Acta Biomed 2022; Vol. 93, N. 2: e2022138 DOI 10.23750/abm.v93i2.12868 



# The reproductive potential of uterus transplantation: future prospects

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**Abstract.** *Background and aim:* Absolute uterine factor infertility (AUFI) is a form of infertility whereby conception and/or maintenance of pregnancy is impossible as a result of uterine absence or its completed dysfunction. It affects 1/500 women of reproductive age while the incidence is about 8% of infertile couples. Uterus transplantation (UTx) has been gaining ground as a viable option to enable women with AUFI to have biological children and as an alternative to surrogacy, a highly controversial practice still banned in many countries. *Methods:* The authors have set out to strike a reasonable balance between UTx benefits and the still numerous risks, whether clinical or ethical, associated with such an innovative form of transplant, which is not life-saving, requires immunosuppression throughout pregnancy and the organ to be removed right after childbirth. For the purpose of this Focus-on, the authors have laid out an analysis of uterus transplantation (UTx) taking into account its potential in terms of enabling patients with AUFI to achieve motherhood and its ethical viability, by virtue of its unique traits as a life-giving/enhancing intervention. *Results:* While still far from achieving mainstream status, considerable strides have been made in UTx outcomes, with many live births already recorded. Procedures from living donor are reportedly more effective in terms of success rates. Organ tissue engineering has been explored and developed with promising results. *Conclusions:* UTx entails various risks and ethical quandaries which have to do with reproductive autonomy and rights. New human attempts and clinical trials of UTx should be performed to further optimize the procedure in relation to safety and effectiveness. Techniques such as tissue engineering could lead in the medium-long term to a wholly bioengineered uterus to be used for transplantation, relying on scaffolds from decellularized organs or tissues that can be recellularized by several types of autologous somatic/stem cells. Such advances hold promise in terms of solving UTx-related complications and organ supply difficulties. (www.actabiomedica.it)

**Key words:** Absolute uterine factor infertility (AUFI), Uterus transplantation (UTx), Ethical quandaries, tissue bioengineering

## Introduction

Absolute uterine factor infertility (AUFI) is a form of infertility whereby conception and/or maintenance of pregnancy is impossible as a result of uterine absence or its complete dysfunction. It affects 1 out of 500 women of reproductive age, while the incidence is about 8% of infertile couples (1).

For the purpose of this Focus-on, the authors have laid out an analysis of uterus transplantation (UTx) taking into account its potential in terms of enabling patients with AUFI to achieve motherhood and its ethical viability. The unique distinctive traits of UTx make a risk-benefit assessment particularly challenging. Although it is not a life-saving transplant, UTx can in fact make it possible to give life and to "enhance" the

well-being and quality of life of women or couples. In light of those fundamental elements, in addition to the clinical and surgical complexities which UTx entails, a broad-ranging search was conducted via search engines and databases such as Pubmed/MEDLINE, Web of Science, Scopus, ResearchGate, including research data and findings instrumental in laying out as thorough an assessment as possible. The search led to the identification of 52 sources spanning the 2005-2021 period.

AUFI may be congenital, such as in Mayer–Rokitansky–Küster–Hauser (MRKHS) Syndrome - a genetic disorder characterized by agenesis of the uterus and upper part of the vagina in females with normal ovarian function and normal secondary sexual characteristics - or acquired, for iatrogenic reasons (hysterectomy can be performed in consequence of diagnosis endometrial and cervical cancer, uterine fibroids, uncontrolled postpartum bleeding) (2-4). A dysfunctional uterus may also be due to anatomical or physiological defects (intrauterine adhesions such as in Asherman's Syndrome, severe adenomyosis, congenital uterine malformation). Moreover, when serious complications take place as a result of fundal pressure (5, 6), uterine rupture during induced labor (7, 8), infection-related adverse outcomes (9, 10), or other developments (11), UTx may offer an opportunity to restore fertility. Nonetheless, for such an option to be sound and tenable from a medicolegal standpoint, adherence to recommendations and best practices for both diagnostic and therapeutic interventions needs to be fully documented (12).

Furthermore, patients at risk for ovarian hyperstimulation (OHSS) can resort to vitrification techniques (13) for cryopreserving their oocytes, within the framework of in vitro fertilization (IVF) antagonist protocol (14, 15). Following the diagnosis of AUFI, women often suffer major psychological distress (16) because of the loss of reproductive function and the awareness of permanent and irreversible infertility.

Women with AUFI currently have three options to achieve motherhood: surrogacy, adoption and UTx. Of these, UTx can make it possible to achieve biological, social and legal parenthood, despite the risks it still entails. UTx also represents an alternative to gestational surrogacy, an ethically and legally controversial technique which is banned in most countries (17, 18) and entails legal challenges as well (19, 20).

UTx is the only option to restore reproductive anatomy and functionality (21). The first Living Donor (LD) UTx (LD-UTx) was performed in Saudi Arabia in 2000: the donor was a 46-year-old woman with benign multiloculated ovarian cysts who underwent hysterectomy, and the recipient a 26-year-old woman who lost her uterus following a post-partum hemorrhage. The patient developed acute vascular thrombosis 99 days after transplantation, at which point an hysterectomy was performed. Macroscopic and microscopic histopathological examination revealed acute thrombosis in uterine body vessels. Both Fallopian Tubes remained viable with no evidence of rejection. The acute vascular occlusion appeared to be caused by inadequate uterine structure support, which led to probable tension or torsion of the connected vascular uterine grafts.

The first live birth was achieved in Sweden in 2013: a 35-year-old woman affected by MRKH Syndrome received uterus from a living 61-year-old multiparous woman. IVF was carried out before transplantation. One year after UTx (22, 23), the recipient underwent single embryo transfer resulting in pregnancy. Triple immunosuppression was administered: tacrolimus, azathioprine and corticosteroids, throughout the pregnancy. The patient was admitted with preeclampsia at 31+5 weeks and a male baby with normal birthweight for gestational age (1775 g) and with APGAR scores 9, 9, 10 was delivered via cesarean section 16 hours later.

## Ethical issues

UTx is a complex procedure which entails multiple medical, ethical and legal issues. Both Living Donor (LD) and Deceased Donor (DD) UTxs have been successfully performed. A set of proposed criteria required for a woman to be ethically considered a candidate for uterine transplantation was issued in 2012: "The Montreal Criteria", meant to provide a detailed analysis as to the ethical feasibility of uterine transplantation, and centered around three core elements: the recipient, the donor and the health care team (24).

An organ transplant is generally considered ethically acceptable when it permits the patient to go on living. UTx does not meet that standard, but rather

it can enable women to achieve motherhood and improve their quality of life. It has therefore been described as "life-giving" or "life-enhancing" (25-27). Life-saving organ transplants from deceased donors are morally based on core ethics principles, particularly beneficence. By virtue of that, saving a life may justify the desecration of a dead body. In addition, costs are lower and there are obviously no risks to the donor during postmortem organ removal. However, organs can only be removed from deceased individuals if consent to donation (27) was granted by them or their legal guardians holding power of attorney. When organs are used for life-enhancing, rather than life-saving, transplants, ethical concerns are bound to arise. Despite that, many countries have permitted such kinds of donation, such as vascular composite allografts for face and arm transplantation. Why should UTx not be ethically tenable on the same grounds? After all, psychological repercussions and mental distress may be quite severe in women with AUFI. When infertility results from cancer or its treatment, some patients in fact describe their loss of fertility as causing as much emotional pain as the cancer itself (28). On the contrary, LD-UTx may provide non-vital organs with a higher success rate than DD.UTx. Clearly, the only purpose served by LD-UTx is altruistic in nature: for this reasons donors should be thoroughly counseled as to the medical and psychological risks involved.

## Surgery procedure: success and postoperative complications of LD and DD UTx

Over 62 UTx surgeries have been performed globally thus far, with 24 successful births. Numerous trials and case reports involving either LD- and DD-UTx have been released. As for LD-UTx, 27 procedures have been reported in Europe (17 LD-UTx in Sweden, 5 in Czech Republic, 4 in Germany and 1 in Spain), 18 from USA, 4 from India; single case reports have been released from Saudi Arabia, China and Lebanon (29). On the other hand, fewer DD-UTx cases have been reported: 5 cases from Czech Republic, 4 cases from two separate trials in the USA, one from Brazil and one from Turkey. Based on a comparison of different methodologies among trials and studies, the degree of safety and effectiveness of UTx procedures seems to depend on many variables.

However, donor and recipient outcomes in LD-UTx along with the birth of a healthy baby are common standards defining a successful procedure. The primary objectives are a surgically successful graft, a functioning transplant with established inflow and outflow to the graft, regular menstruation, Embryo Transfer (ET) started within 3-12 months following UTx, according to local protocols, and childbirth (30). The overall surgical success rate in LD-UTx has so far been 78% and, comparing laparotomy with minimal invasive surgery – conventional laparoscopy or robotic-assisted laparoscopy - the accumulated data show surgical success rates of 89% and 73%, respectively (31). As with all surgical procedures, potential complications include clotting, bleeding and death are. Common intra- and postoperative complications ascribable to total abdominal hysterectomy include hemorrhage (1%), transfusion (2–12%), infection including fever of unknown origin (10–20%), surgical site (6.6–24.7%), wound site (4–8%), pelvis (3.2–10%), urinary tract (1.1–5%), pneumonia (0.4–2.6%), bladder injury (1–2%), intestinal injury (0.1–1%), ureteral injury (0.1–0.5%), and vesicovaginal fistula (0.1–0.2%) (32). A 2018 study by Puntambekar **et al. (3**3) has shown the feasibility of laparoscopic-assisted uterus donor retrieval, highlighting how it may yield all the advantages linked to minimally invasive approaches, including lower morbidity rates. The pros of such an approach are indeed noteworthy: more effective dissection of the vessels, shorter operative time, and less tissue handling affecting the harvested uterus and vessels. Damages and infection were avoided by making a small abdominal incision for the retrieval of the uterus and vessels. End to side anastomosis of the harvested vessels to external iliac vessels was carried out to transplant the organ in the recipients. Lastly, supports of the donor uterus were attached and anchored to the recipient's. Six-month follow-up data were acquired, in addition to surgical intra- and postoperative measurements and postoperative investigations were conducted.

The difficulties associated with the dissection along the internal iliac vein were prevented through the use of ovarian veins acting as outflow channels. The donor internal iliac artery was also harvested, which contributed

to easing the tension exerted on vascular anastomosis. While larger studies are needed to confirm such dynamics, the technique could be reproducible through the selection of vessels to be harvested (34).

The first human UTx using ovarian veins for venous drainage, and also the first case of robot-assisted uterus procurement UTx was elaborated on by Wei L. et al in 2017. Within the setting of a UTx clinical trial for women with AUFI, a 21-year-old patient underwent UTx. The patient had been diagnosed with MRKH and had vaginal reconstruction 3 months earlier via biological membrane. In order to reduce the need for immunosuppression, the recipient underwent two IVF cycles, freezing her gametes, prior to the UTx procedure. The cryopreserved oocytes were set to be thawed one year after the UTx, to be transferred into the transplanted uterus. The donor robot-assisted uterus procurement surgery took about 6 hours, with recipient surgery lasting 8.

The time between applying the arterial clamp and chilling in the ice basin (i.e. the first phase of warm ischemia) totaled 3 minutes, while the time between removal of the graft from the ice basin and removal of the arterial clamp (i.e. second phase of warm ischemia) lasted 1 hour. Lastly, cold ischemia (i.e., time from initiation of organ flushing for as long as the organ was kept on ice) lasted 3 hours. Both the donor and the recipient experienced very minor blood loss, hence no transfusion was necessary for either surgery. Doppler showed dominant uterine artery blood flow (35, 36).

Complications are mostly due to the complexity of the operation: the longer procedure time for living uterus donation (10–13 hours), whether by laparotomy or robotic, compared to simple total abdominal hysterectomy may increase the likelihood of complications. Ureteral injuries are the most frequent complication. Moreover, long-term surgical complications in living donor women could lead to sexual dysfunction, and a high risk of ovarian failure and early menopause (37), although data are still inconclusive in that regard.

As for surgical success in DD-UTx performed via a midline laparotomy, anastomosis technique may be easier: utero-ovarian veins can be easily acquired, as can segments of the internal iliac arteries and veins to elongate the graft vessels. Utero-ovarian veins may be reached with a graft. The overall surgical success in DD UTx procedures is 64%, lower than LD-UTx (36).

Common late surgical complications are the development of stenosis in the end-to-end anastomosis between the vaginal rim of the graft and the vaginal vault of the recipient, and infections. Graft rejections are frequent, and they are treated with temporary addition of steroids or an aggressive immunotherapy – such as Immunoglobulin – in severe forms. Immunosuppressants may cause nephrotoxicity, increased risk of diabetes, atherosclerosis, malignancy, anemia, leukopenia and infections. Planned cervical biopsies have been performed to detect rejections based on a clinical score that distinguishes severe, moderate, mild and borderline uterine rejections. Recipient follow-up should continue even after the hysterectomy of the transplanted uterus, and should include psychological counseling and medical examinations focused on potential long-term side effects of immunosuppressants.

**Uterine tissue engineering: future perspective**

Due to the rejection rate after organ transplantation and the side effects of immunosuppressants, uterine tissue bioengineering has been explored as future viable option. Technological progress has paved the way for engineered grafting materials based on the patient's own cells to reduce rejection incidents (38, 39). Ovarian- and follicle-related bioengineering applications have gained attention as a therapeutic option for infertility caused by conventional anti-cancer treatments: fertility preservation is particularly challenging in leukemia patients, for whom cryopreserved ovarian tissue transplantation is unsafe due to the risk of reintroducing malignant cells (40).

Furthermore, engineered three-dimensional uterine tissue has been used in infertility care for many years: this system served to perform decidual differentiation- and embryo implantation studies. In an interesting study by Ding L. et al.(41), bone marrow derived from mesenchymal stem cells – cultured on collagen scaffolds – was used *in vivo* for the functional regeneration of injured rat uterus. The healing process was adequate and made possible by the proliferation of the host's endometrial and muscle cells and vascular regeneration.

Embryo development also took place within the graft area. Young et al. (42) performed Allo- and

Xeno-reassembly of human and rat myometrium from cells and scaffolds: pregnant rat- and human myometrium sample were decellularized and then recellularized with various human and rat myocyte cell lines to be evaluated *in vitro*. These constructs were cultured for up to 51 days *in vitro* and later showed some contractility in an organ bath, indicating elementary uterine functionality. However, no vascular repopulation was observed.

As it is well known, patients with PCOS (Polycistic Ovarian Syndrome) that undergo in vitro fertilization, may need inositol supplementation to improve fertilization and chances of getting pregnant (43-45), to better prevent gestational diabetes in pregnancy (40, 41) and to avoid climacteric symptoms in case of UTx in menopausal transition (46).

## Conclusion

Infertility is a social problem that must be addressed by reproductive specialists through a gender approach (47). UTX is nowadays the only option to restore reproductive anatomy and functionality in women with AUFI. Although associated with considerable risks, UTx can enable women to achieve biological, social and legal parenthood. Further research and clinical trials should be performed to further optimize the procedure in terms of safety and efficiency. Uterine tissue engineering, while promising in terms of future prospects, is still at an early experimental stage.

Hopefully, our ability to complete solid organ transplantation via a minimally invasive approach will be greatly enhanced by technological advances such as the da Vinci Robotic Surgical System. Both LD- and DD-UTx constitute viable options. The latter obviously entails no surgical risk to the donor, less complex surgical procedure, and higher likelihood of recovering large arteries and veins, leading to better anastomosis, which is essential in terms of enhancing the blood flow, with better chances of a healthy pregnancy. Nonetheless, DD-UTx has so far been less successful. Studies have ascribed its lower success rate to protracted ischemic spells and injuries intensifying alloimmune responses. Moreover, inflammation linked to Ischemia/Reperfusion Injury (IRI) could lower endometrial receptiveness and influence menstrual cycles (48, 49). Although not within the scope of this writing, it is worth noting that preliminary data gathered from robotic hysterectomy procedures (50) combined with the concomitant robotic colpectomy seem to point to robotic surgery as a good option in the female-to-male transition surgery. Still, further controlled studies involving larger samples and longer follow-up are needed to back up such a conclusion, although the infrequency of such procedures may delay the acquisition of conclusive data (51).

Given the preliminary success of UTx programs worldwide and rising demand, UTx is expected to grow relatively fast, since it can constitute a viable therapeutic option for AUFI (52).

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 4 February 2022
Accepted: 9 February 2022
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