus, a vaginal cuff and surrounding ligaments and connective tissue. Long vascular pedicles are also harvested bilaterally, including the internal iliac, in addition to the ovarian arteries and veins where possible. The arterial anastomosis is undertaken using an end to side technique with the recipients' external iliac vessels, whereas the venous drainage is anastomosed to the external iliac veins. In those with ovarian veins of satisfactory length, caliber and quality, additional venous drainage is included by anastomosing to the external iliac vessels.[2] One of the main challenges encountered in this initial approach is the complex dissection required for the uterine venous plexus dissection in LDs, particularly when considering their unpredictable course, often tortuous nature, and the close proximity of the ureters. Such intricate dissection is time consuming, as exemplified by the first series of 9 cases undertaken in Sweden, where the mean operative time was > 12 hours.[2]

Which while difficult to quantify, represents an undoubtedly high risk of venous thromboembolism. In addition, there is significant surgical risk, such as the potential for ureteric injury, which was observed in 2 of the first 4 UTx cases performed,[2,5] and risk of hemorrhage.[6]

As such, modification of the surgical technique has predominantly focused on the venous drainage, as observed from cases performed in China,[7] Dallas,[8] the Czech Republic,[6] and India.[9] By utilizing solely the ovarian/utero-ovarian veins instead of the uterine veins, the surgical complexity of the technique reduces significantly. A review of the first 45 UTx cases found the mean operative time in LD procedures utilizing this novel technique was 5 h 51 m ± 1 h 46 m (n = 10; 2 h 40 min to 8 h), which was 3 hours faster than the cases undertaken using the initial surgical approach (n = 25, mean; 8 h 39 min ± 2 h 46 min, range; 4 h to 13 h 8 min).[1]

Further benefits of reducing the number of venous anastomoses performed also include reducing the potentially detrimental warm ischemic time. Such modification in technique is widely supported by animal model studies.[6,10] For example, a recent study investigating orthotopic UTx in Yucatan minipigs identified that bilateral ovarian venous drainage is satisfactory, with immediate reperfusion of the uterus and subsequent viability of the graft was demonstrated.[10]

Another development within fertility restorative transplantation surgery includes the potential to restore fertility in those affected by infertility secondary to a defective endometrium, such as those with the Asherman syndrome, using a less invasive endometrial transplant.[11] However, while an initial study has demonstrated histologic evidence of viability and clinical pregnancies in small animal models, no livebirths were achieved, which was attributed to suboptimal neovascularization between the endo-myometrial interface.[11] Even if subsequently proven feasible, it remains limited in application by the inability to noninvasively detect rejection.

Minimally Invasive Surgical Techniques

Simplification of the surgical technique also facilitates the transition from undertaking the retrievals using laparotomy, to utilizing minimally invasive surgical routes. The implementation of robotic-assisted or laparoscopic retrievals in LDs, offers further risk reduction and an enhanced recovery process.[9,12,13] There are a number of benefits associated with robotic-assisted laparoscopy, including improved surgical access to the pelvis, less tissue trauma, and greater precision obtained intraoperatively.[14] Greater precision and visibility allows for more accurate dissection of the nerve plexuses in close proximity. This is particularly important when considering an open UTx donor retrieval resulted in the donor suffering from prolonged bladder hypotonia.[5] While it resolved with conservative measures, it was a presumed consequence of the trauma sustained to the inferior hypogastric plexus.[9]

To date, there have been at least 14 robotic-assisted UTx retrievals undertaken and 4 laparoscopic assisted.[7,9,13,15,16] The first robotic-assisted donor hysterectomy performed in China utilized an ovarian/utero-ovarian venous anastomosis and incorporated removal of the graft vaginally using a sterile bag.[7] The difficulties in retrieval of the deep uterine veins led to the requirement to perform an oophorectomy in the premenopausal donor, which was thought to be associated with increased risk of morbidity and mortality.[17]

The Swedish UTx team have since published data on the outcomes from 8 donor robotic-assisted retrievals.[16] The the initial dissection of the uterovaginal fossa, uterine arteries, and ureter was undertaken robotically, with the remainder of donor surgery, including removal of the graft, completed by laparotomy. This surgical approach aimed to avoid the need for oophorectomy by harvesting the deep uterine veins bilaterally, reciprocating their initial technique used for open uterus retrievals.[2] Four robotic ports measuring 8 mm and 2 assistant ports of 12 and 5 mm were utilized, which in addition to the dual console, facilitated difficult dissection of the deep uterine veins.

The total surgical time reported was 11.25 hours and the duration of hospital stay 5.5 days.[16] The estimated median blood loss was 125 mL, which was significantly lower than the average of 920 mL observed from the initial series, in which laparotomy was performed.[2] No major surgical complications were reported. However, reversible complications included gluteal pain on exertion, which was attributed to gluteal tissue ischemia,[18] pressure alopecia, and pyelonephritis.[16] The first livebirth following robotic-assisted retrieval has since been reported.[18]

The Dallas team has also reported 5 UTx cases performed following robotic-assisted retrievals, and compared outcomes with their prior 13 cases undertaken through an open incision.[15] The surgical approach included harvesting of the proximal part of the utero-ovarian veins as well as deep uterine. The donors' who had undergone a robotic-assisted retrieval had lower median estimated blood loss, length of hospital stay and sick leave, with no difference in complications.[15] However, the duration of surgery was increased in the robotic-assisted cohort (10.46 vs. 6.27 h).[15]

In further cases performed in India, laparoscopic-assisted retrieval was undertaken from 4 live donors.[9,13] Although the vessels were harvested laparoscopically, the uterus was retrieved through a small abdominal incision. The decision to remove the graft by a larger abdominal incision in these cases reduces potential contusion, while maintaining sterility of the graft, when compared with the alternative of removing it vaginally.

Donor Type and Criteria

Much like other solid organ transplants, donation can be from LD or donation after brainstem death (DBD). In DBD, uterine grafts can be retrieved at the beginning of a multiorgan retrieval,[19,20] or following retrieval of other solid organs,[21–24] with no resulting negative impact upon the logistics of the multiorgan retrieval process, or indeed the other organs retrieved. Each donor type presents a variety of physiological, immunologic, and anatomic differences, and there are important logistical distinctions that require consideration, in addition to ethical considerations that continue to stimulate debate.[4,25–28] Despite this, given the small number of cases performed, it is difficult to accurately analyze outcomes to determine if one donor type is associated with more favorable outcomes. However, if long-term follow-up suggests that DBD donor outcomes are similar or superior to LD, it would be appropriate to prioritize DBD due to the complete removal of donor risk. For this reason, it is likely that DBD will currently continue to be undertaken in countries where there is an established organ retrieval network. However, given the finite supply of DBD donors in the context of an exponential rise in UTx procedures being performed, it is anticipated that a combination of LD and DBD will still be required to meet the potential demand.[29]

A potential option to increase the number of available UTx donors is the possibility of utilizing transgender men undergoing hysterectomy as part of their transition from female to male. Most transgender men undergoing transition will have favorable characteristics; including being of reproductive age, as exemplified from a study whereby the mean age of participants was 28.5 years.[30] Increased donor age is well known to be associated with greater degrees of arterial stiffness and increased vascular calcification,[31,32] and is independently associated with inferior outcomes in other solid organ transplants.[33–35] Moreover, from a reproductive perspective, outcomes are worse in women over the age of 45, compared with younger women, even when controlling for oocyte quality by using donor eggs, with inferior implantation and pregnancy rates, and higher miscarriage rates.[36] As such, by virtue of their gender dysphoria, this pool of donors often do not envisage using their uterus to meet their reproductive aspirations, thereby allowing them to donate at a younger age. This contrasts with cisgender LDs, who need time to meet their reproductive aspirations, before being able to donate their uterus. While it remains unclear whether androgen therapy may have long-term effects on the potential of the uterus, a study among transgender men demonstrated that in those taking testosterone supplementation who experienced irregular menses, their cycles returned to normal following cessation of treatment, suggesting the effect may be temporary.[37]

Another major advantage over cisgender women is that if the transgender donor was already undergoing hysterectomy, bilateral salpingo oophorectomy and vaginectomy as part of their gender reassignment, the increased relative risk is reduced. However, the hysterectomy is undoubtedly more radical in the context of donation, including extensive peritoneal excision and longer vascular pedicles, which may not be acceptable to potential donors. A review of the first 45 UTx cases highlighted that one in 10 donors suffered a postoperative complication requiring further surgical intervention, further highlighting the risk entailed.[1] However, it is reassuring that in a study of 31 transgender men, 84% would still consider uterus donation, after learning more about what the surgery entailed.[30] Moreover, as discussed previously, as the surgical technique evolves, with further adoption of minimally invasive techniques, the overall risk will likely reduce. Moreover, as most transgender men will undergo concomitant bilateral salpingo oophorectomy at the same time, this would facilitate the retrieval of longer and more extensive ovarian vessels.

Another issue in this context is that for most transgender males, it is likely their uterus may have never carried a pregnancy before. As such, if transplanted, there is no way of predicting whether it will function or not. Many initial selection criteria excluded nulliparous women for this reason.[38] However, due to the significant impact on donor pools, there have been various calls to include otherwise suitable nulliparous women, which would certainly be appropriate in this context.[29,39]

Recipients

Whereas UTx has only been undertaken in women assigned female at birth, there has been significant discussion around undertaking the procedure in other groups, such as transgender women.

Gender dysphoria can be defined as a feeling of distress or discomfort arising from a disjunction between a person's felt gender and the gender they were assigned at birth.[40] The reported prevalence of gender dysphoria has increased in recent years, and is now between 0.5% and 2%.[41,42] The mainstay of treatment aims at optimizing psychological wellbeing with focus on self-fulfilment. While for many, partial treatment or social transition provides some acceptance, others only find comfort by changing their external genitalia and sexual characteristics by using hormonal therapy or undergoing surgical intervention. However, hormonal therapy or gender reassignment surgery is inevitably associated with an adverse and potentially irreversible impact upon their fertility.

Following the success of UTx in women assigned female at birth,[1] interest has intensified regarding the possibility of performing UTx in transgender women.[1,43–45] However, while this would enable the opportunity to gestate and give birth to their own children, a number of psychosocial, ethical and legal considerations remain, in addition to significant anatomic, physiological, fertility, and obstetric concerns.

The psychological and social benefits of performing UTx in M2F transgender women may provide a protective factor, particularly considering that parenting reduces suicide risk in transgender women.[46,47] Gestation is thought to often play a pivotal role in conveying and consolidating a female identity.[45] This is supported by findings from a survey of 186 transgender women that identified the vast majority "agreed" or "strongly agreed" that the ability to gestate and give birth to their own children (n = 171; 94%) would enhance the perceptions of their femininity.[48] In addition, nearly all respondents (n = 180; 99%) believed that UTx would lead to greater happiness in M2F transgender women.[48]

Fertility preservation should be discussed in all M2F cases before the commencement of hormone therapy or contemplation of gender reassignment surgery.[49] Exogenous estrogen can influence fertility by impairing spermatogenesis through morphologic changes in the testicular tissue including an absence of typical Leydig cells.[50] M2F transgender women can preserve their fertility before transition utilizing the established technique of sperm cryopreservation, with subsequent IVF or intrauterine insemination. However, whereas approximately a fifth of respondents of the aforementioned questionnaire among transgender women, reported that preserving sperm would conflict with their identity as a female, > 3 quarters (n = 140; 77%) "strongly agreed" or "agreed" that they would be more inclined to cryopreserve sperm if UTx became a realistic option.[48]

With regard to the additional surgical complexity to undertaking UTx in transgender women, there are a number of anatomic considerations that require consideration.[51] The main surgical challenges that have previously been raised include the vascular and neovaginal anastomoses, in addition to the surrounding ligamentous support. Whereas minor modifications to the implantation technique may overcome the issues related to the vascular anastomoses and ligamentous insertions, the neovaginal anastomosis may prove more problematic. As previously elaborated in detail, the vaginal microbiome is closely interlinked with numerous clinical and reproductive issues that are vital to the UTx process.[52] As such, the absence of vaginal mucosa could negatively impact postoperative outcomes following UTx in transgender women, and therefore, consideration of the method used for neovagina creation requires additional consideration. The gold standard technique for neovagina creation is considered to be the penile inversion vaginoplasty technique, with or without full thickness skin graft.[53] However, transgender women with such neovagina have been demonstrated to have lactobacilli deplete microbiomes, with colonization of bacteria traditionally identified in skin, intestine or bacterial vaginosis dominated microbiota instead.[54] Whereas this raised uncertainties surrounding the suitability of a penile skin lined neovaginal anastomosis following UTx, subsequent studies using molecular detection techniques showed that lactobacilli species were actually present in three quarters of transgender women with skin lined neovagina.[55] While it is clear that further scientific progress is needed to help quantify the role of the vaginal microbiome in the context of UTx, a pioneering uterovaginal transplant could also be considered,[51] utilizing as much donor vagina as possible, although at present this would necessitate donation from deceased donors.

Uterine Tissue Bioengineering

Over the last decade, bioengineering strategies for fertility restoration have evolved rapidly. Bioengineering incorporates both the fields of tissue engineering and regenerative medicine, with an aim to regenerate or replace damaged cells, tissues and organs to restore normal biological function.[56] Tissue engineering typically involves combining cells, biomaterial scaffolds and biologically active molecules to generate functional constructs that resemble native tissue. In the context of UTx, bioengineering can overcome the shortfalls experienced in organ transplantation, such as availability of donors and complications following immunosuppression and surgery. For example, those with the Asherman syndrome may not require UTx if novel therapies could regenerate a functional endometrium. As such, various studies have investigated experimental strategies for endometrial regeneration, including stem cell therapy, biomaterials-mediated delivery of drugs and growth factors and bioengineered uterine tissue. Of these, stem cell-based therapies have been the most studied and have resulted in several clinical studies reporting restored fertility and livebirths in previously infertile women diagnosed with severe intrauterine adhesions or thin endometrium.[57–60] Pregnancies have carried to term and livebirths have been achieved from a bioengineered uterus in a large animal model.[61] As such, the long-term future of UTx will likely encompass bioengineering strategies to replace or regenerate a damaged uterus.

Stem cells play a vital role in the reconstruction of the endometrium following menstruation, pregnancy, and trauma.[62] In the last decade there has been considerable effort to use stem cells therapeutically to heal the endometrium following injury in both preclinical models and clinical trials. These studies have included the use of adult stem cells derived from various sources such as bone marrow,[59,63,64] adipose tissue,[65,66] and menstrual blood,[60,67,68] as well as from perinatal tissues such as the umbilical cord.[58,69–71] More recently, researchers have also reported on stem-cell derived exosomes as a promising treatment for endometrial regeneration.[70,72] Stem cells may be delivered systemically or locally, directly or via a biomaterial scaffold to aid survival and retention of grafted cells.[70,73,74] In animal models of intrauterine adhesions, stem cell therapy has demonstrated the ability to reduce fibrosis, regenerate endometrial tissue and significantly improved fertility and pregnancy rates.[63–66] Stem cells have also been used in amenorrheic and infertile women with the Asherman syndrome or endometrial atrophy, with subsequent successful restoration of both menstruation and fertility with successful pregnancy outcomes.[57–60] However, a number of technical challenges and impracticalities still need to be overcome, such as determining the best source and isolation method for cells, optimal delivery method and its longer term safety profile.

Acellular bioengineering strategies for endometrial regeneration have the advantage of greater simplicity and clinical convenience. Researchers have turned to molecular biology and biomaterials to look for novel therapies to enhance endometrial healing. These include biomaterials scaffolds and hydrogels that deliver growth factors,[75–77] or estrogen,[78,79] to the damaged endometrium, and the scaffolds that can be derived from natural, synthetic or decellularized extracellular matrix (ECM) materials. In animal models of posttraumatic intrauterine fibrosis, these methods have successfully reduced scarring, increased neovascularization, and improved fertility.[75–79]

Decellularized ECM is a valuable type of biomaterial scaffold because it retains some essential properties of native tissue ECM and promotes tissue regeneration.[80] The process of decellularization removes immunogenic cellular antigens so that ECM scaffolds are readily incorporated into host tissues without a foreign body immune reaction.[80] This type of biomaterial has been successfully used clinically for reconstructive surgeries and wound healing for decades. In the context of uterine bioengineering, decellularized uterine matrices have been successfully repopulated with stem cells, resulting in recapitulation of native tissue organization in vitro.[81–84] In vivo, these recellularised uterine matrices have demonstrated the ability to result in tissue regeneration when transplanted into rats with uterine defects, with subsequent pregnancies being achieved.[81,82,85] So far, the largest whole reproductive organ decellularization was reported in a porcine uterus, which was subsequently partially recellularized with

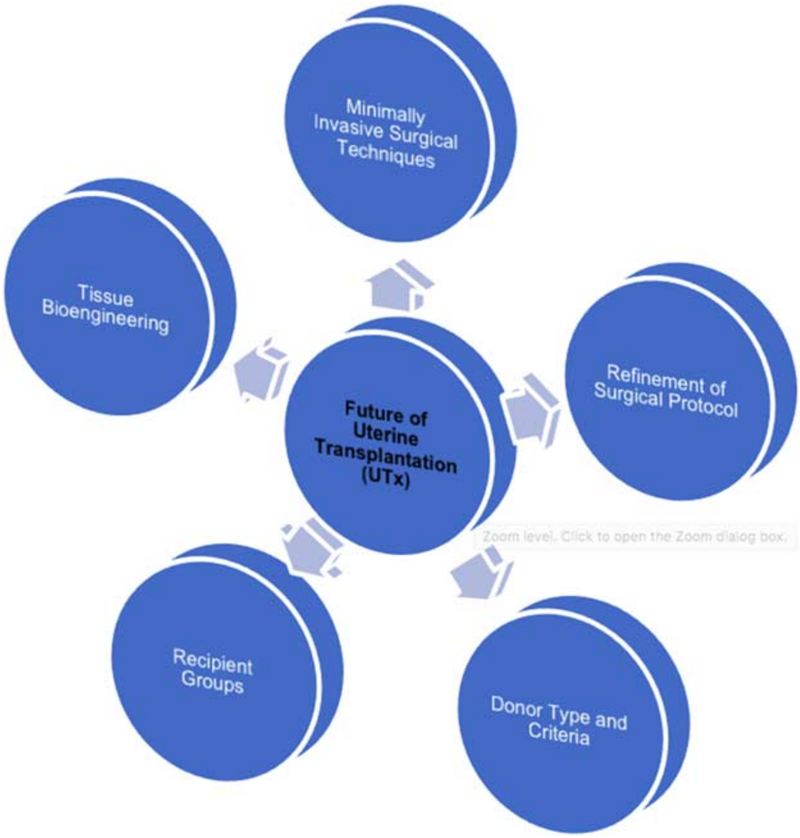

FIGURE 1. Future of uterine transplantation (UTx). full color online

disks of uterine scaffold using human stem cells.[84] More recently, successful decellularization of a whole sheep uterus, with recellularization of scaffold disks has also been described.[86] The decellularization approach brings promise for treatments with engineered, full thickness uterine grafts and an eventual bioengineered whole uterus, though this remains a highly complex objective and distant reality.

Conclusion

Since the first livebirth following UTx was achieved in Sweden in 2014, UTx has evolved rapidly, and several key research themes have emerged, as summarized in Figure 1. From a surgical perspective, implementation of minimally invasive surgical approaches in donors and changes to the venous drainage have raised the potential to reduce the risks of retrievals in donors significantly. Moreover, novel donor pools and changes to selection criteria will help provide greater sustainability as UTx transcends from an experimental procedure to an established method of fertility restoration. In addition, the reproductive aspirations of transgender women are being realised, although further scientific progress is needed to determine if UTx may help realign their reproductive organs with that of their acquired gender. Further development within the field of UTx remains dependent on ongoing research and continually analyzing and assessing outcomes. Over the coming decade, future research within the field of bioengineering has the potential to further transform the applicability and accessibility of UTx for women suffering with infertility.

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