

REVIEW



Evolving clinical challenges in uterus transplantation



BIOGRAPHY

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KEY MESSAGE

This review considers the challenges of uterus transplantation and ways to overcome them so that the procedure could become part of the reproductive specialist's armamentarium when counselling patients with uterine factor infertility.

ABSTRACT

Before the first live birth following uterus transplantation (UTx) in 2014, the 1–2% of women with an absent or non-functional uterus had no hope of childbearing. With 64 cases of UTx and 34 births reported in the scientific literature, this emerging technology has the potential for translation into mainstream clinical practice. However, limitations currently include donor availability, recipient suitability, surgical challenges regarding success and complications, and recipient management after UTx and during pregnancy. This review considers these challenges and ways to overcome them so that UTx could become part of the reproductive specialist's armamentarium when counselling patients with uterine factor infertility.

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KEY WORDS

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INTRODUCTION

Uterine factor infertility (UFI) is classified as either absolute or relative. Absolute UFI (AUF) implies absence of the uterus and encompasses congenital and acquired forms. Congenital AUF, otherwise known as the Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, involves the absence of the uterus and often part of the vagina at birth, and affects 1 in 4500 females (Ledig and Wieacker, 2018). Acquired AUF results from hysterectomy, which, in the USA alone, is performed annually in over 150,000 women under the age of 40 years (Brett and Higgins, 2003).

Relative UFI (RUF) involves a uterus that is so seriously altered that neither naturally conceived nor IVF pregnancies are likely. The primary cause of RUF is Asherman syndrome, although certain congenital uterine malformations also cause it. Women suffering from UFI had no hope of childbearing until the feasibility of uterus transplantation was documented in 2014, following the birth in Sweden of a healthy baby after transplantation from a living donor to a recipient with MRKH (Brannstrom et al., 2015). The ultimate measure of success in UTx is the occurrence of a minimum of side effects for the mother and, if living, the donor, and the safe delivery of a healthy live-born infant. The United States Uterus Transplant Consortium (USUTC) has defined seven progressive stages of success: technical success (defined by established outflow and graft viability 3 months after surgery), menstruation, embryo implantation, pregnancy, delivery, graft removal and long-term follow-up (Johannesson et al., 2020).

The complexities and associated challenges of establishing a successful UTx programme currently present barriers to translation into mainstream clinical practice. This review addresses these challenges, proposes ways to overcome them and discusses the required psychological support for living donors and recipients, as well as the ethical questions. The aim is to provide a roadmap for the successful establishment of new UTx centres, so that this unique non-vital transplantation will become more accessible to patients suffering from UFI.

SUMMARY OF PUBLISHED CASES

The first UTx, performed in Saudi Arabia in 2000 and published in 2002 (Fageeh et al., 2002), was a failure. The second case was performed in Turkey in 2011 and published in 2013 (Ozkan et al., 2013; Ozkan et al., 2021), and this resulted in a live birth 9 years later (Ozkan et al., 2013; Ozkan et al., 2021). The first live birth reported from Sweden, in 2015 (Brannstrom et al., 2015), was one from a trial of nine cases with living donors that was performed after more than a decade of extensive foundational training and research on animal models (Johannesson et al., 2015). In seven of the cases, the grafts were functional. However, two required removal, each because of hypoperfusion and secondary intrauterine infection (Karlsson et al., 2021). Six patients had healthy babies (three with successive pregnancies) and one had repeated miscarriages. A second UTx trial performed by the Swedish team introduced robotic-assisted laparoscopy, including in the living donors (Brucker et al., 2018; Ayoubi et al., 2019; Brannstrom et al., 2020a) and resulted in a birth (Brannstrom et al., 2020b).

Of the 70 recipients to date, 65 have been women with MRKH, four have had a hysterectomy and one had Asherman syndrome (Brannstrom et al., 2021a). Sixty-four UTx procedures have been reported in peer-reviewed journals (TABLE 1), although more than 80 have been undertaken by about 20 teams worldwide, according to media reports and personal communications (FIGURE 1) (Brannstrom et al., 2021a).

The current overall technical success rate of UTx, including four unpublished cases and two cancelled backtable cases, is 72.9% (51/70). Thirty-four healthy children have been born, four being born after a previous birth following UTx (TABLE 1). Most births ($n = 29$) involved transplanted uteri from living donors (Brannstrom et al., 2015; Bokstrom et al., 2016; Brannstrom et al., 2016; Brucker et al., 2020; Chmel et al., 2020; Huang et al., 2020; Johannesson et al., 2021b; Richards et al., 2021), with only five involving deceased donors (Ejzenberg et al., 2019; Flyckt et al., 2020; Fronek et al., 2021a; Johannesson et al., 2021b; Ozkan et al., 2021) (TABLE 1). Although the technical success rate is currently higher with living versus deceased donors (77.6% versus 58.3% [7/12]; Brannstrom et al.,

2021a), this must be balanced against the risks for the living donor. Indeed, some teams choose to work only with deceased donors (Ozkan et al., 2013; Ejzenberg et al., 2019; Richards et al., 2021) while others work with living donors because extensive pre-transplantation evaluation and planned surgery is possible (Brannstrom et al., 2019; Jones et al., 2019a; Richards et al., 2021).

While both technical success and live birth rates after UTx are encouraging, only a few women of the approximately 1 million in the world with UFI have benefited from the procedure to date (Brannstrom et al., 2021a). Numerous reasons exist for this limited translation into clinical practice. UTx involves several unique steps (FIGURE 2): the recipient must undergo IVF to create embryos, ideally prior to the UTx; the likelihood that a transplanted uterus can support a term pregnancy must be considered; pregnancy management presents unique challenges; and the graft of this transitory transplantation procedure must ultimately be removed. Of note, UTx is still at the experimental stage, and the precautionary principle must be widely applied.

SCREENING AND SELECTION OF UTx RECIPIENTS AND DONORS

Recipients

Based on the authors' Swedish and French collaborative experience, the following criteria for UTx recipients include: (i) ideally less than 38 years of age (Brannstrom et al., 2014) (because of the sharp decline in fecundity beyond 37 years (American College of et al., 2014)); (ii) a willingness to undergo IVF (because natural conception is not possible due to devascularization of the fallopian tubes during the surgery); (iii) no severe associated comorbidities or chronic or active infections; (iv) a body mass index less than 30 kg/m²; and (v) being in a stable relationship. Although having only one kidney, a condition often associated with MRKH, is not currently an exclusion criterion, some trials have excluded women with a low-lying pelvic position of the kidneys (Brannstrom et al., 2014). Most studies have excluded women with past vaginal reconstruction with sigmoid or jejunal segments because of the risk of inflammation, miscarriage or implantation failure, as exemplified by the first deceased donor UTx procedure reported in 2013 (Erman Akar et al., 2013).

TABLE 1 STATE OF THE ART OF UTERUS TRANSPLANTATION

		Recipients				Donors					
Year published ^a	Country	Number of UTx cases	Cause of uterus infertility	Number of complications ^b	Reason for transplant-ectomy	Live/deceased	Relationship to recipient	Surgical approach	Number of complications ^b	Transplant result	Clinical outcome
Fully reported cases											
2002	Saudi Arabia	1	1 post-partum hysterectomy	1 thrombosis	1 L	1 non-directed	Open	1 ureteral laceration	1 failure	N/A	N/A
2013	Turkey	1	1 MRKH	0	N/A	1 D	1 non-directed	Open	N/A	1 success	2 SAB, 1 LB
2015	Sweden	9	8 MRKH 1 hysterectomy for cervical cancer	2 transplantectomies 1 thrombosis 1 hypoperfusion	9 L	5 mothers 1 aunt	Open	1 uretero-vaginal fistula	7 successes 2 failures	9 LB (2 LB from each of 3 UTx cases), 1 with 6 SAB	
						1 sister					
						1 mother-in-law					
						1 friend					
2015	China	1	1 MRKH	0	N/A	1 L	1 mother	Robotic	0	1 success	1 LB
2016	USA Dallas	20	18 MRKH 2 hysterectomy for myomas	6 transplantectomies 1 haemorrhagic shock	2 thrombosis 4 surgical complications	18 L	17 non-directed 1 mother	13 open 5 robotic	1 faecal impaction 1 vaginal cuff D-dehiscence 1 bilateral ureteric vaginal fistulae 1 blood clot in ureter	13 successes 5 failures	11 LB (2 LB from 1 UTx case)
2016	Brazil	1	1 MRKH	0	N/A	1 D	1 non-directed	Open	N/A	1 success	1 LB
2017	USA Cleveland	2	2 MRKH	1 transplantectomy	1 fungal infection	2 D	2 non-directed	Open	N/A	1 success 1 failure	1 LB
2017	Germany	4	4 MRKH	0	N/A	4 L	3 mothers 1 sister	Open	0	4 successes	2 LB, 1 SAB
2017	Sweden	8	8 MRKH	2 transplantectomies	2 hypoperfusions	8 L	6 mothers	Robotic	1 pyelonephritis with hydronephrosis	6 successes 2 failures	1 LB, 5 with unpublished outcomes
2018	India	4	3 MRKH 1 Asherman syndrome	0	N/A	4 L	4 mothers	Laparoscopy	0	4 successes	4 with unpublished outcomes
2018	Czech Republic	10	10 MRKH	3 transplantectomies 3 haemorrhage 5 vaginal stenosis 1 vesico-vaginal fistula	2 thrombosis 1 HSV infection	5 L	4 mothers 1 mother's sister	Open	1 ureteral laceration 1 bladder hypotonia	4 successes 1 failure	2 LB, 1 SAB, 1 recipients with 11 ET and no pregnancies, 1 recipient with 5 ET and no pregnancies
2020	Lebanon	1	1 MRKH	0	N/A	1 L	1 mother	Open	0	3 successes 2 failures	1 LB, 2 recipients with SAB
						5 D	5 non-directed	Open	N/A	1 success	1 LB

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TABLE 1 (continued)

		Recipients				Donors					
Year pub-lished ^a	Country	Number of UTx cases	Cause of uterus infertility	Number of complications ^b	Reason for transplant-ectomy	Live/de-ceased	Relationship to recipient	Surgical approach	Number of complications ^b	Transplant result	Clinical outcome
2021	Spain	1	1 MRKH	0	N/A	1 L	1 sister	Robotic	0	1 success	Unpublished
2021	Brazil	1	1 MRKH	0	N/A	1 L	1 non-directed	Robotic	0	1 success	Unpublished
Cancelled procedure											
2017	Germany	1	1 MRKH	1 UTx not performed because non-flushable on backtable	N/A	1 L	1 mother	Open	0	1 failure	N/A
2018	Czech Republic	1	1 MRKH	1 UTx not performed due to vein insufficiency on backtable	N/A	1 L	1 non-directed	Open	0	1 failure	N/A
Authors' personal experience (unpublished to date)											
Unpub-lished	Serbia	1	1 MRKH	0	N/A	1 L	1 monozygotic twin	Open	0	1 success	1 LB
Unpub-lished	Lebanon	1	1 MRKH	0	N/A	1 L	1 sister-in-law	Open	0	1 success	Not yet delivered
Unpub-lished	Sweden	1	1 MRKH	1 EBV infection with PTLD high-grade lymphoma needing transplantectomy	1 PTLD	1 D	1 non-directed	Open	N/A	1 failure	N/A
Unpub-lished	France	1	1 MRKH	0	N/A	1 L	1 mother	Robotic	1 ureteral injury	1 success	1 LB

(B) Summary data			
UTx	Recipients	Living donors	Deceased donors
Total	70	Total 68	Total 58
Success	51/70 (72.9%)	Complications ^b 22/68 (32.4%)	Success 45/58 (77.6%)
LB/UTx ^c	34/70 (48.5%)	From transplantec-tomies 16/68 (23.5%)	Complica-tions ^b 10/58 (17.2%)
LB/success ^c	33/51 (66.7%)		Success 7/12 (58.3%)

^a Year given is year of first publication.

^b Complications: at least one grade III or higher Clavien-Dindo complication.

^c 2 LB/UTx for 4 recipients.

D, Deceased donor; EBV, Epstein-Barr virus; ET, Embryo transfer; HSV, herpes simplex virus; L, Live donor; LB, live birth; MRKH, Mayer-Rokitansky-Kuster-Hauser syndrome; N/A, not applicable; PTLD, post-transplant lymphoprolifera-tive disorder; SAB, spontaneous abortion; UTx, uterus transplantation.

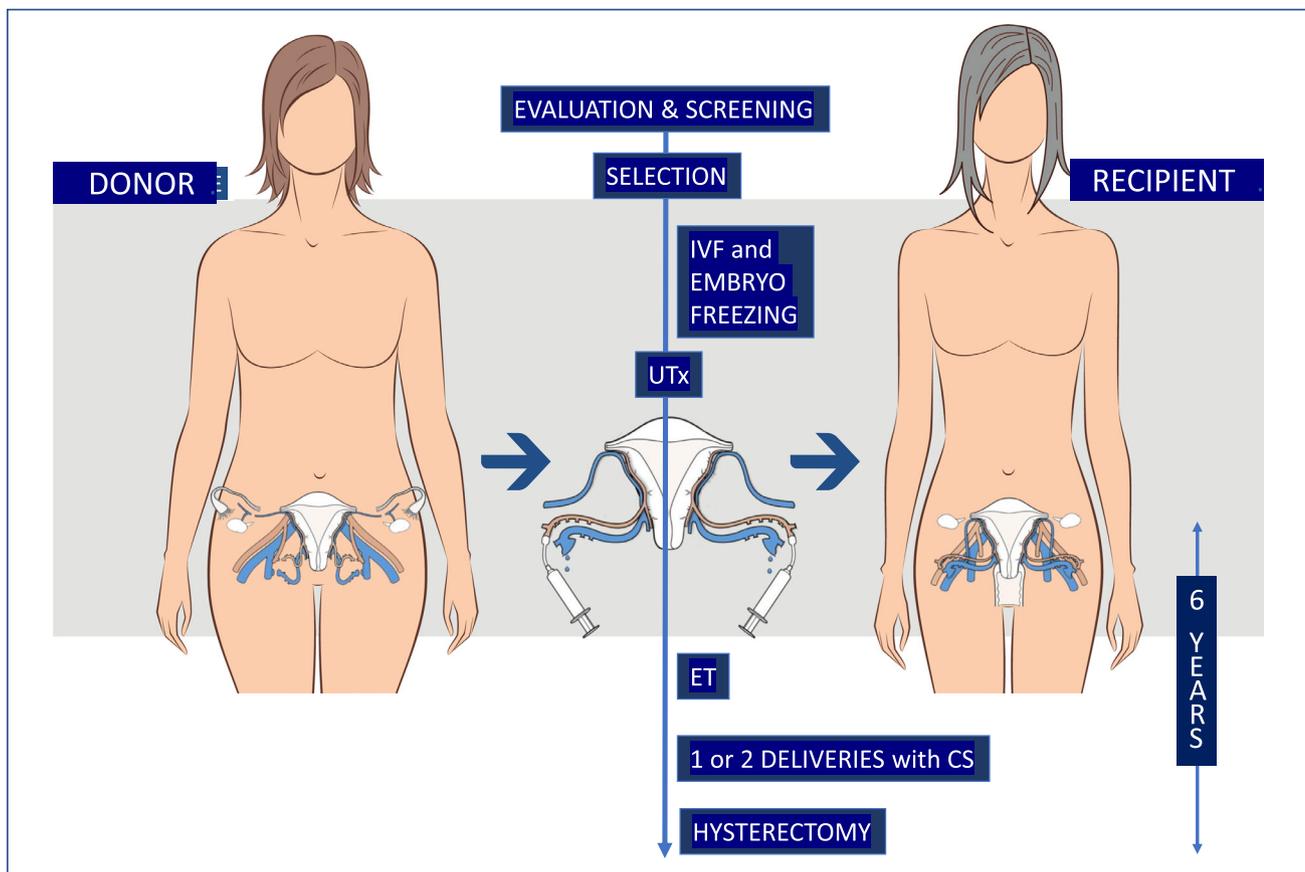


FIGURE 2 The steps involved in the uterus transplantation process from donor/recipient screening to hysterectomy.

perform a pre-evaluation of the vessels in deceased donors, this may not present a problem as these women tend to be younger than living donors (current mean age 32.5 years versus 47.9 years) and so the age-related risk of sub-optimal arterial flow is reduced. Other constraints include less time to evaluate the uterus and to assess donor–recipient compatibility, infection risk including human papillomavirus (HPV) and the overall quality of the vessels.

Recipient–donor mismatching issues

As with other types of organ transplantation, ABO incompatibility and the presence of donor-specific antibodies (DSA) against the donor's human leukocyte antigens are the major, and absolute, reasons for donor exclusion (*Gentry et al., 2005*). In addition, the risk of cytomegalovirus (CMV) and Epstein–Barr Virus (EBV) must also be considered in donor–recipient matching. Although donor-positive/recipient-negative mismatches for EBV and CMV have been permitted by some teams, the risk of severe complications in the case of infection cannot be excluded. The Swedish team experienced one serious and life-threatening complication in a deceased

donor UTx procedure where the donor was EBV positive and the recipient was EBV negative (personal communication, J. Ekberg, Gothenburg, Sweden). The recipient acquired an EBV infection some months post-UTx and then developed post-transplantation lymphoproliferative disorder with multifocal, intestinal lymphoma, with multiple episodes of intestinal bleeding and perforation. Treatment was by hysterectomy with omission of immunosuppression and rituximab. The lymphoma regressed and the patient was in good physical health 2 years later, albeit with a considerable psychological burden.

Considering the potential deleterious transfection of CMV to recipients and their subsequent pregnancies, some teams have avoided transplanting CMV-positive donor grafts into CMV-negative recipients. This mismatch is unfortunately frequent because 50% of adults are CMV positive. Living donors are often positive (older and mothers), while recipients are more likely to be negative (younger and without children) (*Carbonnel et al., 2020*), which reduces the pool of potential living donors. Nevertheless,

preventive and curative treatment is available for CMV. Furthermore, close monitoring for CMV infection during the post-UTx course, with treatment as indicated prior to the embryo transfer, has been reported, with the recipient successfully carrying a healthy child to term (*Rosenzweig et al., 2021b*).

Another concern relating to the health of the recipient post-UTx is the risk of cervical dysplasia. Cervical intraepithelial neoplasia 2 has been reported in recipients after UTx with no previous dysplasia or HPV infection in the donor (*Johannesson et al., 2015*). This observation indicates that HPV vaccination in the recipient and her partner should be encouraged before UTx, and if either the donor or recipient is HPV positive, transplantation should not proceed. This is a limitation on the use of deceased donors as the HPV status is often not known prior to UTx in such cases.

SURGICAL CONSIDERATIONS

Recipients

Surgery in the recipient is traditionally performed by laparotomy and begins

in an adjacent operative room before graft retrieval is completed in the donor. Dissection of the vaginal vault from the bladder and rectum is performed first, followed by exposure of the external iliac vessels. In cases of MRKH, the midline rudimentary uterus, above the vaginal vault, must also be cleaved, followed by lateralization of the halves. The uterine graft is placed in the orthotopic position adjacent to the top of the vagina, and end-to-side vascular anastomoses are performed between the internal iliac segments of the graft and the external iliac vessels of recipient. The recipient's vaginal vault is then opened to allow end-to-end anastomosis to the vaginal rim of the graft. Fixation sutures are usually placed, at least between the stumps of the round ligaments of the graft and the sacro-uterine ligaments of the recipient. The average duration of surgery in the recipient is 4–5 h (Brannstrom et al., 2014).

To date, the risk of at least one complication of grade III or more in recipients according to the Clavien–Dindo classification is 32.4% ($n = 22/68$), with 23.5% ($n = 16/68$) resulting in graft removal (Fageeh et al., 2002; Brannstrom et al., 2014; Testa et al., 2017). In all but four of the 16 uteri that required removal the cause was surgical complications, thrombosis of the donor uterine vessels or hypoperfusion caused by their small size or arteriosclerosis. The four remaining cases were related to bacterial, fungal or viral infection (Brannstrom et al., 2014; Flyckt et al., 2017; Chmel et al., 2019).

Other complications have included vaginal stenosis, vesico-vaginal fistula and haemorrhagic shock (Testa et al., 2017; Fronck et al., 2021b). Vaginal stenosis, probably caused by discrepancies in the vaginal diameters of the donor and recipient, or thermal sectioning of the vagina and/or circumferential anastomosis, has frequently occurred and has often required re-intervention or stenting (Chmel et al., 2019).

A sufficient vaginal length is necessary to perform a good anastomosis with the graft. Self-dilatation, if feasible, is recommended for all women with MRKH during the years to months before UTx, to create a minimal vaginal length of around 7 cm (Kolle et al., 2019). Forced dilatation with Vecchietti surgery also appears beneficial (Chmel et al., 2020). Both dilatation approaches lead to creation of a vagina with normal

epithelium, and most likely a normal bacterial flora. The latter may be of importance for embryo implantation, since the uterine microbiome, in part, mimics the vaginal microbiome (Jones et al., 2020). Adequate vaginal access is important for allowing menstruation, cervical biopsies and embryo transfer.

Appropriate preservation perfusions have to be used to reduce cold ischaemia damage in deceased donors (Ozkan et al., 2013). When the duration of cold ischaemia must be prolonged, an extended normothermic ex-vivo reperfusion model could be developed (Padma et al., 2019). Revascularization of half of the uterus when the anastomoses are completed on one side may reduce warm ischaemia damage (Testa et al., 2017).

Robotic graft transplantation could improve postoperative follow-up and reduce scars in recipients. The first case of fully robotic uterus transplantation (including both graft harvest and graft transplantation) was performed in Sweden in October 2021 (unpublished), and that graft was successful (personal communication, Brännström, Gothenburg, Sweden).

Unfortunately, contrary to functional markers for other organs (such as creatinine for the kidney), no early biological or radiological marker of uterine function exists. Therefore, evaluation is performed using Doppler ultrasound monitoring of the uterine arteries, size of the uterus and growth of the endometrium, and by assessing the regularity of the menstrual periods.

Donors

Living donors

Living donor surgery is associated with risks of major complications. It is far more complex than a simple hysterectomy because the uterine arteries and veins must be preserved and include segments of the internal iliac artery and vein. Dissection of the uterine veins is complex due to their proximity to the ureters, firm attachment to the paracervical tissue and number of venous branches. Complete ureterolysis is also necessary. Moreover, the preservation of substantial portions of the uterine ligaments, an extensive sheet of bladder peritoneum and part of the vagina is also beneficial for easy uterine fixation in the recipient (Testa et al., 2018).

The typically long duration of living donor surgery has been accompanied by risks including uretero-vaginal fistulae, ureter injury, pyelonephritis, faecal impaction, acute anaemia and vaginal cuff dehiscence (TABLE 1). Ten of 58 (17.2%) living donors to date have had grade III or higher complications by the Clavien–Dindo classification (Clavien et al., 2009; Brannstrom et al., 2014; Ramani et al., 2020; Johannesson et al., 2021a). Therefore, efforts have focused on simplifying the procedure and increasing safety. Decreased use of thermal energy near the ureter, systematic use of pre- and post-operative ureteric stents for 4–6 weeks, and use of indocyanine green to identify vessels by fluorescence imaging may reduce the risk of ureteral lesions in living donors (Johannesson et al., 2021a). With increasing experience, many teams have replaced laparotomy by laparoscopy, often with robotic assistance (Wei et al., 2017a; Brannstrom et al., 2018; Puntambekar et al., 2018a; Ayoubi et al., 2019; Johannesson et al., 2021a; Vieira et al., 2021), and some have reported fully robotic removal (Wei et al., 2017b) with faster post-operative recovery times and the same early graft function. However, such comparisons may be confounded as laparotomy cases are typically performed in the initial cases when logistical and surgical competence may not have been fully acquired (Testa et al., 2017).

Additional efforts to simplify UTx and increase safety have included vascular reconstruction, although this has largely been unsuccessful due to the increased risk of thrombosis (Fageeh et al., 2002; Testa et al., 2017). Alternatively, the use of ovarian or utero-ovarian veins instead of uterine veins for the venous outflow has been attempted. This approach has since been found to reduce operative time and donor ureteral complications in humans (Wei et al., 2017a; Puntambekar et al., 2018a; Testa et al., 2018). A team in China used only the ovarian vein in the first case of wholly robotic uterus harvest, completed in 6 h (Wei et al., 2017a); a team in India, also using the ovarian veins, reported surgical times of 3–4 h, with the donor undergoing laparoscopy (Puntambekar et al., 2018a, Puntambekar et al., 2018b); and an American team reported a live birth after the use of laparotomy and only ovarian veins following an 8 h operation for the donor (Jarvholm et al., 2018; Ramani et al., 2020).

These reported successes with ovarian veins require further investigation to confirm that adequate uterine drainage and support of implantation and pregnancy are provided without complications. If confirmed, this approach could significantly simplify and shorten the procedure in living donors. However, these advantages must be balanced against the risk of oophorectomy and early menopause for younger donors (a Clavien–Dindo grade II complication), although this may be reduced if only ovarian veins proximal to the ovaries are used (Testa *et al.*, 2017).

Deceased donors

In deceased donors, uterine removal is facilitated by larger vessels as the dissection can include major parts of the internal arteries and veins and the complicated ureterolysis is not necessary. The ureters can be transected above the ureteric tunnel and close to the bladder, to be included in the uterine vessel-containing parametrial tissue. However, other problems may be encountered, such as: increased cold ischaemia time due to transportation of the organ, which may affect the graft quality; increased risk of haemorrhage when transplantation is performed due to the presence of small, unsealed vessels around the uterus; increased potential for rejection (particularly in non-related donors); decreased functionality due to unknown uterine pathology; and organizational challenges due to any unplanned surgery.

IMMUNOSUPPRESSION THERAPY AND MONITORING FOR GRAFT REJECTION

Immunosuppression therapy

No data currently exist regarding the long-term risk of immunosuppressive therapy in women undergoing UTx. However, a general recommendation is graft removal within 6–7 years to reduce the long-term risks, especially nephrotoxicity and immunosuppression.

Immunosuppressive treatment is like that used with kidney grafts. Early experience in the Swedish trial involved treatment with methylprednisolone (500 mg i.v. on day 0), anti-thymoglobulins (2.5 mg/kg on day 0 and day 1), mycophenolate mofetil (MMF) for 8 months, continuous tacrolimus but with higher trough concentrations during the initial 2 months, and prednisone for 1 week after UTx or in cases of rejection (Brannstrom *et al.*,

2014). As MMF is fetotoxic, switching to azathioprine 2 months before the embryo transfer is recommended (Hoeltzenbein *et al.*, 2012; Brannstrom *et al.*, 2014).

Indeed, more recent protocols eliminate the use of MMF entirely by using azathioprine directly at the time of UTx and waiting only 4 months before embryo transfer (Testa *et al.*, 2018; Johannesson *et al.*, 2019).

Monitoring rejection

Signs of rejection occur most commonly during the first 3–8 months after UTx (Molne *et al.*, 2017). Rejections are almost invariably asymptomatic and so must be closely monitored by assessing the presence of DSA in the peripheral blood, and by regular cervical biopsies. Using the uterine graft primate model (Johannesson *et al.*, 2013), three grades of rejection have been established based on lymphocyte invasion. The overall risk of some degree of rejection following UTx is currently high, although none has resulted in graft removal, and the majority were resolved with additional corticoids (Molne *et al.*, 2017).

Risks of infection

As with other solid organ transplantations, the risk of infection within the first 6 months after transplantation is high, but with UTx this risk also exists during pregnancy due to associated physiological immunomodulation. Removal of grafts for uterine abscess, herpes simplex virus and candida (Brannstrom *et al.*, 2014; Flyckt *et al.*, 2017; Chmel *et al.*, 2019), as well as for a septic abortion (*Escherichia coli*), has been reported (Fronek *et al.*, 2021b). CMV infections have also occurred both with and without pre-transplant mismatches (D+, R–), albeit with some favourable results following treatment (Rosenzweig *et al.*, 2021a). Of note, most infections could be prevented by prophylactic antimicrobial therapy (e.g. 6 months of trimethoprim sulfamethoxazole to prevent *Toxoplasma gondii*, *Nocardia*, *Pneumocystis* and *Listeria*, aciclovir/valganciclovir prophylaxis for 3–6 months to prevent CMV, and antifungal prophylaxis). Although the uterus graft is transitory and so the life-time infection risk should be low, data to assess overall probability of this risk are currently lacking.

PREGNANCY

Challenges relating to IVF

Due to the absence of the oviducts, pregnancy cannot be achieved by

intercourse and so must involve use of IVF embryos frozen for use in a subsequent cryopreservation–thaw cycle.

In all cases to date, the first IVF cycle has been performed before UTx surgery because of the increased risks of infectious and haemorrhagic complications of oocyte harvesting, due to immunosuppressive therapy and the altered vascular anatomy of the pelvis, as well as the assurance of a sufficient number of frozen embryos to warrant a UTx. Many teams require a minimum of 8–10 frozen embryos, which typically requires two pre-UTx IVF cycles (Brännström *et al.*, 2022). Nevertheless, in a few cases additional IVF cycles have been performed after UTx without complications (Brucker *et al.*, 2020; Brännström *et al.*, 2022), either because no pre-UTx embryos remained or, in one case, because the couple separated within a year after transplantation. Although this has not yet been undertaken, it may be prudent for prospective UTx recipients to cryopreserve some oocytes in case of separation from their partner before embryo transfer. This could also be an option for single women.

As in standard clinical IVF for fertility treatment, ovarian stimulation protocols have varied among teams and patients. However, trans-abdominal retrieval may be required in those women with MRKH who have a high localization of the ovaries. In the Swedish laparotomy (Brännström *et al.*, 2022) and robotic (Brannstrom *et al.*, 2020a) trials, 4 out of 9 and 1 of 8 patients, respectively, underwent oocyte retrieval transabdominally.

The original recommendation of 1 year between UTx and embryo transfer is now being questioned (Johannesson *et al.*, 2019). The Dallas team shortened the interval to 6 months, and then reduced this further to 4 months (Testa *et al.*, 2018; Johannesson *et al.*, 2019) with no complications to either mother or fetus. Hence, the timing of embryo transfers may reasonably be standardized to 6 months post-UTx providing the recipient has good post-operative recovery, resumption of uterine function with a return of menstrual cyclicity within 2–3 months and no sign of rejection or infection, and is on immunosuppressive treatment compatible with pregnancy (Johannesson *et al.*, 2015; Chmel *et al.*, 2019). This standardization could provide

the emotional benefit of a shorter time to pregnancy, and reduce the time with the graft and any potential long-term risks of immunosuppressive therapy.

The embryo transfer procedure *per se* has typically not varied among UTx recipients, except when there is vaginal stricture, in which case dilatation and stent insertion may be necessary. Transfer of a single embryo is mandatory to avoid multiple pregnancies and the associated increased risks of obstetric complications. In the first Swedish trial, the mean number of transfers was six per patient, the pregnancy rate per embryo transfer was 32% and the live birth rate per transfer was 19.6% in the seven women with viable grafts (Brännström *et al.*, 2022). The transfers involved cleavage-stage embryos, which probably contributed to the overall lower implantation rate per embryo. The cumulative live birth rate for successful transplants ranged from 71% to 85.7% and for the attempted UTx procedures it ranged from 50% to 55% in the biggest series to date (Fronek *et al.*, 2021b; Johannesson *et al.*, 2021b; Brännström *et al.*, 2022). Despite these promising statistics, repeated implantation failures or miscarriages were observed in some women (Ozkan *et al.*, 2016; Fronek *et al.*, 2021b; Ozkan *et al.*, 2021; Brännström *et al.*, 2022), indicating that research is needed to investigate and prevent them.

Gestational complications

Forty-six pregnancies have led to 34 healthy children. Of the 12 miscarriages, six were experienced by one patient in the Swedish laparotomy trial of 2013 (Brännström *et al.*, 2022). There have been no reported stillbirths, and no neonates of low birthweight for gestational age. There is one reported case of a congenital malformation, which was an anteriorly/caudally displaced urethra, with urethral reimplantation undertaken at the age of 11 months (Johannesson *et al.*, 2021b). There have been complications including pre-eclampsia ($n = 6$, including our French patient who had a single kidney), gestational hypertension ($n = 2$), placenta praevia ($n = 3$), placenta accreta with impaired renal function ($n = 1$), premature rupture of membranes ($n = 3$), gestational diabetes ($n = 3$), cholestasis ($n = 2$), preterm labour ($n = 5$), subchorionic hematomas ($n = 2$), oligohydramnios ($n = 1$), polyhydramnios ($n = 2$) and pyelonephritis ($n = 1$) (Brännström *et al.*, 2021a; Ozkan *et al.*, 2021; Richards *et al.*, 2021). The risks

of such varied complications require the involvement of a multidisciplinary team, including nephrologists. Moreover, careful monitoring and adaptation of immunosuppressive therapy is necessary because of variations in the immune response during pregnancy. Particular attention must also be given to risk of infection, with regular vaginal swabs included in the routine care.

Delivery

Because UTx recipients do not feel contractions due to the absence of uterine innervation (Chmel *et al.*, 2020), the risk of premature delivery must be monitored with special attention. However, even with such monitoring, the incidence of prematurity is high. Overall mean gestational age among all the reported deliveries was 34 + 3 weeks (Richards *et al.*, 2021). In the largest series of 12 births, the mean gestational age at birth was 36 + 6 (range 30 + 6 to 38 + 0) weeks (Johannesson *et al.*, 2021b). Deliveries are performed by Caesarean section due to the risk of uterine rupture and have been mainly uneventful, although one case of placenta accreta has been described (Flyckt *et al.*, 2020). Delivery can be combined with hysterectomy if the woman does not desire more children. Of note, although a maximum of two pregnancies is currently considered the upper limit allowable, only four recipients have delivered two children to date, so the safety of two or more deliveries from one transplant is currently uncertain.

It is ideal for maternal-fetal medicine specialists to be part of the team from the outset and be available to follow the pregnancy and perform the Caesarean section with the UTx surgeons.

PSYCHOLOGICAL CONSIDERATIONS

Extensive psychological evaluation must be part of the screening process. As with all medical procedures, informed consent is required. However, three people must consent when using a live donor: the recipient, her partner and the donor. In cases involving a relative, potential complicated feelings of obligation and pressure must be carefully considered using counselling. Live donors and recipients must also be resilient in case of failure of the UTx or complications.

Aside from the emotional aspects surrounding donation, all involved parties

must understand the intense nature of the surgical and medical treatments involved. Strict adherence to medical follow-up must be agreed to for at least 6 months by live donors, and for the duration of graft retention and for at least a year post-hysterectomy by recipients. Recipients must take daily immunosuppressive medications for years with regular medical appointments and blood tests, and be careful to avoid infections. Regular psychological support is therefore essential throughout the process and most likely for some years after hysterectomy.

The Swedish team developed a psychological pre-transplantation assessment programme (Jarvholm *et al.*, 2015) and evaluated the psychological state of live donors and recipients after transplantation. Compared with baseline, the recipients and their partners showed similar or better scores up to 3 years after UTx. Understandably, recipients with graft failure and failure to achieve parenthood had worse scores (Jarvholm *et al.*, 2020), and donors with unsuccessful outcomes had worse scores for health-related, quality of life, mood and relationship issues (Jarvholm *et al.*, 2019).

ETHICAL QUESTIONS

From the outset of UTx, ethical questions have been raised regarding the need for this transplant surgery, the most common being that the uterus is not a vital organ, its sole *raison d'être* being to enable women to gestate. Indeed, UTx incurs real risks for live donors and the recipients, as well as a risk of prematurity for the offspring. However, childbearing is considered central to maternal, paternal and even extended family bonding to the baby to be born.

Alternatives to UTx are childlessness, adoption or gestational surrogacy. A survey in Japan indicated that the lay public would choose UTx (34.4%), gestational surrogacy (31.9%) or adoption (40.3%) if there were AUI (Nakazawa *et al.*, 2019). Adoption is a long and difficult process. Although gestational surrogacy is perhaps the most common alternative to UTx, it is considered ethically problematic, and is unregulated in most countries and banned in many others (Kisu *et al.*, 2011). Even in the USA, where gestational surrogacy is widely practised in most states, public acceptance of UTx appears to be high.

A survey published 4 years after the first UTx birth revealed that 78% of respondents would support the practice, while only 4% would oppose it. Quite surprisingly, a full 45% of respondents believe that UTx should be covered by health insurance (*Hariton et al., 2018*).

Similarly, a survey among healthcare professionals in the UK revealed that a great majority support UTx medically and consider it ethically appropriate (*Saso et al., 2015*). A more recent survey of US fertility specialists and gynaecological surgeons confirmed majority support of UTx (58%), with the most common ethical concerns relating to medical/surgical complications for the recipient (*Hariton et al., 2018*).

The removal of ethical barriers for the advancement of UTx from experimental status to current clinical practice includes decreasing risks to live donors by further optimizing uterine removal. Nevertheless, the potential for abuse involving trading and financial reward for donation exists and must be fought. An extension of UTx for men transitioning to women raises other complex ethical questions and is being discussed although not yet performed (*Jones et al., 2019b*). The Montreal criteria, updated in 2013, have been published to try to define the indications and limits of UTx candidates (*Lefkowitz et al., 2013*). As limitations, coupled with advances, may evolve, an ethical reflection will be mandatory in parallel to technical progress (*Farrell et al., 2020*).

High overall costs of UTx may seriously limit its development and application. In Sweden, an estimated \$69,000 are needed to cover the pre-surgical work-up of a live donor and the recipient, the IVF, UTx and 2 months of post-operative follow-up for the two patients (*Davidson et al., 2021*). However, the actual cost is higher due to the costs of long-term medication and medical follow-up, which may involve high-risk obstetric care and Caesarean section. Some centres in the USA are offering the procedure outside experimental protocols for a cost of around \$250,000. The cost of surrogacy in the USA is within the range \$75,000–\$120,000 (*Blake, 2018*).

When UTx becomes a mainstream clinical practice, it remains to be seen whether the costs will be covered by public health, national/private health insurance systems

or directly by the patient (*Polk et al., 2022*). The question must be asked of whether it is justified to divert funding from healthcare systems to support the high costs of this non-vital transplantation procedure, particularly in settings of limited medical financial resources. On the other hand, in countries that widely cover assisted reproductive technology, UFI patients may have clear claims of a right to access UTx: relative to other patients with infertility, patients with UFI were left without clinical treatments until UTx was introduced and have had to either forego reproduction or pay out of pocket for surrogacy or adoption (*Blake, 2018*).

INCREASING ACCESS TO UTx AND STANDARDIZING CARE

Increasing the donor pool

A central challenge to translating UTx into mainstream clinical practice concerns the availability of donors. Several possible ways in which the donor pool could be expanded include the following.

The first group is women with a normal uterus who require a hysterectomy for an unrelated reason. For example, in cases of female-to-male transitioning, 84% of individuals reported that they would volunteer for donation (*Api et al., 2017*). This is a particularly interesting possibility in view of advances in minimally invasive UTx surgery resulting in reductions in the duration, complications and post-operative recovery. However, this group are often treated with high doses of androgens for prolonged periods before surgery, which may affect the functionality of the uterus.

The second possibility is altruistic donation by women who otherwise do not require a hysterectomy. A US survey found that 70% of US women were willing to donate their uterus in 2016, only 2 years after the first birth following UTx (*Rodrigue et al., 2017*). However, the willingness for such altruistic donation must be weighed against the risks of a complex donor hysterectomy, which hopefully will be minimized in the future with the introduction of robotics.

Third, there could be reuse of a uterus from another recipient. However, the risks of rejection by the new recipient are currently unknown (*Yeo et al., 2017*).

Fourth, live donors aged over 60 years or at 5 years after menopause could

be accepted if a pre-surgery evaluation of their uterine vessels deemed them appropriate. Magnetic resonance imaging, including magnetic resonance angiography (MRA), is the initial modality to examine potential UTx donors to acquire valuable details regarding the uterine anatomy, and if the uterine arteries are fully visualized, there is no need for further angiographic methods involving radiation. However, in about 50% of cases the uterine arteries are not well visualized by MRA, and so computed tomography angiography should be performed to evaluate uterine arteriosclerotic lesions. In selected cases, digital subtraction angiography with the addition of an invasive modality may be required (*Leonhardt et al., 2021*).

Fifth, the administration of oestrogen treatment for a few months before UTx might improve graft quality even years after menopause.

Sixth, the donor age could be lowered. A precedent for this has already been set in the Dallas trial (*Testa et al., 2017*), which included 17 pre-menopausal altruistic donors. However, in such cases, extensive psychological evaluation regarding an irreversible loss of infertility is mandatory to be certain that donors would not later regret their loss of childbearing.

Finally, women with two or more Caesarean sections could be included, although to date, only one team has allowed this approach (*Johannesson et al., 2021b*). Screening would need to include evaluation of the thickness of the lower uterine segment to exclude those with a thin niche after Caesarean section.

Developing a new UTx centre

Starting a new UTx programme is complex. An optimal setting and meticulous preparation are necessary for the responsible introduction of UTx (*Moore, 2000; McCulloch et al., 2009*). Much advanced preparation is needed, including surgical training on large animal models (*Favre-Inhofer et al., 2018*). Indeed, prior to performing the first UTx procedure in a woman, the Swedish team worked on rodents (*Racho El-Akouri et al., 2003*) and then pigs (*Wranning et al., 2006*), sheep (*Wranning et al., 2008*) and baboons (*Enskog et al., 2010*) for over a decade. This team has continued with regular training on sheep, the closest model to humans for UTx.

Aside from surgical training, developing a new UTx centre requires a multidisciplinary team, which is only available at a tertiary care hospital, typically a university hospital, with a large division of transplantation surgery (Brannstrom, 2021b). The surgical team should involve not only transplant surgeons, but also gynaecological surgeons with skills of extraperitoneal pelvic surgery. Other team members should include the following: specialists in reproductive medicine who perform the IVF and prepare the endometrium for embryo transfer; maternal-fetal medicine specialists, particularly those with experience in managing high-risk pregnancies; physicians who routinely follow patients with MRKH syndrome; and specialists in anaesthesiology, internal medicine, nephrology, pathology, psychology and radiology. Furthermore,

in centres using deceased donors, organization is further complicated by the need to coordinate with a procurement team and a surgical team available 24 h a day.

An institution with a UTx programme should provide long-term support, including resources and commitment to care for the recipient, her partner, the donor and the children. A centralization of UTx procedures is necessary to provide enough volume for the approach to be efficient and reproducible, as for pancreas or live liver donor transplantations (Brannstrom, 2021b). Finally, given the complexities, it is highly recommended that centres are developed in collaboration with a UTx team with considerable experience and repeated surgical successes.

International guidelines

The USUTC has recently proposed guidelines for nomenclature related to the operative technique, vascular anatomy and donor, recipient and offspring outcomes to improve the quality of evidence available on the efficacy and value of the procedure (Johannesson *et al.*, 2020). However, it is still an experimental procedure, and guidelines for UTx have not yet been established. The International Society of Uterus Transplantation (ISUTx), which was created in 2016 and recently incorporated into the Transplantation Society, holds an international registry for data collection. Annual reports on activities and with group data on donors, recipients, operations, complications, immunosuppression, pregnancies and live births will be published and all cases

TABLE 2 TYPICAL CURRENT LIMITATIONS AND POSSIBLE ADVANCEMENTS FOR UTERUS TRANSPLANTATION.

Procedure	Patient	Typical current limitations/practice	Possible advancements
Evaluation and screening	Deceased donor	<40 years	Extend age beyond 40 years providing vessels are suitable
		Parous with at least one live-born baby	Nulliparous
	Live donor	Mainly limited to relatives	Expand use of altruistic donation to hysterectomy patients with a normal uterus
		Age limited to <60 years or 5 years post-menopausal	Increase age to >60 years + HRT, regardless of the interval between menopause and donation, providing the vessels are suitable
		Parous with at least one live-born baby	Nulliparous
		Angio-MRI	If the uterine arteries are not well visualized, use CT angiography or digital subtraction angiography: exclude patient if uterine artery is <1.5 mm in diameter and arteriosclerosis is present
Recipient	Mainly limited to women with MRKH	Expand to all cases of AUF1 and RUF1	
Donor and recipient	Matching: typically no CMV, EBV, HPV (D+, R-)	Allow mismatching of CMV, EBV and HPV	
IVF	Recipient	Embryos frozen	Oocytes as well as embryos frozen Possible use of PGT-A/blastocysts
Surgery	Live donor	Midline laparotomy	Robotic surgery with laparoscopy rather than midline laparotomy
		Use of deep uterine vein	Use of utero-ovarian vein
		Risks to urethral integrity	No thermal use near ureter Ureteric stent for 4–6 weeks
	Recipient	Long surgical time: up to 10 h	Reduce surgical time to 5 h
		Midline laparotomy	Robotic surgery with laparoscopy
		Risk of graft failure	Improve warm/cold ischaemia (hemi-uterus vascularization and use of a perfusion machine for deceased donors)
ET	Recipient	Risk of vaginal stenosis	Improve sectioning, suturing of vagina
		MMF/azathioprine started 2 months before ET	No MMF and start azathioprine immediately after UTx
		ET after a minimum of 1 year	ET after 4–6 months
Post-UTx	Recipient	1 or 2 pregnancies	More than 2 pregnancies
		Life of transplant no more than 6 years	Increase life of the transplant beyond 6 years
		Regular cervical biopsies for signs of rejection	Non-invasive biomarkers for signs of rejection

AUF1, absolute uterine factor infertility; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; ET, embryo transfer; HPV, human papillomavirus; HRT, hormone replacement therapy; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; PGT-A, preimplantation genetic testing for aneuploidies; RUF1, relative uterine factor infertility; UTx, uterus transplantation.

will be followed until hysterectomy. In the future, the registry could be used to extract data for purely scientific questions. It is essential that all teams continue to report their experience and outcomes so that the procedure can be further optimized to increase the safety and efficacy, and to develop reasonable international guidelines.

MEETING THE CHALLENGES

With 34 healthy children born, the feasibility of UTx has been proven. However, as highlighted in this review, there are several challenges currently preventing the translation of this emerging area of medicine into mainstream clinical practice. As discussed, possible advancements are underway including widening the criteria for the acceptance of donors and recipients, freezing oocytes as well as embryos, improving surgery, shortening the time to pregnancy and improving post-UTx management such as developing non-invasive biomarkers for rejection (TABLE 2). As these collective advancements continue, UTx will represent a realistic and accessible alternative to gestational surrogacy for the treatment of UFI and should become part of the armamentarium of reproductive specialists worldwide.

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