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REVIEW

Uterus transplantation: A clinical breakthrough after systematic preclinical research

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Abstract

Background: Uterus transplantation is a groundbreaking solution for absolute uterine factor infertility, offering women the potential for full biological motherhood. Since the first human trial in 2012 and the birth of the first baby in 2014, over 140 procedures have been performed globally, resulting in more than 70 live births.

Methods: This review synthesizes data from foundational animal research, patient eligibility criteria, and advancements in surgical techniques for uterus transplantation. It examines live and deceased donor grafts, the role of assisted reproductive technologies, and obstetrical outcomes.

Main Findings: Animal studies have been pivotal in transitioning uterus transplantation into clinical practice. Surgical advancements, including robotic-assisted live donor hysterectomy, have improved precision. Protocols for in vitro fertilization have evolved, optimizing treatment before and after transplantation and reducing the time between transplantation and embryo transfer. Obstetrical outcomes show increased risks, such as hypertensive disorders and preterm births, underscoring the importance of thorough monitoring during pregnancy.

Conclusion: Despite its complexities, uterus transplantation represents a transformative advance in reproductive medicine. It provides a viable path to biological motherhood for women with uterine infertility and marks significant progress in both transplantation and fertility treatments, paving the way for further refinement and broader application.

KEYWORDS
assisted reproduction, infertility, obstetrics, transplantation, uterus

1 | INTRODUCTION

Over the past few decades, uterus transplantation (UTx) has emerged as a promising treatment for absolute uterine factor infertility (AUFI). AUFI is characterized by either the absence of a uterus or the inability of the uterus to sustain a pregnancy to a viable stage. Initial advancements were made through extensive animal studies conducted on five species, including non-human primates.[1] Much of the research work on non-human primates was performed by Japanese researchers. Building upon these findings, the first human UTx trial was initiated in 2012, involving nine live donor (LD) procedures,[2] which culminated in the birth of the world's first UTx baby in September 2014.[3]

In December 2024 it was estimated that more than 140 UTx surgeries have been performed, resulting in more than 70 babies born. In the eastern Asia/Oceania region UTx procedures have been performed in China, South Korea, Singapore and Australia. Table 1 presents an estimation of the number of procedures conducted in each country worldwide. Drawing on data from ongoing and completed clinical trials and our own experience, we review essential animal studies and discuss potential patient groups for UTx and explore the various surgical techniques and assisted reproductive technologies utilized.

1.1 | Animal studies

Extensive animal studies have been conducted to refine UTx, ensuring the procedure is optimized and as safe as possible before its introduction as an experimental treatment in humans.[1,6,7] Key research in mice, rats, pigs, sheep, and non-human primates is discussed in the following sections.

Systematic studies of UTx in mice began over two decades ago and produced several key findings. Fertility after UTx was first demonstrated in syngeneic transplants with surgery by deceased donor (DD) principle.[7] The grafted uterus was placed in an orthotopic position while the native uterus remained in situ. Pregnancies occurred in both uteri. Further research refined the procedure by exteriorizing the uterine cervix, which resulted in successful pregnancies with normal placental weights, birthweights, and offspring growth.[8] Importantly, no differences in implantation or miscarriage rates were observed between transplanted and native uteri, and normal outcomes persisted into the second generation. Cold ischemia tolerance was also evaluated in the mouse, showing that uteri subjected to 24 h of cold ischemia time supported normal pregnancies, whereas those with 48 h of cold ischemia did not.[9] Offspring from the 24-h cold ischemia grafts exhibited normal growth trajectories, highlighting the uterine resilience to ischemic conditions. Another study examined the effects of immunosuppression (IS) on reproductive performance in mice. Female mice exposed to cyclosporine A during mating and pregnancy experienced a dose-dependent decrease in implantation rates and an increase in miscarriage rates.[10] However, second-generation in utero IS-exposed offspring showed no fertility issues. Together, these findings in mice established key principles for UTx, including its feasibility, ischemic tolerance, and the impact of IS on reproductive outcomes.

Fundamental studies in rats have also provided critical insights into UTx. An initial study demonstrated pregnancy through natural mating in a syngeneic model, where a uterine graft (with one horn removed) was transplanted.[11] Although mating and pregnancy rates were comparable between UTx and control groups, the delivery of live pups was lower in the UTx group, likely due to uterine denervation or vaginal strictures. Subsequent research in rats explored fertility following allogeneic UTx with tacrolimus IS.[12] Reasonable pregnancy rates were achieved, but pup numbers were lower in tacrolimus-treated groups, highlighting its negative impact on implantation and pregnancy progression. The study confirmed the feasibility of pregnancy after allogeneic UTx for the first time. A follow-up rat study examined postnatal outcomes, showing decreased pregnancy rates in the UTx-tacrolimus group compared to controls.[13] However, birth weights and growth trajectories of offspring remained unaffected. This was the first study to evaluate postnatal development after allogeneic UTx, reinforcing earlier findings of compromised implantation and increased miscarriages due to IS.

A pivotal study included 10 allogeneic UTx procedures in minipigs using the DD concept, with aortic-aortic and vena cava-vena cava anastomoses and heterotopic uterine placement.[14] The IS involved 2 weeks of intravenous tacrolimus, followed by oral steroids and cyclosporine. Long-term graft survival was achieved in 50% of the recipients, with study durations extending up to 1 year. This groundbreaking work was the first to report sustained graft survival in a large animal model for allogeneic UTx.

The first method for autologous UTx in sheep involved excision of one uterine horn, allowing unilateral anastomoses to the external iliac vessels.[15] The first successful UTx pregnancy occurred via uterine-tubal-ovarian transplantation, where three live births were reported.[16] In allogeneic UTx studies in sheep, uteri were exchanged between breeds with cyclosporine IS and a live birth was reported.[17] Further studies focused on tailoring IS, where a triple protocol of tacrolimus, mycophenolate and corticosteroids, gave long-term graft viability.[19,20] Investigations into ischemia–reperfusion tolerance showed severe tolerance to 24 h of cold ischemia.[20] Sheep

TABLE 1 Countries and numbers (given as intervals), where human uterus transplantation procedures have been performed. The number of centres in each country are given in brackets. Data is obtained from references[7,46], as well as from personal communications.

Country (number of centres)	Number of cases in each country
United States (4)	40–45
Mexico (1)	<5
Brazil (2)	<5
Sweden (1)	20–25
Czech Republic (1)	5–10
Germany (1)	5–10
Belgium (1)	<5
France (1)	<5
Spain (1)	<5
Italy (1)	<5
Serbia (1)	<5
India (3)	10–15
Turkey (1)	<5
Lebanon (1)	<5
Saudi Arabia (1)	<5
China (2)	<5
South Korea (1)	<5
Singapore (1)	<5
Australia (2)	<5

UTx has also greatly supported human UTx development through team-training.[21]

Two non-human primate species, the baboon and cynomolgus macaque, have been central to UTx research. Early autologous studies in baboons tested vascular pedicles of ovarian veins and internal iliac arteries, but only two of ten resumed menses, highlighting surgical complexity of UTx.[22] Refinements included procuring entire internal iliac arteries, with six baboons resuming regular menses, though pregnancy did not occur, likely due to ischemia-induced tubal blockage.[23] Subsequent allogeneic baboon studies compared three groups: no IS, "IS-mild" (tacrolimus), and "IS-moderate" (thymoglobulin induction with tacrolimus, mycophenolate, and corticosteroids). Necrosis occurred in non-IS and IS-mild groups, while hormonal cyclicity resumed in five IS-moderate animals.[24] Cervical biopsies effectively diagnosed rejection. One baboon study of DD UTx utilized thymoglobulin induction, followed by tacrolimus and corticosteroids. Severe weight loss led to sacrifice in some animals, but one resumed cyclicity and displayed a viable graft 4 months post-transplant, reinforcing the importance of induction and combination IS.[25] Research groups in Japan have performed very valuable studies in the field of UTx, utilizing the cynomolgus macaque model. These studies include a successful autologous-UTx with 3 h of warm ischemia, resulting in resumed menses and a live birth, proving UTx feasibility and supporting future human trials.[26] In the allogeneic cynomolgus macaque model rituximab, thymoglobulin, and triple maintenance IS were used and this led to a live birth, the first after allogeneic UTx in non-human primate species.[27] While significant, the result of the latter study followed numerous human UTx live births, limiting its broader scientific impact.

In conclusion, animal UTx studies have been instrumental in advancing UTx research. These studies demonstrated key milestones, including live births, development of IS protocols, and insights into surgical techniques, ischemia tolerance, and graft rejection diagnostics. Collectively, they provided essential preclinical data that shaped planning of human UTx trials and subsequent clinical success.

1.2 | UTx patients

AUFI is diagnosed in approximately 20 000 women of childbearing age within a population of 100 million, as estimated from UK data.[28] While the absence of a uterus is the most evident cause of AUFI, some women with a uterus that is dysfunctional and unable to sustain pregnancy also fall under this category.

The most obvious cause of AUFI is anatomical absence of the uterus, with the most common cause of uterine absence being hysterectomy. Cervical cancer is the leading malignancy-related reason for hysterectomy, with over 30% of cases diagnosed during reproductive age.[29] In select cases with smaller cervical tumors, trachelectomy may be a fertility-sparing option. However, for patients requiring radical hysterectomy without adjuvant radiation, UTx may be considered. Less common uterine malignancies, such as endometrial cancer, leiomyosarcoma, and endometrial stromal sarcoma,[30] could also warrant post-hysterectomy UTx, provided at least 5 years have elapsed since diagnosis. This precaution minimizes the risk of IS triggering dormant cancer cells. Non-malignant causes for hysterectomy at a young age are less frequent. Emergency peripartum hysterectomy occurs in approximately 5 out of 10 000 deliveries,[31] with repeated cesarean delivery being the major risk factor.[32] Large or multiple leiomyomas in women of reproductive age can also necessitate hysterectomy after other treatments, such as ablation and myomectomy, have been exhausted. Around 2% of women aged 35 to 40 undergo hysterectomy due to leiomyoma.[33] Congenital uterine absence, as in Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), is another cause of anatomical absence of the uterus. MRKH syndrome, characterized by uterine aplasia in females with normal karyotype and secondary sex characteristics, has a prevalence of approximately 1 in 4500 women.[34] Notably, the great majority of more than 140 uterus recipients worldwide have MRKH syndrome, similar to the distribution of AUFI causes in the original Swedish study.[2]

Some causes of AUFI arise from a uterus that is present but dysfunctional, without any associated malformation. For example, leiomyomas are present in about 25% of IVF patients.[35] Submucous and large intramural fibroids can significantly reduce implantation potential and pregnancy outcomes.[36] While myomectomy or ablation can be effective, persistent implantation failure may lead to consideration of hysterectomy followed by UTx. Intrauterine adhesions, typically caused by endometritis or postpartum curettage, have a prevalence of approximately 1.5%.[37] Hysteroscopic resection restores fertility in about 70% of moderate and 30% of severe cases.[38] Radiotherapy, whether local pelvic or total body irradiation, significantly reduces uterine volume and causes infertility, sometimes leading to infertility and adverse pregnancy outcomes.[39] UTx can be considered in these types of cases, but they should be considered high-risk UTx procedures, because of irreversible radiation changes to surrounding tissues, including the blood vessels.

Congenital malformations result from disruptions in the development, formation, or fusion of the Müllerian ducts during fetal life. These malformations affect 5–7% of the general population, with most not linked to infertility.[40] However, in women with recurrent miscarriages, the prevalence of partial uterine malformations is around 15%.[40] The most common uterine malformation is septate uterus[40] and hysteroscopic resection effectively improves outcomes for infertility and recurrent pregnancy loss.[41] The bicornuate uterus represents 25% of uterine malformations. Spontaneous abortion rate among women with this malformation is around 35%, with limited benefit from corrective surgery.[41,42] The unicornuate uterus and uterus didelphys account together for 20% of malformations. These conditions are associated with a 30% miscarriage rate and a live birth rate of around 50%.[41] The hypoplastic and T-shaped uterus are rare malformations with live birth rates below 10%.[41,42] The most severe congenital anomaly is MRKH syndrome,[34] where only rudimentary uterine tissue exists.

In summary, both anatomical absence and functional impairment of the uterus due to congenital, acquired, or radiation-induced causes can result in AUFI.

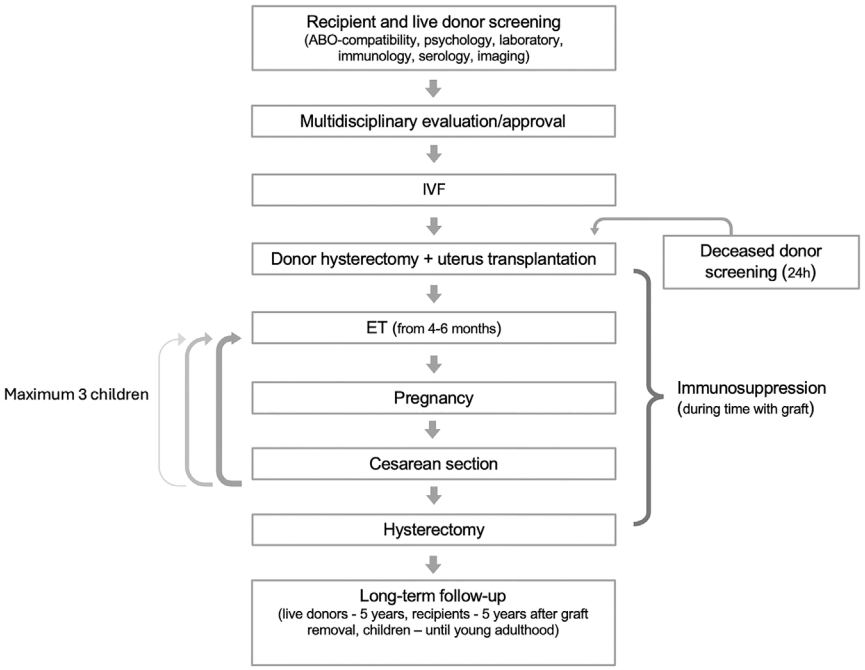

FIGURE 1 Flow chart of a uterus transplantation procedure with childbirth(s).

1.3 | Clinical flow of UTx

The clinical flow of UTx is outlined in Figure 1. A meticulous screening process is conducted for the potential recipient and her dedicated LD, followed by a comprehensive review by a multidisciplinary team to confirm their suitability for UTx. In cases involving a DD, a rapid 24-h screening and evaluation process is conducted, which is less detailed but still followed by approval procedure. Before the UTx, in vitro fertilization (IVF) is performed to cryopreserve embryos, unfertilized oocytes, or both. To ensure a high probability of achieving at least one live birth, a minimum of 6–8 high-quality blastocysts or 20–25 unfertilized oocytes should be preserved. The surgical phase includes the donor hysterectomy (LD or DD) and the transplantation into the recipient. The recipient requires IS therapy from the time of UTx until the uterus is removed. Embryo transfer (ET) can begin some months after UTx, and delivery is planned via Cesarean section to avoid strain on the transplanted uterus and vaginal anastomosis. If desired and medically feasible, additional ETs can be conducted for up to two more children. Following childbirth, hysterectomy is performed to eliminate the need for continued IS. Long-term follow-up is conducted for the LD, recipient, and child(ren).

1.4 | Types of UTx

UTx can be performed using a graft from either a LD or a DD, the latter often referred to as a multi-organ donor. Deceased donor UTx offers significant advantages, such as eliminating surgical risks for the donor and providing long vascular pedicles with large-diameter vessels, which simplify anastomosis. In contrast, LD UTx allows access to a complete medical history and facilitates thorough pre-surgical planning with a well-prepared multidisciplinary team. Surgical approaches differ depending on the donor type. For DDs, hysterectomy is always performed via laparotomy. In LDs, hysterectomy can be carried out either through laparotomy or robotic-assisted laparoscopy. Regardless of the type of donor, transplantation into the recipient is conducted through laparotomy. Overviews of the major components of these surgical procedures are provided below.

1.5 | Deceased donor hysterectomy—Technique of open surgery

This hysterectomy is part of multi-organ recovery, including thoracic and abdominal organs. Dissection of the uterine vascular pedicles should be completed before retrieving vital organs to prevent prolonged warm ischemia. A full midline incision, with optional bilateral inguinal extensions, is used. Figure 2 provides an overview of the positions for transecting the ureter and vascular pedicles. The internal iliac arteries are dissected distally, to about 2 cm proximally to the uterine artery-ureter crossing, where the ureters are transected. The round ligaments are divided, and a large bladder peritoneal flap is preserved. The ureters are further dissected at a position near their entry points into the bladder and transected, avoiding damage to deep uterine veins that may curve towards the bladder in the space between the artery-ureter crossing and the bladder. Obliterated umbilical vessels are ligated around 2 cm from the branching of the uterine arteries. The internal iliac arteries and veins are dissected with ligations of branches, leaving only the uterine vessels intact. The dissection then focuses on the parametrial tissue containing the uterine artery and 1–3 uterine veins, with venous branches divided and secured. The rectovaginal space is dissected, and the utero-sacral ligaments are transected. Finally, the external iliac arteries are exposed for later uterine flushing. After cross-clamping the aorta and vena

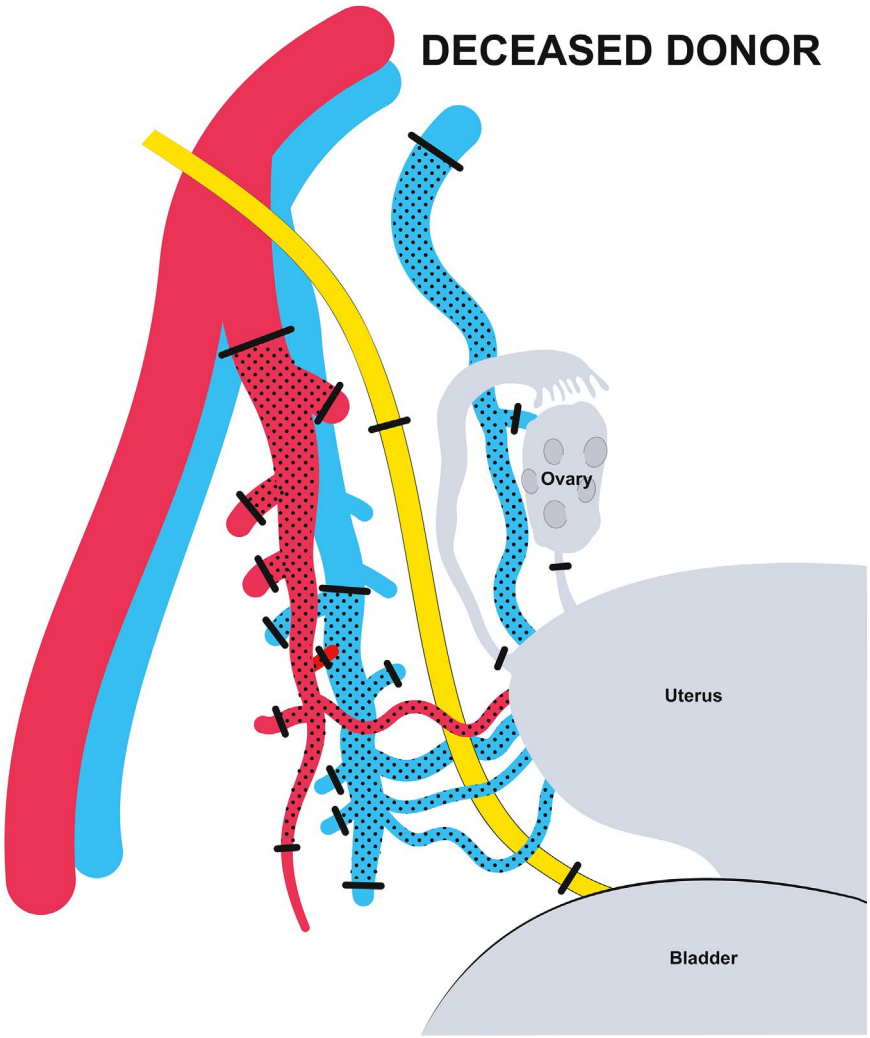

FIGURE 2 Schematic illustration of the left side of the pelvis of a deceased donor, highlighting the major veins, arteries, and ureter. The transection sites for vessels and the ureter are indicated with black lines. The vascular pedicles connected to the uterus at the time of removal from the deceased donor are represented by dotted vessels.

cava, traditional organs are flushed and removed. The uterus is then flushed through catheters inserted into the external iliac arteries, directing flow through the internal iliac arteries and into the uterine arteries. The vagina is transected around 2 cm from the fornix, and the internal iliac vessels are clamped and transected to optimize segments for anastomosis. The utero-ovarian veins are also harvested, and the uterus is removed. On the back-table, the ovaries and oviducts are bilaterally excised after ligations. The added duration for preparation of the uterine graft and flushing is estimated to 1–2 h.

1.6 | LD hysterectomy—Technique of open surgery

The procedure starts with that double J ureteric stents are placed, and surgery is then via a sub-umbilical midline laparotomy. The round ligaments are divided, and a large peritoneal bladder-flap is carefully dissected to preserve it for graft fixation. Bilateral pelvic sidewall dissections follow, with identification and division of the obliterated umbilical arteries near the bifurcation of the uterine arteries. Figure 3 illustrates the positions for transecting the vascular pedicles. Careful mobilization of the ureters is performed, from the level of the iliac crossing and towards the ureteric tunnel. Proximal to and inside the tunnel, small arterial and venous branches are coagulated, using bipolar diathermy, or ligated to protect the ureters from heat damage. Once the ureter is sufficiently mobilized along the entire length of the ureteric tunnel, with only the uterine artery and any overlying uterine veins covering the ureter, and without ureteric attachment to paracervical tissue in that area, it can be identified anterior to the uterine artery as it progresses towards the bladder. A rubber sling is placed around the ureter and uterine artery and veins are cautiously dissected, and any venous plexuses connected to the ureters are gently separated. It is important to note that the uterine veins may curve towards the bladder in a knee-like fashion before arching downward to connect with the pelvic sidewall and enter the internal iliac vein. The arterial segment, extending from the internal iliac artery to the uterine artery, is preserved for use as a conduit. Major arterial branches, including iliolumbar, sacral, and vaginal arteries, are ligated, while blood flow to the gluteal artery is preserved. One or two large uterine veins on each uterine side are carefully procured with segments of the internal iliac veins to optimize anastomosis. The uterine branch of the utero-ovarian vein is also preserved for additional venous outflow if needed. Salpingectomy and transection of the utero-ovarian ligament is performed during this dissection. In case of a postmenopausal donor,

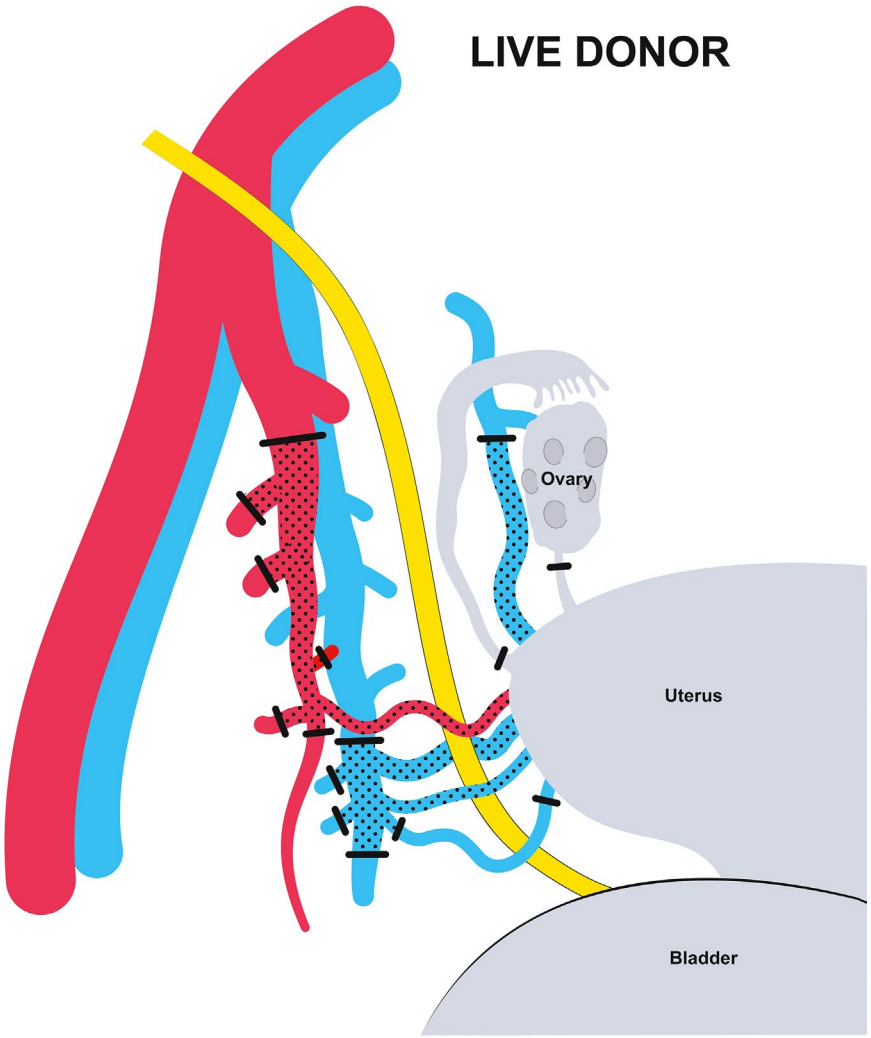

FIGURE 3 Schematic illustration of the left side of the pelvis of a live donor, showing the major veins, arteries, and ureter. The transection sites for vessels are indicated with black lines. The vascular pedicles connected to the uterus at the time of removal from the live donor are depicted with dotted vessels.

oophorectomy may be considered, and one or two long segments of the complete utero-ovarian vein can be preserved on the graft. Once bilateral dissections are complete, the rectovaginal space is opened, and the utero-sacral ligaments are divided. The vagina is transected with a 2 cm rim on the uterine side to facilitate later anastomosis. Vascular clamps are placed sequentially on the internal iliac arteries, veins, and the utero-ovarian vein branches, and the vessels are sharply divided to prepare for anastomosis. The uterus is immediately transferred to the back table for flushing and cooling. The donor surgery concludes with vessel closure, ovarian fixations to the pelvic sidewalls, and standard closure techniques, including hemostatic control and suturing. The duration of this procedure is 8–11 h.

1.7 | LD hysterectomy—Technique of robotics

A robotic system with a 4-arm setup and dual-console is used, involving two robotic surgeons and one laparoscopic surgeon. Double J ureteric stents are placed. The donor is positioned in a 28° Trendelenburg position with side-docking for optimal uterine manipulator access. Instruments include bipolar forceps, monopolar scissors, needle driver, clip applier, grasping forceps, and vessel sealer. The surgery begins with transection of the round ligaments and dissection of the bladder flap. Pelvic sidewall dissection starts and is completed first on the right side for better ergonomics. An identical procedure is then repeated on the left pelvic sidewall. The positions for transecting the vascular pedicles are identical to those used in laparotomy for LD hysterectomy, as shown in Figure 3. The ureter is carefully dissected from the iliac vessel and through its tunnel, freeing it from uterine artery attachments. Bipolar diathermy controls small vessels and larger vessels are sealed by hemostatic clips. Branches of the internal iliac arteries are dissected and sealed. The challenging part is freeing the ureter for the 3–4 cm length between its tunnel outlet and inlet into the bladder, preserving uterine veins and avoiding damage. A rubber sling around the ureter aids ureter manipulation. Internal iliac veins and branches are then dissected using clips, sutures, or vessel sealer. Steps are repeated on the left side (Figure 3). Once bilateral pelvic dissections are complete, salpingectomy and dissection of the uterine branches of the utero-ovarian vein are performed for venous outflow. Usage of only these branches will not necessitate oophorectomy, but the latter procedure, with harvesting of the complete utero-ovarian veins can be considered in a post-menopausal donor. The posterior uterus is approached via the pouch of Douglas, separating the rectum and

dividing uterosacral ligaments. Finally, the vagina is opened, leaving a 2 cm cuff. Vessels are clamped and divided, and the uterus is bagged and removed through the vagina. The vaginal cuff is closed, hemostasis confirmed, and instruments are removed. The duration of this procedure is 8–11 h.

1.8 | UTx—Technique of open surgery

A sub-umbilical midline incision is made for laparotomy. Preparatory steps vary between MRKH patients and non-MRKH patients, including those with previous hysterectomy or dysfunctional uteri.

In MRKH patients, the rudimentary uterus near the bladder dome and pelvic sidewalls is addressed. The transplanted uterus of typical MRKH patient, along with its anastomotic connections and fixations, is schematically depicted in Figure 4. External iliac vessels are dissected (5–7 cm), and round ligaments are cleaved to avoid interference with graft vascular pedicles. The vaginal vault, covered by the bladder, is identified and dissected using upward pressure with a sphere-shaped vaginal probe for clarity, allowing separation from the bladder and rectum. The midline rudiment uterine tissue is cleaved over the vault to acquire full exposure of the vaginal vault and for later fixation. An oval area over the vault is prepared with only the vaginal fascia covering the dome. Fixation sutures are placed in the bisected uterine rudiments and round ligaments for structural support after insertion of the graft.

For non-MRKH patients, dysfunctional or absent uteri require varying levels of dissection. The externa iliac arteries and veins are dissected, as described above. Cervical stumps are removed in subtotal hysterectomies, while full hysterectomy includes optional use of uterine vessels for the graft. An open vagina, after removal of uterus or vaginal stump, may be closed temporarily to minimize contamination into to abdomen in a patient that receives IS.

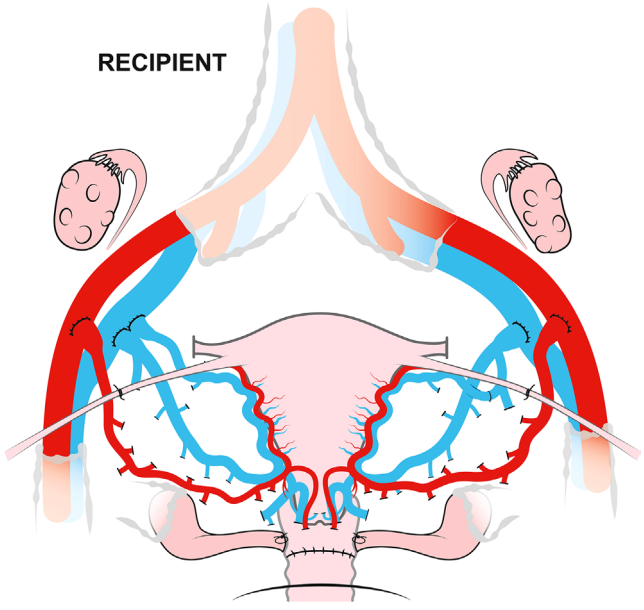

FIGURE 4 Schematic illustration of the pelvis of a uterine transplant recipient, showing the vascular anastomoses, vaginal anastomosis, and fixations.

After completed preparation of the recipient, having a duration of 1–1.5 h, the chilled uterus is placed anatomically. Vascular anastomoses are performed end-to-side between the graft's internal iliac segments, as well as additional utero-ovarian veins, and to the recipient's external iliac vessels using 5–0 to 7–0 polypropylene sutures. On each side vein anastomoses (one to two) precede artery connections, with clamps ensuring hemostasis. After the uterus is properly perfused by the recipient's blood flow, the vagina is opened (5 cm sagittal incision) for end-to-end vaginal-vaginal anastomosis using resorbable sutures. The two bilateral fixation sutures on bisected uterine rudiments and round ligaments provide additional structural support, and the peritoneal bladder flap is sutured to prevent herniation. After confirming hemostasis, the midline incision is closed. The duration of this procedure is 3–5 h.

1.9 | UTx success

Unlike other organ transplants, UTx requires a significant period before being deemed truly successful, which occurs only when a healthy child is born. The UTx success is generally divided into two phases: surgical success and definitive success. Surgical success is achieved when the graft demonstrates viability and functionality, indicated by normal blood flow on abdominal Doppler ultrasound and spontaneous menstruation, which signifies a hormonally responsive endometrium. This can typically be assessed around 3 months post-transplant after observing at least two menstrual cycles. Importantly, once adequate blood flow and menstruation occur, graft failure due to vascular complications or rejection becomes highly unlikely. However, true success is defined not by pregnancy alone—given the risk of miscarriages—but by the birth of a healthy child. The surgical successes of UTx were recently summarized from 71 published cases.[4] It is important to note that many of these cases represented pioneering attempts at specific centers, where the steep learning curve inherent to such a complex surgical procedure must be considered. Overall, surgical success was achieved in 77% of cases. The success rate for laparotomy-based LD UTx (73%) was comparable to DD UTx (71%) but lower than robotic-assisted LD UTx (88%).[4] However, the introduction of robotic-assisted UTx occurred more than 5 years after laparotomy UTx, likely benefiting from the experience and insights gained during earlier cases. This highlights the role of continuous refinement and accumulated expertise in advancing UTx surgical outcomes.

1.10 | Complications in recipients

Acute surgery-related complications in UTx recipients have been very uncommon. However, one notable complication, which typically present 3–9 months after UTx is vaginal stenosis at the anastomosis site between the graft's vaginal rim and the recipient's vaginal vault. Reported incidences vary: 14% in the Swedish

laparotomy LD study,[2] 25% in the Swedish robotic LD UTx study,[42] and 57% in the Czech mixed LD-DD trial.[43] Vaginal stenosis complicates cervical biopsy procedures for rejection diagnosis and ET, but can be addressed through diathermic incision, forced dilation, stenting, or combinations of these methods. Graft rejection is relatively common following UTx, though most rejection episodes are mild to moderate in severity and respond well to increased IS.[44] Severe rejections are rare after UTx and has not yet led to graft removal.[4]

1.11 | Complications in LDs

LD hysterectomy, either by laparotomy or robotics, for UTx is complex and lengthy, with typical durations of >9 h. In the Swedish laparotomy LD UTx study, one donor developed a unilateral ureterovaginal fistula, which was successfully repaired 4 months later, while no other major complications occurred among the nine donors.[2] In the Czech trial, two of five laparotomic LD donors experienced significant complications: one developed urinary bladder hypotonia requiring a suprapubic catheter, and another sustained a ureteric laceration repaired during the initial surgery and then managed with a JJ-stent.[43] Similarly, in the Dallas. LD laparotomy arm of their UTx trial, two of thirteen donors faced major complications: one required anesthesia for fecal impaction, and another underwent surgery for vaginal vault prolapse.[5] Robotic-assisted LD surgery showed the same rate of LD complications. In the Swedish robotic trial, one out of eight donors developed pyelonephritis with hydronephrosis, successfully managed with antibiotics and a temporary JJ-stent.[45] In conclusion, ureteric-related injuries seem to be the most common complication in LDs for UTx, and in the future surgical modifications should be implemented to decrease the risk of surgery-related ureteric injuries.

1.12 | IVF treatment in UTx

In vitro fertilization is routinely performed before UTx to confirm fertility, minimize risks of post-UTx oocyte retrieval, and reduce IS exposure time. Pre-UTx IVF assesses ovarian function, particularly in patients with MRKH syndrome, where ovarian reserve may be reduced.[46] Advances, such as random-start antagonistic stimulation protocols, have improved outcomes by optimizing embryo yield, reducing ovarian hyperstimulation syndrome risks, and allowing flexible initiation regardless of cycle timing. In cases where pre-UTx embryos are exhausted or other specific needs arise, post-UTx IVF is performed. Challenges include altered ovarian positioning and vascular changes as well as IS, increasing risks of bleeding and infection during oocyte retrieval. Despite these concerns, successful oocyte retrieval and stimulation have been reported[47] using protocols tailored to the immunosuppressed state and anatomical alterations. ET typically occurs between 3 and 8 months post-UTx, depending on the patient's stability and rejection pattern. Strict single ET policies are essential to avoid multiple pregnancies, which may pose significant risks due to the vascular and anatomical limitations of the transplanted uterus. Unique challenges post-UTx include cervical hypertrophy, extreme uterine-cervical angulation, and vaginal stenosis, often requiring careful pre-ET assessments, mock transfers, and advanced tools like extended ET catheters. Ultrasound-guided ET ensures optimal embryo placement and increases success rates. Currently, only one comprehensive report exists on reproductive and obstetric outcomes following UTx with IVF, summarizing results from the Swedish laparotomy LD UTx trial of 2012–13.[47] Seven of nine women had successful transplants, commencing ETs 12 months post-UTx. Six women gave birth, with three having two children each, resulting in altogether nine live births. Across 46 ETs, the clinical pregnancy rate was 32.6%, while the live birth rate per ET was 19.6% overall and 30.0% among those who gave birth. Five of the nine live births resulted from IVF treatments performed after UTx. One patient, despite 16 ETs, experienced six miscarriages (four at weeks 7–8 and two at week 15), with histopathology of the late losses revealing acute chorioamnionitis. The cumulative live birth rate was 86% for seven women with viable grafts and 67% for all nine attempted UTx procedures.[47]

1.13 | Obstetrical and neonatal outcome after UTx

Pregnancy following UTx represents the final phase of a prolonged and intricate process that includes highly complex uterine procurement surgery, uterine ischemia with reperfusion injury, precise vascular anastomosis surgery in the recipient, pregnancy achieved through IVF and ET, as well as fetal exposure to maternal IS. These combined factors can negatively influence pregnancy outcomes in women with uterine allografts. A recently published systematic review, which included live births following UTx, analyzed maternal and neonatal outcomes for women who underwent this procedure.[48] Data from 40 live births in 36 women were included in the final analysis. The review reported a hypertensive disorder of pregnancy rate of 22.5%, comprising 7.5% for gestational hypertension and 15.0% for preeclampsia. Gestational diabetes occurred in 7.5% of pregnancies, while intrahepatic cholestasis of pregnancy was noted in 5.0%.[48] Placental complications were also observed, including placenta accreta spectrum in 5.0% and placenta previa in 10.0% of cases. Premature rupture of membranes occurred in 15.0% of pregnancies. All 40 deliveries were singleton and via cesarean section. Of these, 52.5% were elective cesarean sections, while 47.5% were emergency cesarean sections. Preterm birth before occurred in 70.0% of cases, with 39.3% of these preterm births following provider-initiated elective cesarean sections. Fetal growth restriction was observed, in 20% and respiratory distress syndrome was reported in 35.0% of cases. Notably, there were no reports of APGAR score below 5 at 2 minutes. In conclusion, the elevated rates of maternal and perinatal complications emphasize

the need for close monitoring of pregnancies following UTx, along with the implementation of suitable treatments and interventions during pregnancy. Additionally, provider-initiated cesarean sections should be delayed until after gestational week 37 to reduce the risk of prematurity and its associated complications, such as respiratory distress syndrome.

2 | CONCLUSION

In summary, UTx represents a groundbreaking treatment for AUFI, made possible through extensive animal studies, evolving surgical techniques, and assisted reproductive advancements. Essential milestones in animal research, including the establishment of viable grafts, live births, optimized IS protocols, and team-training have paved the way for its clinical success. However, the procedure remains highly complex, with risks for LDs, recipients, and offspring, necessitating careful patient selection, thorough preoperative preparation, and close postoperative monitoring. Maternal and perinatal complications, including hypertensive disorders and preterm birth, underscore the need for vigilant obstetric care and delayed delivery beyond 37 weeks when possible. Moreover, long-term studies of children born after UTx should be implemented, preferentially through multicenter collaborations. While further research is required to enhance outcomes and reduce risks, UTx offers a promising option for women with AUFI to achieve full biological (gestational and genetic) motherhood, marking a significant advancement in reproductive medicine.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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