10.5005/jp-journals-10016-1130

ORIGINAL RESEARCH

Uterus Transplantation: An Update and Preparations for Introduction in India

[1]Kamini A Rao, [2]P Dahm-Kähler, [3]Mats Brännström

ABSTRACT

The clinical field of composite tissue transplantation now also includes uterus transplantation (UTx), a new type of quality-of-life enhancing and in this case also life-giving transplantation. The purpose of UTx is to enable live birth from a woman who lacks uterus or in a woman who has a defective uterus.

Keywords: Human, Infertility, Transplantation, Uterus.

How to cite this article: Rao KA, Dahm-Kähler P, Brännström M. Uterus Transplantation: An Update and Preparations for Introduction in India. Int J Infertil Fetal Med 2016;7(2):61-67.

Source of support: Nil

Conflict of interest: None

Date of received: 8-3-2016

Date of acceptance: 10-5-20

Date of publication: August 2016

INTRODUCTION

The clinical field of composite tissue transplantation now also includes uterus transplantation (UTx), a new type of quality-of-life enhancing and in this case also life-giving transplantation. The purpose of UTx is to enable live birth from a woman who lacks uterus or in a woman who has a defective uterus.

Absolute uterine factor infertility (AUFI) affects around 1 in every 500 women of fertile age,[1] which would correspond to around 1.5 million women worldwide. The traditional motherhood options for women with AUFI are adoption or use of a gestational surrogate carrier. However, both these options are not accessible for many women due to religious, ethical, and/or legal concerns. Adoption would only provide legal motherhood. A surrogacy arrangement would give genetic motherhood, and after adoption of the child from the childbearing mother, also legal motherhood. Uterus transplantation would mimic a normal situation, with the primary components of genetic, gestational, and legal motherhood. Moreover, the normal health risks that are associated with pregnancy, such as thromboembolism, hypertension, diabetes, and birth complications, would be taken by the mother with the uterine graft and not, as in gestational surrogacy, by another woman who in most cases would carry the pregnancy only for economical incitement.

Uterus transplantation is likewise the first type of allogeneic transplantation, i.e., ephemeral, since the allograft would just be kept for a restricted time, until the recipient has delivered the desired number of children. The uterus would then be surgically removed to allow the recipient to discontinue immunosuppressive medications, and this would thereby minimize the long-term side effects of these potent pharmaceuticals.

Our preparation and introduction of UTx have followed the recently launched IDEAL concept[2] for a structured and research-based introduction of a novel, major surgical procedure. This concept emphasizes the importance of preclinical research, and the procedure is introduced under a strict research protocol and after approval by the local or national ethics board. The development toward the first clinical UTx trial has included a step-by-step research protocol in several animal models,[3] which is described in more detail below.

PATIENT GROUPS WITH AUFI

The causes of AUFI are either uterine absence, which can be congenital or surgical, or an existing uterus which is nonfunctional.

The uterus is formed during early fetal life by fusion of the paired Müllerian ducts. Aberrations in their development and fusion exist in around 4% of women.[4] Some uterine malformations, such as the septate uterus and the bicornuate uterus, can be surgically treated to allow for normal pregnancy. There exist no effective surgical treatments for the didelphic and the hypoplastic uteri, which go with high rates of implantation failure and miscarriage.[4] Around 1 in 4,500 women is born with total absence of the uterus and the upper part of the vagina, as part of the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.[5] The vast majority (9/11) of women in the world who had undergone UTx procedures have MRKH

[1]Founder and Medical Director, [2]Assistant Lecturer, [3]Professor

[1]Department of Reproductive and Fetal Medicine, Milann - The Fertility Center, Bengaluru, Karnataka, India

[2,3]Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden

Corresponding Author: Mats Brännström, Professor, Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden, e-mail: mats.brannstrom@obgyn.gu.se

syndrome, which will be discussed in detail further below in this article.

Leiomyoma is likely to be the most frequent cause of AUFI, since the incidence of leiomyoma in reproductive age women is as high as 10%,[6] and that large and subendometrial myoma causes implantation failure. Moreover, leiomyoma is the most common underlying cause of hysterectomy.[7] Other causes of hysterectomy at young age are life-saving surgery at cervical cancer, endometrial cancer, or massive obstetric bleeding due to uterine rupture/atony or invasive malplacentation.

Intrauterine adhesions, in most cases secondary to endometritis or surgical abortion, may also cause AUFI. After attempts to treat this condition with hysteroscopic adhesiolysis, around 50% of women remain infertile.[8] Genital tuberculosis is an important cause of intrauterine adhesions in India.[9]

ANIMAL RESEARCH

Mats Brannstrom initiated an animal-based UTx research project in 1999. A woman in her mid-twenties underwent a radical hysterectomy because of cervical cancer, and before surgery, she promptly suggested that she would later restore her fertility by transplanting the womb of her mother. This proposal by the young woman led to the initiation of a translational research project, leading up to the first successful UTx procedure in 2014. The research program has involved experiments in several animal species, and the key findings from this project and other groups are described below.

Mouse

In the mouse model, we could already in 2002 for the first time ever demonstrate pregnancy in a truly transplanted animal,[10] and this finding was later followed by demonstrations of live offspring after syngeneic UTx.[11] Importantly, the offspring showed normal postnatal growth trajectory and were fertile. However, the influence of immunosuppression was not tested since the transplantations were between animals of the same inbred strain, with no need for immunosuppression. Further experiments showed normal pregnancy and offspring development from uteri that had been subjected to cold ischemia for 24 hours before transplantation.[12] In the allogeneic mouse UTx model, the rejection process was characterized.[13,14] We could also demonstrate that cyclosporine monotherapy partly suppressed graft rejection in the allogeneic mouse UTx model,[15] but also that cyclosporine exposure during pregnancy negatively influences reproductive performance[16] by reducing implantation rates and fetal survival.

Rat

The UTx rat model was later developed as a model more comparable to the human situation in regard to therapeutic levels of immunosuppressive drugs. The uterus was transplanted to an orthotopic position, with vascular anastomoses to the common iliacs.[17] This allowed for spontaneous conception, and we could initially show successful pregnancies in the syngeneic rat UTx model.[18] In the allogeneic rat UTx models, tacrolimus[19] was found to be more effective than cyclosporine[20] to prevent rejection. Thus, tacrolimus was used in the experiments, where the first ever pregnancies were demonstrated in an allogeneic UTx setting in any species.[21] Subsequent studies showed normality of these offspring that developed inside a uterine graft and under the influence of immunosuppression.[22] In separate experiments, it was found that the uterus is an organ, i.e., fairly resistant to warm ischemia.[23]

Rabbit

The rabbit UTx model was explored by Smith et al in London. In their initial study, a large vessel aortocaval patch technique was used in an allogeneic model with tacrolimus immunosuppression.[24] Two out of five animals survived the postoperative period, and only one had a lasting uterus, albeit of decreased size, at necropsy 10 months after UTx. In a follow-up study, including nine UTx procedures, only one rabbit survived more than 1 month, showing the difficulty of this major surgical procedure in this species.[25] Three rejection episodes in this doe were controlled with prednisolone plus a temporary doubling of tacrolimus dose. After embryo transfer, one early pregnancy was noted by ultrasound, but the pregnancy ended with miscarriage.[26] Thus, no live births have been demonstrated after UTx in the rabbit.

Sheep

The advantage of the sheep UTx model is the similarities in size and anatomy of the pelvic vasculature, as compared with the human. We initially developed an ovine auto-UTx model[27] with excision of one uterine horn and retrieval of a unilateral vascular pedicle down to and including the anterior branch of the internal iliac artery and the complete utero-ovarian vein. Anastomosis was then performed end-to-side to the external iliacs. This model was also characterized concerning reperfusion events after ischemic preservation.[28] In subsequent experiments, we demonstrated live births after autotransplantation.[29] Notably, the graft had been subjected to an extended warm ischemic period of 3 hours. This demonstrates that a uterus with a similar size as the human is quite tolerable to the cellular changes that are induced by extended warm ischemia.

The Ramirez group in Colombia utilized an allogeneic UTx model in the sheep and already in 2008 demonstrated long-term uterine survival with cyclosporine immunosuppression.[30] This finding was followed by the accomplishment of the first live birth after allo-UTx in a large animal in 2011.[31] In that study, 3 out of 12 sheep achieved pregnancy after embryo transfer, with one resultant live birth. The two studies[30,31] used a surgical protocol with end-to-end anastomoses on the uterine vessels. This principle of uterine-to-uterine vessel anastomosis can only be accomplished when the recipient undergoes a hysterectomy at the time of transplantation. This would in the human situation be relevant in the rare situations of AUFI because of intrauterine adhesions or malformed uterus. The same anastomosis technique was used by a Chinese group, with demonstration of graft survival for 1 month after allo-UTx with induction immunosuppression, followed by standard triple immunosuppression.[32] In another study from the Miami group around Andreas Tzakis, a technique for heterotopic placement of the uterine graft, with a cutaneous vaginal stoma, and vascular anastomoses on the aorta and vena cava was used.[33]

Pig

The pig has also been used as a large animal model in UTx research. We examined the venous effluents from the autologous transplanted uterus[34] for blood gases, lactate, and thiobarbituric acid-reactive species (TBARS), the latter an indicator of oxidative stress. The blood gases and lactate concentrations were normalized after about 60 minutes, and the levels of TBARS were not different from before transplantation.[34] In the long-term studies of auto-UTx by the Smith group, it was described that thrombosis developed over the uterine vessel anastomosis lines,[35] pointing toward the susceptibility of these small vessel anastomoses. A follow-up study on allogeneic UTx in the pig utilized a macrovascular patch, including the lower aorta and *vena cava* for anastomosis[36] and with the uterus placed in a heterotopic position. The immunosuppression was initially with intravenous tacrolimus and then maintenance immunosuppression with oral cyclosporine. During the 12-month follow-up period, animal survival rate was 50%. Importantly, acute rejection episodes could effectively be reversed by increased maintenance immunosuppression and corticosteroids.

Nonhuman Primates

Our group initiated nonhuman primate UTx research with vascular anastomosis by a study utilizing autologous UTx in the baboon. The success rate, in terms of restored menstruation, was only 20% in the initial study.[37] The methodology was modified in relation to flushing of the graft and anastomosis surgery, and this resulted in a threefold higher success rate.[38] Nevertheless, no pregnancy occurred, despite breeding attempts over several months. This was due to tubal blockage, possibly secondary to ischemic damage. We have also performed allogeneic UTx in the baboon with transplantation from live donors and anastomoses to the external iliac vessels.[39] The recovery surgery lasted about 3 hours, and the donor survival was 100%. In that study, various immunosuppression protocols were tested, and it was found that induction therapy, with antithymocyte globulin, followed by triple immunosuppression with tacrolimus, mycophenolate mofetil, and corticosteroids, was compatible with 3 months graft survival. In our study of allogeneic UTx in the baboon, using grafts from deceased donors, anastomoses were performed with the aorta and vena cava of the graft to the recipient's aorta and *vena cava*.[40] The initial immunosuppression protocol was induction with triple immunosuppression for some months and then only tacrolimus. Although episodes of graft rejection occurred, these were successfully treated and graft survival over 12 months occurred.

In the smaller cynomolgus macaque, a Japanese research team performed autologous UTx experiments with 6 to 8 hours of recovery surgery and 4 to 6 hours of anastomosis surgery.[41] A great achievement was the first pregnancy ever after any type of UTx in a nonhuman primate species.[42] The animal had undergone auto-UTx, involving bilateral uterine artery and vein anastomosis to external iliac arteries. Natural mating resulted in a pregnancy that developed normally until placental abruption occurred near term. A live offspring was delivered. In a follow-up study on allogeneic UTx in this species, resumed menstruation was seen in an animal on immunosuppression with tacrolimus, methylprednisolone, and mycophenolate mofetil.[43]

PRECLINICAL HUMAN UTx STUDIES

There is limited experience of human preclinical UTx research. In one study on human uterine tissue, we assessed the tolerability to cold ischemia.[44] Uterine tissue from hysterectomy specimen that was subjected to cold ischemia for 24 hours in proper preservation solutions exhibited well-preserved ultramorphology and myometrial contractions.[44]

There also exist two studies in humans that have investigated techniques for uterus recovery from brain dead donors. In the initial study, almost 150 multiorgan procurements in New York City were identified as potential procedures for uterine donation with a research purpose.[45] Uterine donation was accepted in only 6% of cases. The research protocol for uterine procurement was to secure the complete internal iliac vessels, but in

most cases only the anterior portions of the internal iliacs were harvested. In a later study performed in France with the same purpose, also seven uteri were harvested for research purposes, but with a much higher (50%) consent rate.[46] The uteri were harvested after retrieval of thoracic and abdominal organs, and the *in situ* flushing of the organs was through femoral artery catheters. The bilateral internal iliac arteries and veins could be preserved in six out of seven cases. It was concluded that uterus retrieval could be part of a multiorgan procurement procedure with reproducible results. The retrieval procedures from multiorgan donors, as described above, would allow for bilateral anastomoses to the external iliac vessels since long vascular pedicles can be obtained and the ureters, which are tightly attached to the uterine vessels, can be transected above and below the uterine vessels.

In a live donor UTx procedure, the vascular pedicles due to natural reasons will be shorter. In order to explore what lengths of the vascular pedicles could be anticipated in a live uterine donation situation, we performed a study with addition of uterine vein dissection to the normal uterine artery dissection during radical hysterectomy surgery for cervical cancer.[47] The additional dissections of the uterine veins added around 30 minutes to the 3 and 4 hours procedure, but it did not affect postsurgical morbidity. Importantly, the lengths of the uterine vessels were >5 cm, and this would allow bilateral end-to-side anastomosis to the external iliacs that are about 9 to 10 cm apart.[47]

HUMAN UTx

As mentioned above, so far eleven human UTx attempts have been published. Our team in Sweden performed the last nine of these.

Two Single Human UTx Cases

The first two human cases were performed without any research preparations. This has of course put the patients at unnecessary risks and most likely also been reasons why they have been unsuccessful.

In 2000, a 26-year-old woman, who had undergone emergency peripartum hysterectomy during her first childbirth, received a uterus from a 46-year-old live donor.[48] The procedure took place in Jeddah, Kingdom of Saudi Arabia. The short uterine vessels on the recovered uterus were extended by segments of the saphenous veins, and anastomoses were accomplished with these extended vascular pedicles end-to-side to the external iliac vessels of the recipient. The donor had a perioperative ureteral injury. It is questionable whether the uterus was properly perfused, and a necrotic uterus was removed after 3 months.

In 2011, the world's second human UTx procedure was attempted. In Antalya, Turkey, a 21-year-old MRKH patient received a uterus from a 22-year-old deceased donor.[49] The recovery from the donor lasted 2 hours, and the uterus was the first organ to be recovered. The transplantation procedure took 6 hours and included bilateral end-to-side anastomosis of the common iliac vessels of the graft to the external iliac vessels. Immunosuppression was thymoglobulin for 10 days and then triple maintenance therapy by prednisolone, mycophenolate mofetil, and tacrolimus. Eighteen months after UTx, embryo transfer attempts were initiated. The patient has had multiple *in vitro* fertilization attempts, but with only two very early miscarriages as the end result.[50] The reason for the pregnancy failure in this case is unknown, but an important fact to take into consideration is that a nulliparous uterus was transplanted and the capacity to carry a normal pregnancy of this uterus had never been demonstrated.

The First Human Clinical UTx Trial

Our team performed nine human UTx surgeries in 2013, with the uterus from live donors.[51] Eight recipients were MRKH patients, with congenital uterine absence, and one was a patient with cervical cancer 7 years prior to UTx. *In vitro* fertilization, with cryopreservation of at least 10 embryos, had been performed prior to UTx. The donors were mothers (age 50–58) in five cases, close relatives in three cases [mother's sister (age 54), sister (age 37), mother-in-law (age 62)], and family friend (age 61) in one case. Five of the donors were postmenopausal, and all of them had more than one normal pregnancy and delivery during the reproductive period. These postmenopausal donors were given cyclic hormonal treatment for some months before uterine recovery to ascertain that a normal menstrual pattern would occur.

The recovery surgery comprised isolation of the uterus with bilateral vascular pedicles, including the internal iliac arteries distal to the branching of the gluteal artery as well as the major uterine veins down to the internal iliac vein.[51] This surgery of the donors lasted much longer than expected, with durations of >10 hours in all cases. However, the perioperative outcome was favorable in all cases and with a stay in the hospital of 6 days. In one patient, a ureteric-vaginal fistula was diagnosed after 2 weeks and this was later repaired. The surgeries of the recipients included bilateral end-to-side anastomoses to the external iliacs, vaginal anastomosis, and fixation of the uterus to the pelvic ligaments. This lasted 4 to 6 hours and postoperative hospitalization was between 3 and 9 days. The immunosuppression regimen was perioperative administration of thymoglobulin plus methylprednisolone, and then 4 days of oral glucocorticoids.

Double maintenance immunosuppression, consisting of tacrolimus and mycophenolate mofetil, was given from surgery and during the initial 6 months.[51] The aim was to only give tacrolimus after 6 months, but if more than one acute rejection episode occurred during the initial 6 months, mycophenolate mofetil would be replaced by azathioprine with or without oral glucocorticoids.[52] The 6 months outcome[51] was that seven uteri remained in good condition, with regular menstruations from 1 to 2 months after UTx.[52] Two uterine grafts were removed within the first 4 months. One hysterectomy was because of bilateral thrombotic occlusion of the uterine artery already 3 days post-UTx.[52] This patient was heterozygote for the Leiden mutation, and this may have been an underlying cause. The second patient with hysterectomy was readmitted to the hospital 1 month after UTx because of fever and vaginal discharge. An intrauterine infection with *Enterococcus faecalis* was diagnosed. Despite intense antibiotic treatments and several attempts of surgical drainage, she developed a persistent intrauterine abscess. After 2 months of intense treatment attempts, she showed initial signs of septicemia and the uterus with areas of necrosis was removed 3.5 months after UTx.[51]

Mild rejection episodes, although subclinical, were diagnosed on protocol cervical biopsies in five out of the seven patients with viable grafts past 6 months.[52] The rejection episodes were all effectively reversed by 2 weeks' corticosteroid treatment or dose increments in tacrolimus. The uterine artery blood flow remained within normal ranges during the first posttransplantation year.[52] The psychological outcome of recipients and partners during the first posttransplantation year shows a general optimistic view, with little anxiety and stress.[53] Attempts to achieve pregnancy were initiated after 12 months by single embryo transfers. The first live birth from this patient cohort took place in early September 2014,[54] and this event is also the first human birth ever after UTx. It should also be regarded as the first UTx procedure that by definition is successful, since the goal of the transplantation was achieved. The recipient had an uneventful pregnancy and worked normally until she was admitted at 31 full weeks and 5 days because of headache and high blood pressure. Preeclampsia was diagnosed, and because of signs of abnormal fetal cardiotocography, a cesarean section was performed the following day. A healthy and normal-sized male baby was delivered. The birth weight was around 1.8 kg, and today, the 2-year-old boy is in excellent shape. The cause of preeclampsia may be related to unilateral renal ageneneis of that patient.[55] Subsequently, four more uterus recipients have given birth (unpublished observations). All these children are healthy and developing well. Interestingly, in three of these five pregnancies preeclampsia developed, and that occurred only in patients with single kidney. The other two patients had double kidneys and did not develop preeclampsia.

Preparation for introduction of UTx in India was initiated with a collaboration with Dr. Kamini Rao, and the necessary background work with respect to permission from the government is being worked up. Though gestational surrogacy is an option in India, UTx gives the opportunity of childbearing in women with AUFI.

CONCLUSION

Uterus transplantation has now shown its potential as a highly effective treatment for uterine factor infertility, which is due to the absence of the uterus or the presence of a nonfunctional uterus. Further prospective observational studies should follow both with the live and deceased donor concept. The collective results of the studies will be important to establish sound inclusion and exclusion criteria. Furthermore, the surgical and medical management of the patients will become more efficient and safer with proper scientific results as the fundamental for the UTx procedure, when it is introduced at new centers around the world.

REFERENCES

1. Milliez J. FIGO committee for the ethical aspects of human reproduction and women's health: uterine transplantation. Int J Gynaecol Obstet 2009 Nov;107(2):168.
2. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, Balliol Collaboration, Aronson JK, Barkun JS, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009 Sep 26;374(9695): 1105-1112.
3. Diaz-Garcia C, Johannesson L, Enskog A, Tzakis A, Olausson M, Brännström M. Uterus transplantation research: laboratory protocols for clinical application. Mol Hum Reprod 2012 Feb;18(2):68-78.
4. Grimbizis GF, Camus M, Tarlatzis BC, Bontis JN, Devroy P. Clinical implications of uterine malformations and hysteroscopic treatment results. Hum Reprod Update 2001 Mar-Apr;7(2):161-174.
5. Oppelt P, Strissel PL, Kellerman A, Seeber S, Humeny A, Beckmann MW, Strick R. Correlation of DNA sequence variations of the entire anti-Müllerian hormone (AMH) gene promoter and AMH protein expression with the Mayer-Rokitansky-Kuester-Hauser syndrome. Hum Reprod 2005 Jan;20(1):149-157.
6. Borgfeldt C, Andolf E. Transvaginal ultrasonographic findings in the uterus and endometrium: low prevalence of leiomyoma in a random sample of women age 25-40 years. Acta Obstet Gynecol Scand 2000 Mar;79(3):202-207.
7. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997 Dec;90(6): 967-973.

8. Fernandez H, Al-Najjar F, Chauveud-Lambling A, Frydman R, Gervaise A. Fertility after treatment of Asherman's syndrome stage 3 and 4. J Minim Invasive Gynecol 2006 Sep-Oct;13(5):398-402.
9. Sharma JB, Roy KK, Pushparaj M, Gupta N, Jain SK, Malhotra N, Mittal S. Genital tuberculosis is an important cause of Asherman's syndrome in India. Arch Gynecol Obstet 2008 Jan;277(1):37-41.
10. Racho El-Akouri R, Kurlberg G, Dindelegan G, Mölne J, Wallin A, Brännström M. Heterotopic uterine transplantation by vascular anastomosis in the mouse. J Endocrinol 2002 Aug;174(2):157-166.
11. Racho El-Akouri R, Kurlberg G, Brännström M. Successful uterine transplantation in the mouse: pregnancy and postnatal development of offspring. Hum Reprod 2003 Oct;18(10): 2018-2023.
12. Racho El-Akouri R, Wranning CA, Mölne J, Kurlberg G, Brännström M. Pregnancy in transplanted mouse uterus after long-term cold ischaemic preservation. Hum Reprod 2003 Oct;18(10):2024-2030.
13. Racho El-Akouri R, Groth K, Kurlberg G, Mölne J, Brännström M. Rejection patterns in allogeneic uterus transplantation in the mouse. Hum Reprod 2006 Feb;21(2):436-442.
14. Groth K, El-Akouri RR, Wranning CA, Mölne J, Brännström M. Rejection of allogenic uterus transplant in the mouse: time-dependent and site-specific infiltration of leukocyte subtypes. Hum Reprod 2009 Nov;24(11):2746-2754.
15. Wranning CA, El-Akouri RR, Groth K, Mölne J, Parra AK, Brännström M. Rejection of the transplanted uterus is suppressed by cyclosporine A in a semi-allogeneic mouse model. Hum Reprod 2007 Feb;22(2):372-379.
16. Groth K, Brännström M, Mölne J, Wranning CA. Cyclosporine A exposure during pregnancy in mice: effects on reproductive performance in mothers and offspring. Hum Reprod 2010 Mar;25(3):697-704.
17. Wranning CA, Akhi SN, Kurlberg G, Brännström M. Uterus transplantation in the rat: model development, surgical learning and morphological evaluation. Acta Obstet Gynecol Scand 2008;87(11):1239-1247.
18. Wranning CA, Akhi SN, Diaz-Garcia C, Brännström M. Pregnancy after syngeneic uterus transplantation and spontaneous mating in the rat. Hum Reprod 2011 Mar;26(3):553-558.
19. Akhi SN, Diaz-Garcia C, El-Akouri RR, Wranning CA, Mölne J, Brännström M. Uterine rejection after allogeneic uterus transplantation in the rat is effectively suppressed by tacrolimus. Fertil Steril 2013 Mar 1;99(3):862-870.
20. Groth K, Akhi S, Mölne J, Wranning CA, Brännström M. Effects of immunosuppression by cyclosporine A on allogenic uterine transplant in the rat. Eur J Obstet Gynecol Reprod Biol 2012 Jul;163(1):97-103.
21. Diaz-Garcia C, Akhi SN, Wallin A, Pellicer A, Brännström M. First report on fertility after allogeneic uterus transplantation. Acta Obstet Gynecol Scand 2010 Nov;89(11):1491-1494.
22. Diaz-Garcia C, Johannesson L, Shao R, Billig H, Brännström M. Pregnancy after allogeneic uterus transplantation in the rat: perinatal outcome and growth trajectory. Fertil Steril 2014 Dec;102(6):1545-1552.
23. Diaz-Garcia C, Akhi SN, Martinez-Varea A, Brännström M. The effect of warm ischemia at uterus transplantation in a rat model. Acta Obstet Gynecol Scand 2013 Feb;92(2):152-159.
24. Saso S, Petts G, Chatterjee J, Thum M-Y, David AL, Corless D, Boyd M, Noakes D, Lindsay I, Del Priore G, et al. Uterine transplantation in a rabbit model using aorta-caval anastomosis: a long-term viability study. Eur J Obstet Gynecol Reprod Biol 2014 Nov;182:185-193.
25. Saso S, Hurst S, Chatterjee J, Kuzmin E, Thum Y, David AL, Hakim N, Corless D, Boyd M, Noakes DE, et al. Test of long-term uterine survival after allogeneic transplantation in rabbits. J Obstet Gynaecaol Res 2014 Mar;40(3):754-762.
26. Saso S, Petts G, David AL, Thum M-Y, Chatterjee J, Vicente JS, Marco-Jimenez F, Corless D, Boyd M, Noakes D, et al. Achieving an early pregnancy following allogeneic uterine transplantation in a rabbit model. Eur J Obstet Gynecol Reprod Biol 2015 Feb;185:164-169.
27. Dahm-Kähler P, Wranning CA, Lundmark C, Enskog A, Mölne J, Marcickiewicz J, El-Akouri RR, McCracken JA, Brännström M. Transplantation of the uterus in the sheep: methodology and early reperfusion events. J Obstet Gynaecol Res 2008 Oct;34(5):784-793.
28. Wranning CA, Dahm-Kähler P, Mölne J, Nilsson UA, Enskog A, Brännström M. Transplantation of the uterus in the sheep – oxidative stress and reperfusion injury after short-time cold storage. Fertil Steril 2008 Sep;90(3):817-826.
29. Wranning CA, Marcickiewicz J, Enskog A, Dahm-Kähler P, Hanafy A, Brännström M. Fertility after autologous ovine uterine-tubal-ovarian transplantation by vascular anastomosis to the external iliac vessels. Hum Reprod 2010 Aug;25(8): 1973-1979.
30. Ramirez ER, Ramirez DK, Pillari VT, Vasquez H, Ramirez HA. Modified uterine transplant procedure in the sheep model. J Minim Invasive Gynecol 2008 May-Jun;15(3):311-314.
31. Ramirez ER, Ramirez-Nessetti DK, Nessetti MB, Khatamee M, Wolfson MR, Shaffer TH. Pregnancy and outcome of uterine allotransplantation and assisted reproduction in sheep. J Minim Invasive Gynecol 2011 Mar-Apr;18(2):238-245.
32. Wei L, Xue T, Yang H, Zhao GY, Zhang G, Lu ZH, Huang YH, Ma XD, Liu HX, Liang SR, et al. Modified uterine allotransplantation and immunosuppression procedure in the sheep model. PLoS One 2013 Nov 22;8(11):e81300.
33. Gonzalez-Pinto IM, Tryphonopoulos P, Avison DL, Nishida S, Tekin A, Santiago S, Tzakis A. Uterus transplantation model in the sheep with heterotopic whole graft and aorta and cava anastomoses. Transpl Proc 2013 Jun;45(5):1802-1804.
34. Wranning CA, Racho El-Akouri R, Lundmark C, Dahm-Kähler P, Mölne J, Enskog A, Brännström M. Autotransplantation of the uterus in the domestic pig: surgical technique and early reperfusion events. J Obstet Gynecol Res 2006 Aug;32(4): 358-367.
35. Sieunarine K, Zakaria FB, Boyle DC, Corless DJ, Noakes DE, Lindsay I, Lawson A, Ungar L, Del Priore G, Smith JR. Possibilities for fertility restoration: a new surgical technique. Int Surg 2005 Nov-Dec;90(5):249-256.
36. Avison DL, DeFaria W, Tryphonopoulos P, Tekin A, Attia GR, Takahashi H, Jin Y, Palaois E, Pararas N, Carreno MR, et al. Heterotopic uterus transplantation in a swine model. Transplantation 2009 Aug 27;88(4):465-469.
37. Enskog A, Johannesson L, Chai DC, Dahm-Kähler P, Marcickiewicz J, Nyachieo A, Mwenda J, Brännström M. Uterus transplantation in the baboon: methodology and long-term function after auto-transplantation. Hum Reprod 2010 Aug;25(8):1980-1987.
38. Johannesson L, Enskog A, Dahm-Kähler P, Hanafy A, Chai DC, Mwenda JM, Diaz-Garcia C, Olausson M, Brännström M. Uterus transplantation in a non-human

primate: long-term follow up after autologous transplantation. Hum Reprod 2012 Jun;27(6):1640-1648.

39. Johannesson L, Enskog A, Mölne J, Diaz-Garcia C, Hanafy A, Dahm-Kähler P, Tekin A, Tryphonopoulos P, Morales P, Rivas K, et al. Preclinical report on allogeneic uterus transplantation in non-human primates. Hum Reprod 2013 Jan;28(1):189-198.
40. Tryphonopoulos P, Tzakis AG, Tekin A, Johannesson L, Rivas K, Morales PR, Wagner J, Mölne J, Enskog E, Diaz-Garcia C, et al. Allogeneic uterus transplantation in baboons: surgical technique and challenges to long-term graft survival. Transplantation 2014 Sep 15;98(5):e51-e56.
41. Kisu I, Mihara M, Banno K, Hara H, Yamamoto T, Araki J, Iida T, Hayashi Y, Moriguchi H, Aoki D. A new surgical technique of uterine auto-transplantation in cynomolgus monkey: preliminary report about two cases. Arch Gynecol Obstet 2012 Jan;285(1):129-137.
42. Mihara M, Kisu I, Hara H, Iida T, Araki J, Shim T, Narushima M, Yamamoto T, Moriguchi H, Kato Y, et al. Uterine autotransplantation in cynomolgus macaques: the first case of pregnancy and delivery. Hum Reprod 2012 Aug;27(8):2332-2340.
43. Kisu I, Mihara M, Banno K, Masugi Y, Araki J, Iida T, Yamada Y, Kato Y, Shiina T, Suganuma N, et al. Uterus allotransplantation in cynomolgus macaque: a preliminary experience with non-human primate models. J Obstet Gynaecol Res 2014 Apr;40(4):907-918.
44. Wranning CA, Mölne J, Racho El-Akouri R, Kurlberg G, Brännström M. Short-term ischaemic storage of human uterine myometrium – basic studies towards uterine transplantation. Human Reprod 2005 Oct;20(10):2736-2744.
45. Del Priore G, Stega J, Sieunarine K, Ungar L, Smith R. Human uterus retrieval from a multi-organ donor. Obstet Gynecol 2007 Jan;109(1):101-104.
46. Gauthier T, Piver P, Pichon N, Bibes R, Guillaudeau A, Piccardo A, Pesteil F, Tricard J, Gardet E, Laskar M, et al. Uterus retrieval process from brain dead donors. Fertil Steril 2014 Aug;102(2):476-482.
47. Johannesson L, Diaz-Garcia C, Leonhardt H, Dahm-Kähler P, Marcickiewicz J, Olausson M, Brännström M. Vascular pedicle lengths after hysterectomy: toward future human uterus transplantation. Obstet Gynecol 2012 Jun;119(6):1219-1225.
48. Fageeh W, Raffa H, Jabbah H, Marzouki A. Transplantation of the human uterus. Int J Gynaecol Obstet 2002 Mar;76(3):245-251.
49. Ozkan O, Akar ME, Ozkan O, Erdogan O, Hadimioglu N, Yilmaz M, Gunseren F, Cincik M, Pestereli E, Kocak J, et al. Preliminary results of the first human uterus transplantation from a multiorgan donor. Fertil Steril 2013 Feb;99(2):470-476.
50. Erman Akar M, Ozkan O, Aydinuraz B, Dirican K, Cibcik M, Mendilcioglu I, Simsek M, Gunseren F, Kocak H, Ciftcioglu A, et al. Clinical pregnancy after uterus transplantation. Fertil Steril 2013 Nov;100(5):1358-1363.
51. Brännström M, Johannesson L, Dahm-Kähler P, Enskog AS, Mölne J, Kvarnström N, Diaz-Garcia C, Hanafy A, Lundmark C, Marcickiewicz J, et al. The first clinical uterus transplantation trial: a six months report. Fertil Steril 2014 May;101(5):1228-1236.
52. Johannesson L, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog AS, Diaz-Garcia C, Olausson M, Brännström M. Uterus transplantation trial: 1-year outcome. Fertil Steril 2015 Jan;103(1):199-204.
53. Järvholm S, Johannesson L, Brännström M. Psychological aspects in pretransplantation assessments of patients prior to entering the first uterus transplantation trial. Acta Obstet Gynecol Scand 2015 Oct;94(10):1035-1038.
54. Brännström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog A, Milenkovic M, Ekberg J, Diaz-Garcia C, et al. Live birth after uterus transplantation. Lancet 2015 Feb 14;385(9968):607-616.
55. Brännström M, Diaz-Garcia C, Johannesson L, Dahm-Kähler P, Bokström H. Livebirth after uterus transplantation – authors' reply. Lancet 2015 Jun 13;385(9985):2352-2353.