Uterus transplantation: animal research and human possibilities

Mats Brännström, M.D., Ph.D.,[a] Cesar Diaz-Garcia, M.D.,[b] Ash Hanafy, M.D.,[c] Michael Olausson, M.D., Ph.D.,[d] and Andreas Tzakis, M.D.[e]

[a] Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; [b] Department of Obstetrics and Gynecology, La Fe University Hospital, University of Valencia, Valencia, Spain; [c] Department of Obstetrics and Gynecology, Griffith University, Gold Coast, Queensland, Australia; [d] Department of Surgery, Sahlgrenska Transplant Institute, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; and [e] Department of Surgery, Miami Transplant Institute, Miller School of Medicine, University of Miami, Miami, Florida

Uterus transplantation research has been conducted toward its introduction in the human as a treatment of absolute uterine-factor infertility, which is considered to be the last frontier to conquer for infertility research. In this review we describe the patient populations that may benefit from uterus transplantation. The animal research on uterus transplantation conducted during the past two decades is summarized, and we describe our views regarding a future research-based human attempt. (Fertil Steril® 2012;97:1269–76. ©2012 by American Society for Reproductive Medicine.)

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Transplantation surgery has during the past two decades introduced several additional organs/tissues to transplant, and all of these novel transplantation types can be categorized as nonvital/quality-of-life enhancing, rather than vital, such as transplantation of the heart, liver, or lung. Examples of these novel nonvital tissue transplants are the hand/arm, lower limb, larynx, and face (1, 2). Likewise, large developments have occurred in infertility treatment, and this has led to uterine-factor infertility remaining one of the few types of infertility that remain untreatable. Cooperative research efforts of gynecologists and transplant surgeons may lead to uterus transplantation (UTx) becoming a clinically established method as a nonvital transplantation type with the aim to treat absolute uterine-factor infertility (3). At present, the options to attain motherhood for women with unconditional uterine factor infertility are either adoption of a child to acquire legal motherhood or gestational surrogacy to acquire genetic motherhood, which has to be followed by adoption of the child from the surrogate mother to also accomplish legal motherhood. Gestational surrogacy is permitted in only a restricted number of countries/societies worldwide and it may be associated with numerous ethical and legal problematic issues (4, 5).

The initial, and hitherto only published, human UTx case took place 12 years ago (6), and the majority of animal research on UTx has been performed after that time point (7). The UTx research area needs particular concern, because in possible future human UTx the associated risks will not only involve the transplant patient and a possible live donor, but also a future child.

The research front in UTx research will most likely reach a stage during the coming years that may warrant UTx to be introduced in human clinical trials as an experimental surgical procedure. The introduction of such a major surgical procedure as UTx should naturally conform to the newly launched IDEAL (Innovation, Development, Exploration, Assessment, Long-Term Study) concept that should be used to introduce new surgical methods in a scientific and systematic way (8–10).

In the present review we summarize the progress in UTx research during recent years, and we identify issues to take into consideration for possible future human UTx.

PROSPECTIVE UTX PATIENTS

The patient groups that may benefit from UTx are those with no uterus or those with a uterus that is nonfunctional in terms of pregnancy capability with the causes of this uterine-factor infertility being either congenital or acquired. The patient group may also be divided into those with complete infertility and those with relative infertility (Table 1). The latter group should naturally be considered for UTx only after positive results of other treatment options, such as corrective surgery, have been ruled out.

The most common cause of both complete and relative uterine-factor infertility is leiomyoma, which will lead to complete infertility if hysterectomy is performed because of leiomyoma-related symptoms. The incidence of uterine leiomyoma increases with age (11), with a prevalence of ~10% in women 33–40 years old (12). Submucosal (13) and larger intramural

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Reprint requests: Mats Brännström, M.D., Ph.D., Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden (E-mail: mats.brannstrom@obgyn.gu.se).

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TABLE 1

Causes of uterine-factor infertility and estimated prevalences.

Cause	Prevalence (%)	Cause-specific infertility/sterility (%)	Congenital (C) or acquired (A)
Leiomyoma	21–26	40	A
Hysterectomy (leiomyoma)	1–1.5	100	A
Arcuate uterus	1.3–6.2	17.3	C
Intrauterine adhesions	1–2	70	A
Septate uterus	0.8–1.4	38	C
Bicornuate uterus	0.7–1.3	37.5	C
Hysterectomy (peripartum)	0.04–1.25	100	A
Unicornuate uterus	0.3–0.5	56.3	C
Didelphic uterus	0.1–0.3	40	C
Uterine hypoplasia	0.038	100*	C
Uterine agenesis (MRKH)	0.0002	100	C
Hysterectomy (cervical cancer)	0.00004–0.0001	100	A

Note: Data from references (17, 18, 20, 23, 26, 62–67).
* Probably close to 100% (estimation based solely on case reports).

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(14) leiomyoma may be related to infertility. Corrective surgery by hysteroscopic resection of submucosal leiomyoma (15) and myomectomy of large (>4 cm) intramural leiomyoma (16) are effective treatments in a majority of cases. The leiomyoma patients of the latter groups that do not respond to surgical treatment could be candidates for a combined procedure of hysterectomy and UTx, with the added benefit compared with many other potential UTx patients that the native uterine arteries and veins can be partly preserved and then used for vascular anastomosis to the vessels of the uterine graft. This combination of hysterectomy and UTx in a one-step procedure would also be applicable in the large group of uterine-infertile patients with congenital uterine malformations that have not responded to surgical treatment. The total prevalence of uterine malformations among women is ~7% (17). Septate uterus and bicornuate uterus represent the majority of these uterine malformations. These two conditions are associated with subfertility, and surgery will treat a majority of these cases. Unicornuate uterus and uterus didelphys, which are not surgically correctable, constitute ~20% of uterine malformations (18). The spontaneous abortion rate associated with unicornuate/didelphic uterus is high, with a live birth rate of just above 50% (18).

Another group of women with relative uterine-factor infertility are those with intrauterine adhesions, with an overall infertility rate of ~50% before attempts of surgical treatment (19). A majority of women with infertility due to mild or moderate intrauterine adhesions are treatable by hysteroscopy, but ~70% of patients with severe intrauterine adhesions remain infertile despite surgical interventions (20).

Several subgroups of uterine-factor infertile patients have no uterus at all or only a remnant cervical stump. In the rare (1:4,500) cases of müllerian agenesis (Rokitansky/Mayer-Rokitansky-Küster-Hauser syndrome), both the uterus and the upper two-thirds of the vagina are missing (21) and there only exists small rudimentary uterine tissue along the pelvic sidewalls. These women usually undergo neovagina surgery some years after puberty and are otherwise of normal female phenotype with normal ovaries. Importantly, the syndrome has not been reported in female genetic children of these patients in gestational surrogacy programs (22).

The gynecologic malignancy that is most common during the reproductive years is cervical carcinoma, with ~50% of affected women being under the age of 40 years (23) and with a substantial part also seen in women <30 years of age (24). Fertility-sparing surgery (trachelectomy) is recommended in cervical cancer of a size <2 cm, but ~50% of fertile-age cervical cancer patients present with larger tumors and need to be treated by traditional radical hysterectomy (25) and will therefore become uterine-factor infertile after surgery. The survival rate for this latter group of patients is extremely good, with virtually no risk of cancer recurrence after the usual 5-year follow-up period. Hysterectomy may also be performed as an emergency peripartum intervention in the event of a life-threatening obstetric bleeding, usually due to uterine atony or rupture as well as placenta acreta (26).

ANIMAL RESEARCH IN THE UTX FIELD

The research in the UTx field has been conducted in several animal models, including rodents (mouse, rat) (27–30), large domestic species (sheep, pig) (31–34), and lately also nonhuman primates (baboon, macaque) (35–37). In general, the initial observations and key experiments have been done in rodents, and the conclusions from these experiments have then been used in experiments in the large domestic species with sizes of pelvic organs and vasculature closer to human. It has been essential to also include nonhuman primates as the last step in this experimental development, where the ultimate goal is a safe introduction of the procedure in humans.

One important issue in experimental transplantation research is to enable separation of the different harmful events that may lead to unsuccessful transplantation. These potentially damaging events are surgery at organ recovery, ischemia-reperfusion damage, surgery at transplantation, rejection, and effects of immunosuppressive medication. The first steps are generally autologous and syngeneic (between genetically identical individuals) transplantations. Syngeneic transplantations can easily be used in experiments involving rodents, because large numbers of commercially available inbred rat/mouse strains are available. In larger animals, autologous transplantation is used to exclude the potential harmful effects of rejection and immunosupression, but it should be acknowledged that this experimental situation exposes the animal to a much longer surgical time than in a normal transplantation situation, because the same animal undergoes both organ recovery surgery and transplantation surgery.

After syngeneic/autologous transplantation models have been used to optimize the procedure from a surgical standpoint and regarding ischemic preservation, the data acquired from these optimally conditioned animal models can be used as an experimental control situation where effects of rejection and immunosuppression are added in the allogeneic transplantation model. Regarding UTx, it is important to also point out that the term successful transplantation should not only include resumed cyclic function of the uterus but also full capacity to harbor a pregnancy to term and with birth of live offspring. Thus, the duration from transplantation until the transplanted organ has demonstrated its capacity is much longer for the uterus than for other solid organs that are transplanted.

Autologous UTx

The animal models that have been subjected to research involving autologous UTx are the pig, the sheep, and two nonhuman primate species (baboon, cynomolgus macaque). Our collaborative research group (31) and others (38) initially used the pig model to develop UTx surgery in a large animal species. The surgery in both of these initial studies involved a supracervical hysterectomy with dissection of the uterine arteries and veins down to a level just above the ureters, where the vessels were transected. In our hands, the surgery time for this uterus recovery was ~2 hours (31). Flushing was performed either with cold University of Wisconsin or Celsior solution (38) or with Ringer acetate (31), and the uterus was on the back table for 1–2 hours before retransplantation. Bilateral end-to-end anastomosis of the uterine arteries and the major uterine veins were performed with 7-0 to 9-0 sutures. Notable is the fairly long time (2 hours) of vascular anastomosis surgery (31), which is a time when the uterus is subjected to damaging warm ischemia. The reason for this excessively long anastomosis time was that it was performed by gynecologist rather than transplant/vascular surgeons who are trained in anastomosis surgery. The autologous transplanted uteri were followed for only a short time, but with indications of normalized blood gases and lactate levels in the venous effluent after ~1 hour, indicating reversal to normal tissue perfusion (31). In the other study of autologous UTx (38), the grafts were followed for several days with signs of gradual and progressive thrombosis developing in the uterine vessels at the anastomosis sites. There exist no studies on long-term function of the pig uterus after autologous transplantation.

The sheep model has proved to be a superior model of autologous UTx to that of the pig, because the uterus has a comparatively much smaller size and the pelvic vasculature is large, with dimensions similar to those of humans. Our research group developed a method by which uterine blood supply/drainage included both uterine vessels as well as the anterior portions of the internal iliacs (39). After flushing of the organ and cold ischemia for ~1 hour, the uterus was transplanted with end-to-side vascular connections to the external iliacs.

The early changes at reperfusion of the sheep uterus were studied after the 1 hour of cold ischemia and after another 1 hour of warm ischemia (40). During reperfusion, several parameters related to glucose metabolism, oxidative stress, and inflammation reversed to normality within 1–2 hours, indicating that the uterus has the capacity to tolerate 1 hour of the tissue-damaging warm ischemia. However, it should be pointed out that ~30% of the transplants did not show immediate blood flow, which we think this was due to suboptimal anastomosis surgery.

The long-term functions, including fertility potential, of an autologous uterine graft from a sheep were subsequently tested. We used a modification of our previous technique (39), including one ovary and the connecting oviduct in the graft (32). The reason for including the ipsilateral adnexae with the graft was that we wanted to test the fertility potential after natural mating, and that this would rely on ovarian cyclicity, which in the sheep is partly regulated by uterine-derived luteolytic prostaglandins that are locally transported to the ovary (41). Although only 50% of the ewes showed normally resumed ovarian and uterine cyclicity, pregnancy occurred in 60% of the mated sheep, and the offspring were similar in size to offspring from control ewes (32). The study demonstrated for the first time that normal pregnancies can be achieved after uterine transplantation (though autologous) in a larger animal.

During recent years, UTx research has come to also include nonhuman primate species. In our first study on autologous UTx in the baboon (37), we included the ovaries and the oviducts in the graft to use the typical cyclic perineal skin changes of the female baboon (42) as an easy and noninvasive method to assess graft function. The uterus recovery surgery included bilateral dissection of the uterine arteries and the anterior portions of the internal iliac arteries, and venous outflow was secured bilaterally by the ovarian veins. This surgery took almost 3 hours, and the complex back-table preparation, with fusion of the bilateral arteries and veins to common venous and arterial ends, lasted another 2 hours under cold conditions to minimize ischemic damage. At UTx, the single arterial and venous ends were anastomosed unilaterally to the external iliac vessels. Because only 20% of the uteri resumed menstruation, it was concluded that UTx is a difficult procedure and modifications of the surgical method would be necessary.

In a follow-up study (43), the autologous transplantation technique of the baboon was modified with extensive dissections of the ovarian veins to include their inlets into the caval vein and the left kidney vein to accomplish a vascular anastomosis with venous walls that are thicker. Furthermore, the arterial anastomosis at transplantation was modified to be unilaterally end-to-end to the internal iliac artery, and importantly, the anastomosis surgery was now performed by a transplant surgeon. The overall results were 60% of animals with resumed menstruation. These baboons were subjected to repeated mating, but pregnancies did not occur, which most likely was due to blocked oviducts.

In the other nonhuman primate experimental model, autologous UTx was accomplished in the cynomolgus macaque, with bilateral anastomosis of the uterine artery and the deep uterine vein to the external iliacs (35). That study included only two animals, and menstruation resumed in the surviving animal despite a lengthy operation of >13 hours. In a follow-up study it was indicated that the complete macaque uterus can be adequately perfused with only unilateral anastomosis of one uterine artery and one uterine vein, provided that the side of the dominant blood flow is chosen (36).

Syngeneic UTx

Syngeneic transplantation models are available only in rodents, with the existence of several inbred strains. The initial rodent UTx model was the mouse (27). The recovery surgery included isolation of one uterine horn and the common uterine cavity with ipsilateral dissection of a vascular pedicle including the vessels from the uterine artery/vein up to the aorta and the vena cava above the mesenteric artery. The duration of this uterine recovery decreased to ~45 minutes with experience (27). The aortic and caval ends of the graft were then attached end-to-side, by 11-0 nylon microsutures, to the subrenal parts of the aorta and the vena cava of the recipient mouse which was of the same strains as the uterus donor. The native uterus of the recipient was left in situ and the cervix of the graft was placed free inside the abdomen. The complexity of the transplantation procedure in these small animals is illustrated by the survival rate for the first 20 animals of only ~40%, which increased to >70% for the next series of animals (27), with a graft survival rate of ~90% in the survivors as well as demonstration of midterm pregnancy after embryo transfer in one uterine graft.

This heterotopic syngeneic UTx mouse model was later modified, because it was evident that the intrabdominally placed cervix would not accurately drain cervical fluid, and in this new model the cervix ended in a cervical-cutaneous stoma on the lower abdominal wall (28). This model showed uteri of normal macroscopic appearances, and after transmyometrial embryo transfer, to both the native and the transplanted uteri, similar pregnancy rates were seen in the native and grafted uteri. Live offspring was for the first time reported from a truly transplanted uterus, although it was a syngeneic model with no need of immunosuppression. The birth weight, postnatal growth, and the fertility of the offspring from the uterine graft were normal. The modified heterotopic UTx model, with a cervical-cutaneous stoma, was also used to investigate the influence of cold ischemia on the function of the uterus. After recovery of the uterus and its vasculature from the donor mouse, the organ was flushed and then kept in cold University of Wisconsin solution for 24 or 48 hours before vascular transplantation into the recipient (44). The results were that uterine grafts that had been under cold ischemia for 24 hours, but not those for 48 hours, were viable after transplantation, with pregnancies and deliveries following embryo transfer 2 weeks after transplantation (28). The offspring exhibited normal birth weight and growth trajectory.

Additionally, syngeneic UTx has been performed in the rat, with the obvious advantage over the mouse being that the body and vascular size is about six times greater than that of the mouse. In the first syngeneic rat model performed with inbred Lewis rats, the graft contained the right uterine horn, the common uterine part, the cervix, and a vaginal rim (45). The isolation of the graft, with a vascular pedicle up to the right common iliacs, took ~1 hour. In this model, the native uterus of the recipient was kept and the heterotopically placed uterine graft was anastomosed end-to-side to the midabdominal part of the aorta and the vena cava of the recipient by 10-0 suture (45). After an initial surgical learning phase, the animal survival was >95%, but with a 30% loss of grafts due to thrombosis formation. This heterotopic rat UTx method, with the cervix of the graft connected to a cutaneous stoma, was later modified to an orthotopic model that would allow spontaneous mating and thereby test of pregnancy potential (46). The anastomoses were done end-to-side between the common iliac vessels of the graft and those of the syngeneic Lewis recipients. The mating rates were >85% in both groups, and the pregnancy rates were ~50% in both control and transplanted animals. Importantly, number of pups and postnatal growth were normal in the transplanted group.

Allogeneic UTx

Allogeneic animal models of UTx are important to study rejection mechanisms, find suitable immunosuppressants, and study pregnancy in a situation that will be close to clinical UTx. We studied the time course of rejection in the mouse model with BalbC mice as uterus donors and C57BL/6 mice as recipients (47). Minimal inflammatory changes were seen 2 days after transplantation, and major inflammation occurred from day 10 to 15, followed by necrosis. The first leukocytes to invade the uterine allograft are the macrophages, which are followed by neutrophils and cytotoxic T cells (48). The mouse model was later used to study whether monotherapy with the immunosuppressant cyclosporine would inhibit uterine graft rejection (49). Although high doses of cyclosporine were used, rejection could not be fully inhibited. The other major calcineurin inhibitor, tacrolimus, was later tested in an allogeneic rat model of UTx with Dark Agouti rats as donors and Lewis rats as recipients (29). This was also the first time pregnancies were reported after allogeneic UTx in any species. The experiments ended with cesarean section to be able to assess rates of both ongoing and resorbed pregnancies, with the results showing similar rates in the transplanted animals and the control groups (29). In subsequent experiments with the same strain combinations and tacrolimus, the pregnancies were allowed to go to term and the delivered offspring were of normal body weight and developed normally well into adulthood (unpublished data).

In the sheep, allogeneic UTx has been carried out with either end-to-end anastomosis of the uterine arteries and veins (50) or anastomosis of an aortacaval patch to the external iliacs (51). The former procedure could only be applied in a clinical situation where hysterectomy is performed as part of the procedure in the recipient, and the latter procedure would be applicable when the organ is recovered from a deceased donor. In a first experimental series involving allogeneic UTx in the sheep, with anastomosis on the level of the uterine vessels, ten animals received cyclosporine continuously and corticosteroid during the first 2 weeks (50). After a long follow-up time of 6 months, viable uterine tissue and patent anastomosis sites were present in 6 of 10 ewes. A later study (52) by the same group used an identical surgical technique and switched the uteri between two different subgroups of sheep. These experiments were done with an increased cyclosporine dose, and five out of 12 uteri were considered to be good candidates for embryo transfer 4 months after UTx. Pregnancies occurred in three out of these five sheep, with one ending in miscarriage and one in ectopic pregnancy. The remaining pregnant sheep carried the pregnancy almost to term and was delivered by cesarean section. Unfortunately, the offspring was not followed further, because it was euthanized 5 hours after delivery.

The group using the aortocaval patch anastomosis technique approach in the sheep used an immunosuppression protocol based on cyclosporine and mycophenolate mofetil and with corticosteroids used for only 1 week (51). All uterine allografts showed thrombosis of vessels and signs of uterine necrosis 10 weeks after transplantation, and it was speculated whether this was due to poor fixation of the graft, the anastomosis technique, or rejection due to suboptimal blood levels of immunosuppressants after oral intake.

Our collaborative group carried out allogeneic UTx in the pig model, using major histocompatibility complex–defined minipigs (33). The surgical technique involved isolation of the entire uterus on a vascular pedicle including the inferior vena cava and the infrahepatic aorta. At transplantation, the uterus was placed retroperitoneally behind the ascending colon, and the anastomoses were done end-to-side to the recipient aorta and vena cava. The native uterus was left in situ and the vaginal vault of the heterotopically placed graft was exteriorized as a stoma. The immunosupressants used were induction with intravenous tacrolimus during the first 12 days, followed by maintenance with oral cyclosporine and steroids. The follow-up period was up to 12 months; episodes of acute rejection occurred during the second and third months after transplantation. These episodes were treated successfully with increased doses of steroids and cyclosporine. We have also performed allogeneic UTx in the baboon with long-term maintenanace of the graft after induction therapy with antithymocyte globulin and triple maintenance immunosuppression (unpublished data).

HUMAN UTX POSSIBILITIES

The first human UTx (6) in modern times was performed 12 years ago in Saudi Arabia when a 26-year old patient, who some years earlier had undergone peripartum hysterectomy because of life-threating bleeding, received a uterus with attached oviducts from a 46-year-old unrelated live donor. The donor was scheduled for elective surgery because of bilateral ovarian cysts, which were removed as an initial surgical procedure. The hysterosalpingectomy involved isolation of 3-cm-long vascular pedicles of the ovarian arteries with uterine veins attached. Due to the relatively short vascular pedicles, both arteries and veins were elongated with saphenous grafts to facilitate bilateral end-to-side anastomosis to the external iliacs of the recipient. The recipient was treated with standard triple immunosuppression with one episode of acute rejection being controlled by antithymocyte globulin. The surgeries of the recipient and donor were eventful and the uterus showed functionality regarding menstruation. Inadequate structural support of the uterus resulted in uterine prolapse after 3 months, and a necrotic prolapsed uterus with thrombosed vessels was removed. Apart from this initial case, a second human UTx trial was performed in Turkey in 2011, with the uterus coming from a deceased donor (Ö. Özkan, personal communication, October 21, 2011). This case has not yet been published in the scientific literature.

In planning the next human UTx, it is of importance to extract all of the possible useful clinical information from these two human cases and to combine that with all of the scientific data on animal UTx. We think that the next set of human UTx attempts should be performed under strict scientific protocols and with a small group of patients participating in the trials to draw firm scientific conclusions that may facilitate the optimization of the UTx procedure. The introduction of human UTx should be performed and evaluated under the newly formed IDEAL guidelines for a science-based approach at introduction of surgical innovations (8).

There are several issues concerning both the uterus donor and the transplant patient that have to be worked out before a possible human UTx trial. The uterus donor could be either a live donor, which is a common situation in renal and partial liver transplantation, or a deceased donor (brain-dead heart-beating donor). The advantage of a deceased donor in human UTx is that a surgical risk is not imposed on a second party. A disadvantage with use of an organ from a deceased donor, compared with a live donor, is that at brain death major systemic inflammatory changes occur which may negatively affect graft survival (53), with the effects being related to the time interval between brain death and organ recovery. The age of the donor uterus could be $\geq$50 years, because it is known that pregnancy rates are still acceptable in an aged uterus (54). However, it should be acknowledged that incidence of adverse perinatal outcome is worse in mothers $>$45 years old than in younger mothers (54), but this may well be due to a probable higher incidence of systemic diseases in the older population. The uterus recipient should be of fairly low age ($<$38 years) and with assurance by ultrasound and antimüllerian hormone measurements that a good ovarian reserve exists. Naturally, the recipient should be of extremely good general health, and in cases of cervical cancer $\geq$5 years should pass after cancer surgery to ensure that there is no risk for recurrence of the disease.

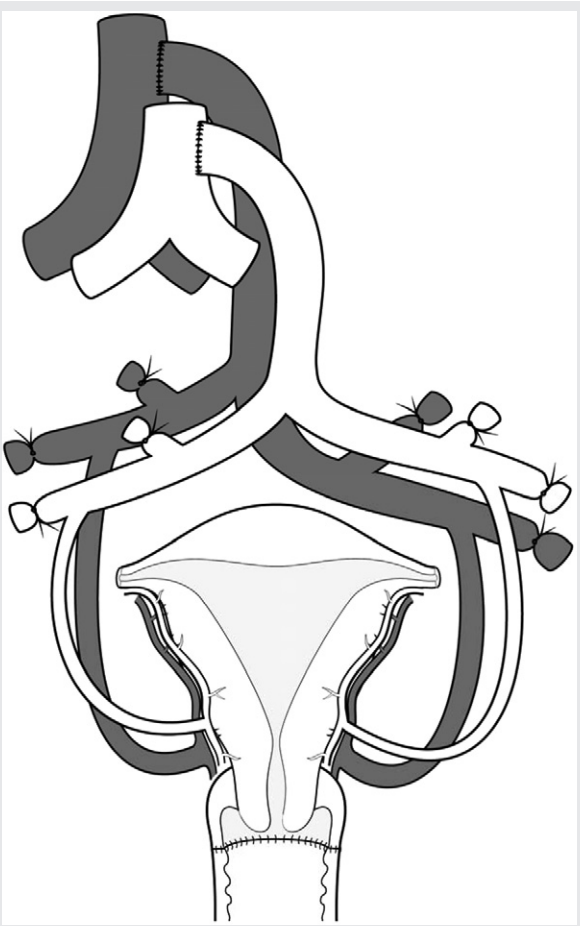
In a situation of uterus donation from either a live or a deceased donor, it is important to rule out several uterine-associated pathologic conditions before transplantation, and this may take time that is disadvantageous in deceased donation. Human papillomavirus infection, cervical dysplasia, leiomyoma, and endometrial polyps are some conditions that have to be ruled out with the appropriate tests. With both types of uterus donation, a blood type match has to be ensured but tissue type matching is of less importance, according to modern standards in transplantation surgery (55). In the initial phase of human UTx and live donation, we think that a close relative, such as an older sister (after her childbearing years), the mother, or an aunt (paternal or maternal) would be suitable donors because the chance of matching blood/tissue type would be high. The live donor has to be in good general health to minimize the surgical risk at hysterectomy. The uterus to be donated by a live donor should also be investigated preoperatively by imaging, including magnetic resonance imaging, to diagnose vascular anomalies or atherosclerosis of uterine vessels, which may disqualify the uterus from transplantation.

The vascular tree on the uterine graft would naturally be more extensive in deceased uterus donation than in live donation. In recovery of a uterus from a deceased donor, large arteries and veins can be recovered with the uterine graft, and this would make anastomosis surgery at transplantation easier (Fig. 1). In one study investigating the practicability of uterus recovery from deceased donors (56), the complete and bilateral internal iliac arteries and veins were recovered with two out of seven grafts, and the vascular pedicle included the vessels up to the anterior portions of the iliacs in five grafts but with unilateral loss of uterine vessels in two out of these. These uterine recoveries were performed by gynecologists. In our collaborative group, transplant surgeons have recovered uteri from seven multiorgan donors, and in these trials vascular pedicles including the complete uterine vessels, internal iliac vessels, common iliac vessels, and lower part of the aorta and vena cava could be recovered (unpublished data).

We have also recently conducted a study with vascular dissection of the uterine arteries and veins at radical hysterectomy in patients with cervical cancer (Johannesson L, et al. Vascular pedicle lengths after hysterectomy: towards future human uterus transplantation. In Press.). That study was performed to gain information about whether the uterus could be recovered at live donation with long enough vascular pedicles so that elongations with saphenous grafts, as used in the published human UTx attempt (6), would not be needed. The free lengths of the uterine arteries were almost 70 mm and that of the uterine veins were 50 mm or slightly longer. These lengths would be sufficient for direct bilateral anastomosis to the external iliacs, with an estimated distance between the vessels of ~100 mm. In the event of a postmenopausal live uterus donor, it would also be possible to use one or two of the ovarian veins (Fig. 2), but obviously oophorectomy has to be part of the procedure in that case.

Another important aspect to take into consideration is the fixation of the uterus (Fig. 2), which may have failed in the published human UTx attempt (6), where uterine prolapse occurred. The vaginal rim of the graft will naturally be anastomosed to the vaginal vault of the recipient. The uterine

FIGURE 1



Schematic figure of possible anastomosis sites for uterus transplantation from deceased donor.

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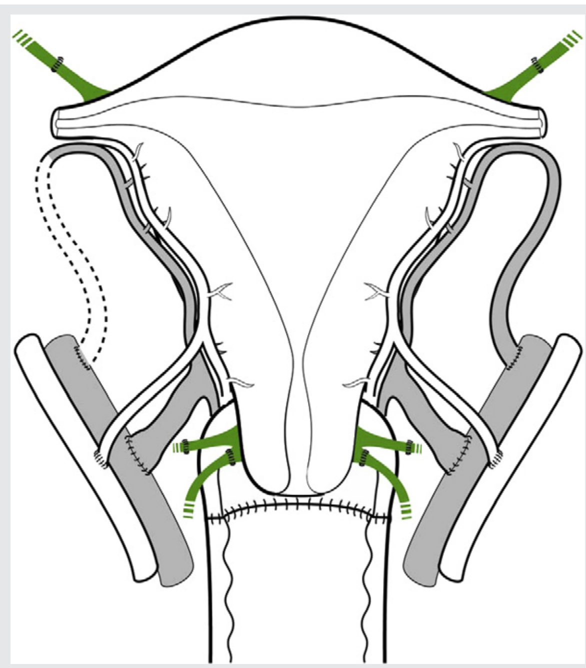
FIGURE 2



Schematic figure of possible anastomosis sites for uterus transplantation from live donor. Suggested sites of uterine fixation are shown in green color.

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graft should be recovered with lengthy round ligaments to be fixed to the pelvic sidewalls. In all patient groups with uterine-factor infertility, except ultraradically hysterectomized patients with cervical cancer, the uterosacral ligaments are preserved, and it is important to fix these to the lower posterior part of the uterus. These uterosacral ligaments and possible reconstructions of the cardinal ligaments would provide the most important structural supports for the lower portion of the uterus and the cervix to avoid displacement and prolapse. We also suggest that part of the bladder peritoneum should be recovered on the uterine graft and that this can sutured on top of the bladder as extra fixation.

The immunosuppression at UTx should be that of modern induction therapy, including antithymocyte globulin to lower the numbers of circulating T cells, and this should be followed by standard triple immunosuppression (tacrolimus/cyclosporine, corticosteroids, antiproliferative agent). This type of immunosuppression protocol results in a 100% graft survival of highly immunogenic composite tissues such as the hand and the face (57). More than 14,000 births among women with solid organ transplants have been reported (58), and data suggest that there is an increased risk of mild prematurity, decreased birth weight, and hypertension/preeclampsia (58–60), but no increased rates of congenital malformations were seen. The only complete population-based study on pregnancy outcome after maternal organ transplantation (61) showed similar results with an increased risk for preterm birth, preeclampsia, and small for gestational age in this population, but similar odds ratios were found in pregnancies before and after transplantation. The authors suggested that the underlying disease morbidity of the mother and not the immunosuppressants per se may be the cause of the pregnancy-associated morbidity. We advocate IVF treatment of the couple before undergoing UTx to ensure fertility within the couple and to enable storage of embryos for transfer trials taking place ≥ 12 months after transplantation, in line with international recommendations for transplant patients.

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