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Uterus transplantation: From animal models through the first heart beating pregnancy to the first human live birth

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Abstract

Absolute uterine factor infertility affects 3–5% of the general population, and unfortunately this condition is untreatable. There are some available options, including surrogacy or adoption, but neither of these suits each and every woman who desires to have her own genetic child. With recent advances in surgery and transplant immunology, uterus transplantation may be a source of hope for these women with uterine infertility. In the last decade, a number of animal species including rats, mice, rabbits, pigs, sheep, and primates have been used as experimental models, and pregnancies were achieved in some of these. Human data consist of 11 subjects yielding positive pregnancy results with no live births in the second trial from Turkey and, more fortunately, live births from the latest trial from Sweden. In the light of all these studies, uterus transplantation has been proven to be a viable option for women with uterine factor infertility.

Keywords

Absolute uterine factor infertility, deceased donor, infertility, uterus transplantation

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Introduction

Absolute uterine factor infertility (aURI) affects 3–5% of the general population. Congenital absence of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, iatrogenic causes (hysterectomy due to intractable postpartum hemorrhage as well as hysterectomy due to uterine benign/malignant tumor such as early cervical cancer), or Ashermann syndrome are the leading factors associated with URI.[1] Unfortunately, this condition is untreatable. Surrogacy by means of assisted reproductive techniques (ARTs) is one option for overcoming URI but is not yet legal in many countries. Adoption is another option, but neither of these suits each and every woman who desires to have her own genetic child, for ethical, religious, or personal reasons. Thanks to advances in sophisticated surgical techniques, microsurgical innovations, tissue preservation techniques, and a better understanding of transplantation immunity, uterus transplantation (UT) may now represent a source of hope for these women with URI. Animal studies have elicited successful pregnancies and newborns, and a limited number of human UTs have also been performed.[2–6] Live birth after UT was recently reported, and URI is now certainly not untreatable.[7] In this review, we evaluate the technical, ethical, and historical aspects of UT in the light of current studies.

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Materials and methods

A detailed search of PubMed from 2000 to 2015 December including the key words "uterus transplantation" or "uterine transplantation" revealed a total of 144 articles. A total of 13 of these were in languages other than English. A total of 54 articles involving humans and animals were retrieved. The most recent articles particularly those published in the last 5 years were included in this review.[2,4–30] Only five articles involved human subjects, two of which reported the same patient cohort at 6-month and 12-month follow-ups.[4–7,20]

Results

Historical perspectives

The first studies related to UT date back as early as the 1960s. At that time, ovarian and Fallopian tube transplantation were discussed, and animal models were established.[31] These experiments included tubal or uterotubal transplantation for the treatment of Fallopian tube–related infertility. In one of the first reports from those years, Sir John Peel from the United Kingdom said, "Perhaps in another fifty years someone of the younger generation will be reporting cases of successful homografts of healthy fallopian tubes taken from donors but that, too, is another story." These early studies may reflect the first thinking regarding UT. The first successful autotransplantation of uterus and oviducts was achieved in 1966. Eraslan et al.[32] later successfully operated and transplanted an autologous uterus and ovaries in a dog model and achieved pregnancy. In the 1970s, successful pregnancies with transplanted tubes were demonstrated in animal models, but Fallopian autologous transplant failed in human trials, probably due to inadequate immunosuppressant agents at that time.[33] After the birth of the first in vitro fertilization (IVF) baby, tubal factor lost its significance as an untreatable cause of infertility. To date, there have been three attempts with humans described in the literature. The first was performed by a Saudi Arabian team[4] in 2000. We performed the first transplant from a deceased donor in 2011.[5] Following our success, Brannstrom and coworkers[4–7,20] reported their experience of nine women undergoing transplant from live donors. Finally, a new era dawned in October 2014 with the announcement of the first live birth after UT.[7]

Animal studies

A number of animal species including rats, mice, rabbits, pigs, sheep, and primates (rhesus, cynomolgus monkeys, and baboons) have been used as experimental models, and pregnancies have been achieved in some experimental models.[2,3,13] To date, only rat, sheep, and rabbit models have resulted in allogeneic graft pregnancies.[2,3,19,21]

Pregnancies and delivery after UT were previously reported in a syngeneic mouse model,[15] but it was not until 2010 that the first allogeneic transplant in rats was performed, with reports of early pregnancy results.[2] The same group of authors from Sweden[21] subsequently reported the first postnatal outcomes in further rat models with allogeneic transplantation.

In this study with rats, three groups of animals (the first group, allogeneic UT with tacrolimus; the second group, left uterine horn excision with immunosuppression; and the last group, left uterine horn excision without any suppression) were compared. Although not statistically significant, pregnancy rates were higher in the control group (80%) than in the uterus transplanted animals (50%). Pups of rats undergoing UT with tacrolimus had comparable birthweights to those of the control animals. In contrast, at morphological analysis, microvessel densities were lower in the uterus and placenta of the UT group subjects compared with the non-treated animals. Moreover, at further follow-up, female offspring from the transplant group exhibited normal growth at all time points in the postnatal period and also after sexual maturation. Although not directly demonstrated in higher-order species, these are important data showing the feasibility and relative safety of immunosuppressants in UT surgery.

In terms of human transplantation, allogeneic transplant with the use of immunosuppressants, particularly with nonhuman primates, is of paramount importance. Primates bear a close resemblance to humans in terms of genitourinary anatomy and reproductive physiology. However, results with primate models have been unsatisfactory, in that in the first attempts, only half of the animals demonstrated recovered ovarian functions, and resumption of menstrual cyclicity was only demonstrated in very few animals.[14] In subsequent studies, most uterus transplanted animals failed to survive. Only a quarter of primates survived with restoration of menstrual cyclicity. Moreover, in subsequent studies using modified surgical techniques, no pregnancy was achieved, probably due to pelvic adhesions.[11] In addition, no tubal passage was demonstrated in the second-look surgeries. All these indicate the need for ARTs to improve the chances of conception and pregnancy in primate models.

Kisu et al.[12] reported an allotransplantation experimental model in two cynomolgus monkeys with the use of immunosuppressants. The uteruses of two monkeys were exchanged synchronously. Following successful transplantation, immunosuppressant levels decreased on the postoperative 11th day, with clear evidence of rejection, but that rejection resolved in 2 weeks. In one of the animals, restoration of menses was observed on the third month, but menstruation ceased thereafter. The other animal was unable to menstruate. Laparotomy revealed a normal uterus densely adhered to surrounding organs in the menstruating animal, but there was no even "histologically" visible endometrial

tissue in the endometrial cavity. In the non-menstruating animal, laparotomy revealed again a densely adherent uterus with no pulsating uterine artery. The uterus was atrophic with no endometrial lining. In 2012, the same group from Japan reported the "first ever" natural pregnancy in cynomolgus monkeys.[13] Different vessel anastomoses were used in these two animals. At angiographic examination, the presence of only one anastomosed uterine artery was shown to perfuse the whole autografted uterus, but unfortunately, atrophy was observed in this anastomosed uterus at follow-up. Additionally, at angiographic observation, the main suppliers of the uterus were shown to be the uterine artery and vein, rather than the ovarian vein or vaginal vein, indicating the crucial nature of uterine artery and vein anastomosis. One of these two animals menstruated and gave birth by cesarean section. During the course of pregnancy, the animal experienced genital bleeding, and the authors were immediately able to diagnose abruption and decided to perform cesarean section, resulting in a live birth, although the fetus was in distress. Postmortem necropsy was performed with normal pathological findings.

Human data

The first published human UT was reported in 2000 by Fageeh et al.[4] of Saudi Arabia. Unfortunately, on the 99th day of transplantation, the patient experienced symptoms of a feeling of heaviness and a foul-smelling vaginal discharge. Vaginal examination revealed a dark-colored cervix protruding into the vagina, and the uterus had to be removed. The authors suggested that loose suspension might have led to both uterine prolapsus and ischemic necrosis of the graft with no histological evidence of rejection. Interestingly, following reports in the media, a paper appeared in the *Lancet* claiming that the relatives of the donor had been deceived without the consent of the donor and her family and that the donor had suffered severe ureteral injury. Subsequently, however, another publication appeared in the *Lancet* apologizing to Dr Fageeh because of incorrect information.[34,35]

The second UT, the first ever from a deceased donor, was performed by our team in 2011.[5,36] The patient was a 22-year-old woman with a diagnosis of MRKH syndrome. She underwent vaginal reconstruction surgery with jejunum segment 2 years before transplantation.[37] The donor was a deceased 22-year-old woman with brain death resulting from a car accident. The whole procedure took 8 h: 2 h for retrieval from the donor, 30 min for transfer, and 4.5 h for the recipient operation. The retrieval procedure resembled radical hysterectomy. Long vascular pedicles including hypogastric (including uterine artery), ovarian vessels were dissected from surrounding tissues. The anterior reflection of the bladder peritoneum was dissected and included within the retrieved uterus. In our opinion, resection of the bladder peritoneum is clinically important for better graft support.

The donor uterus was placed in its proper position to the recipient after dissection of the hypogastric and external iliac vessels. Vessel anastomosis was performed between the recipient's external iliac vessels and the donor uterus hypogastric artery pedicle. By the postoperative 20th month, the recipient was doing well with no signs of rejection. She is currently continuing to menstruate. We have attempted six IVF cycles to date, with one chemical and three missed abortive pregnancies (two of which had fetal cardiac activity).

In our case, we elected to use a deceased donor. The main advantage of a deceased donor is the avoidance of postoperative morbidity related to retrieval of the uterus graft. Longer and enhanced vascular grafts can also be achieved within a significantly short time. Drawbacks include less time for detailed tests and also a possible adverse effect of the inflammatory process related to brain death.

The use of deceased donors in transplant surgery may also involve an impaired graft quality, enhanced immunological response, and a clinically lower probability of graft survival. Brain death triggers a series of events, including hemodynamic, hormonal, metabolic, and immunological responses which may be significant even if no clinical consequences are evident. In animal models, after brain death, a transient hyperdynamic cardiovascular response (catecholamine storm) follows a hemodynamically unstable hypotensive state, leading to cardiovascular collapse. Moreover, anaerobic metabolism (followed by tissue acidosis) predominates, leading to a full-blown clinical picture. Vascular endothelial and complement activation ultimately lead to release of proinflammatory cytokines. In order to prevent this cascade of events, treatment of the brain dead donor with steroids and hormones has been proposed for improved outcomes.[38] In contrast to these negative effects, one of the main objectives in brain dead donors is proper human leukocyte antigen (HLA) matching with the recipient. As in our case, a high HLA match will reduce the risk of immunological load and eliminate most of the disadvantages of cadaveric donors compared with live relative donors in terms of immunological response.[5]

Our surgery team has been involved in so-called "composite tissue transplants" for nearly 10 years, including double-hand and five-face transplants. We also have significant experience of autotransplantation of amputated extremities, face avulsions, and so on. We have acquired wide experience in cadaveric pelvic dissections (Figure 1).[39] We believe that such expertise (including microsurgical experience) will be of considerable assistance with future uterine-related transplant issues.

Following our successful UT, Brannstrom et al. performed nine UTs.[6] They published 6-month and 12-month follow-up findings from nine women, eight of which were

Figure 1. Harvested uterus based on hypogastric vessels in a cadaver.

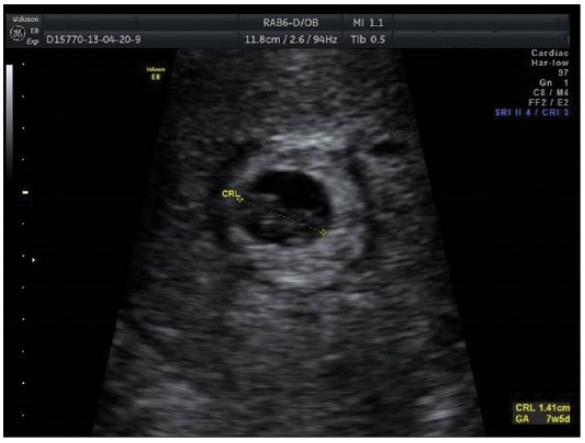

Figure 2. Transabdominal ultrasonographic view of intrauterine pregnancy at 7 weeks of gestation: CRL: 14 mm. CRL: crown-to-rump length.

MRKH patients and one of which was a patient with cervical cancer who had previously undergone radical hysterectomy.[20] Donor surgery lasted 10–13 h. One donor experienced ureterovaginal fistula, which was treated by ureter reimplantation on postoperative day 134. Follow-up was reported to be uneventful, with full recovery.

The first two recipients required intensive care unit admission due to dyspnea. One patient developed retroperitoneal hematoma and received a blood transfusion. The uterus had to be removed in two cases due to resistant *Enterococcus faecalis* infection in one and thrombotic ischemia in the other. Three patients experienced several mild rejection attacks within 1 month after surgery, treated by pulse steroid administration. The authors suggested a long operative time (in one patient) and heterozygosity for protein C deficiency as the main factors involved in infection and thrombosis. Such lengthy surgery with extensive dissection of ureters may lead to long-term urological morbidity in live donors.

The first heart beating pregnancy following deceased donor transplantation

Before the UT procedure, our patient underwent two IVF cycles yielding a total of eight grade I embryos, and the retrieved embryos were vitrified.[5] Induction immunosuppression with antithymocyte globulin and prednisolone was started after the UT procedure. Maintenance immunosuppression was carried with tacrolimus, mycophenolate mofetil, and prednisolone for the first 12 months. We then replaced the mycophenolate mofetil with azathioprine. One and a half years after transplantation, once we were assured of the integrity of the graft and of the absence of rejection, preparation for embryo transfer (ET) was initiated.[10] The immunosuppressive therapy during transfer was prednisolone, azathioprine, and tacrolimus. At the first attempt, an increase in human chorionic gonadotropin (hCG) up to 35 IU/L was observed, but this then decreased to non-pregnant levels with no ultrasonographic signs of pregnancy. At the third attempt, an intrauterine pregnancy with a normal increase in hCG was observed (Figure 2). A viable fetal pole with an ultrasonographically visible heart beat confirmed with transvaginal ultrasound was achieved for the first time (Supplementary Video). Unfortunately, at 8 gestational weeks, embryonic cardiac activity ceased. Following the negative outcome of the third ET attempt, the patient again underwent IVF, yielding a total of eight grade I embryos. In the following ETs, the fourth and the fifth attempts resulted in heart beating (confirmed by Doppler ultrasonography (USG)) fetal pole, but unfortunately, these last two pregnancies ended with missed abortions at 7 weeks of gestation. We suspended the ET trials in order to investigate the probable causes of these recurrent miscarriages, such as immunological and acquired hematological factors.

The first heart beating pregnancy following deceased donor transplantation is a paramount step in uterus trial attempts in proving the success of a uterus harvested from a deceased donor. We achieved two consecutive pregnancies with a heart beating fetus. Although these pregnancies ended with missed abortion, in our opinion, these pregnancies are still direct evidence of the viability of a uterus retrieved from a deceased donor. In another point in our case, the nulliparous state of the donor with unproven fertility may adversely affect the chances of pregnancy. Moreover, previous neovaginal reconstruction with an intestinal flap may create an unfavorable environment for the implantation process, similar to the adverse effect of hydrosalpinx on IVF cycles.[40] To the best of our knowledge, there have been no pregnancies following neovaginal reconstruction with intestinal or colonic flaps. The majority of these patients have had MRKH syndrome or cervical agenesis, making pregnancy through classical

routes impossible. There is, therefore, no direct evidence regarding the possible adverse effect of neovaginal reconstruction with intestinal or colonic flaps. Although the intestinal neovagina no longer performs a fecal storage function, normal bacterial flora may lead to diminished endometrial receptivity and abnormal expression of factors related to implantation.[41]

The birth of the first human baby

The first ever live birth from a UT donor was reported from Sweden in October 2014.[7] Live birth after UT was a breakthrough success and also one of the milestones in reproductive medicine. It represents ultimate proof that aURI is now a treatable condition. A 35-year-old woman with MRKH syndrome received a uterus from a 61-year-old multiparous woman. One year after the operation, she became pregnant at the first IVF attempt. She experienced three courses of mild rejection. One of these attacks occurred during pregnancy and was managed with steroid treatment. The course of pregnancy was uneventful, until 31 weeks and 5 days of gestation when she was hospitalized with a presumed diagnosis of preeclampsia.

Due to this preeclampsia and because of repeated patterns of abnormal cardiotocography, a cesarean section was performed in order to avoid any problems with the fetus, and a 1775-g healthy male baby was delivered. The uterine graft was left in situ for the next potential pregnancy. A recent review article by Brannstrom[42,43] announced three more uneventful births with normal weight appropriate to gestational age and one more ongoing pregnancy, although these births had not been reported separately at the time of writing of this article. In our opinion, following the report of other live births in this cohort, UT trials will enter into a new phase, becoming reality rather than fantasy.

Ethical issues

There are various aspects to the ethical issues in UT. First, in addition to the donor and recipient, a third individual, the unborn fetus, is involved, as well as the spouse of the recipient. UT is an ephemeral transplantation, not a life-saving procedure, rather similar to other transplantation procedures such as the face, hand, arm, and larynx, which all improve the quality of life. Such procedures should improve the quality of life without significantly increasing risk for either donor or recipient. The UT will be the first ephemeral transplant in which the transplanted organ will be removed after the goals have been achieved, but this raises the question of the probable lifespan of the transplanted uterus and the optimal time for immunosuppression.

An extensive surgery with a live donor may lead to permanent long-term morbidity. This was the main reason why we performed UT from a deceased donor. At the very least, it is clear that such lengthy surgery with extensive ureteral dissection may result in long-term urological morbidity in a live donor. In the UT series reported by Brannstrom, one donor had fistula (grade IIIB, a major complication according to the Clavien–Dindo classification). Also in this study, long-term urinary morbidity or function (i.e. with standard questionnaires or urodynamic investigation) and long-term sexual function were all lacking and were not reported. These issues should, therefore, be extensively discussed with donors and should be included in informed consent forms in the preoperative period.[44]

A UT from a multi-organ deceased donor would reduce surgery-related donor morbidity to zero. Gauthier et al.[45] recently reported the feasibility of uterus retrieval process from brain dead donors. A total of 14 multi-organ donors were included in this study, and seven uteri were removed along with other vital organs. Uterine-related surgery did not interfere with other retrieval procedures. Long vascular pedicles up to the hypogastric vessels were successfully retrieved. Only one vein-related failure was reported, in the first patient. Our team was also involved in a cadaveric dissection study in order to experience the feasibility of uterus and related vessel acquisition with four fresh frozen cadavers. We were able to retrieve three uteruses with entire hypogastric vessels and an adequate proximal vagina.[39] As experience with cadaver donor increases, donor-related morbidity will be of no more concern, and more radical uterine retrieval procedures would increase the chances of successful transplantation. From another point of view, techniques such as laparoscopic-assisted robotic surgery will facilitate deep uterine dissection in a live donor and may also reduce surgery-related morbidity to a considerable extent.

Moreover, the use of immunosuppressants in utero poses potential risks to the fetus. A significant number of pregnancies in organ donors have been published with favorable perinatal outcomes.[46,47] Furthermore, the Swedish group used a low-dose immunosuppressive protocol that lowered the problems associated with immunosuppression.[7]

The optimal time for delivery; the right time for removal of transplanted uterus; complications unique to this particular circumstance, such as major rejection necessitating termination of pregnancy; intrauterine fetal demise; and long-term outcomes in the newborn are also still unclear.

Another point is the exact time when the transplanted uterus should be removed. In our case, the patient still has a strong desire for fertility. She is fully informed about the possible risks of immunosuppression or the possibility of serious rejection, and she has opted to continue with the procedures. Similarly, the transplanted uterus was not removed after the birth of the first baby by the Swedish team. As discussed by Farrell, the issue of removing the transplanted uterus should also be discussed thoroughly with the recipient. Although her partner's thoughts are

important, the recipient is the only person with the right to make any decision regarding her own body.[48]

In order to increase the chances of pregnancy, IVF procedures should be employed in these patients, which may lead to multiple pregnancies. In case of a twin or higher order pregnancy, a dilemma between early selective termination of twin pairs or continuing without any intervention could be another source of ethical discussion.

A full discussion of ethical issues is outside the scope of this article. Interested readers are referred to a comprehensive review by Dickens[49] for the discussion of ethical issues in UT.

Conclusion

Scientists have traveled a long way from the first experiments in tubal transplant to successful human transplants. We have learnt a lot and improved our skills, and basic science has improved significantly. With the live birth of the first baby after UT, we are stepping into a new era. However, there is still a long way to go. Nevertheless, we believe that in the near future, UT will take its place among other routine everyday transplant procedures.

Future perspective

The main problem in UT is the "serious" possibility of rejection and the obligatory use of immunosuppressants. In the near future, with increased understanding of transplant immunology, it could be possible to reduce the immunosuppressant dose to a minimum or even to zero! Moreover, with the advent of cell and tissue cultures, it would be possible to create a woman's own uterus from her own stem cells and to implant it without the use of immunosuppression.

Executive summary

- Absolute uterine factor infertility (aURI) affects 3–5% of the general population and is unfortunately untreatable.

Animal studies

- A number of animal species, including rats, mice, rabbits, pigs, sheep, and primates have been used as experimental models, and pregnancies have been achieved in some of these.
- To date, only rat, rabbit and sheep models have led to allogeneic graft pregnancies.

Human data

- The first published human UT was achieved in 2000, but the uterus had to be removed on the 99th day of transplantation.
- The second UT, the first ever from a deceased donor, was performed by our team in 2011.
- The third trial included nine UTs from Sweden, and the first ever live birth from a UT donor was reported in October 2014.
- Advantages of deceased donors include the avoidance of postoperative morbidity related to retrieval of uterus graft. Longer and enhanced vascular grafts could also be achieved in a significantly short time period.
- Drawbacks include less time for detailed tests and also possible negative effects of the inflammatory process related to brain death.
- UT is an ephemeral transplantation and not a life-saving procedure. Such procedures should improve the quality of life without increasing risk significantly for either donor or recipient.
- As experience with cadaver donors increases, donor-related morbidity will be of no more concern, and more radical uterine retrieval procedures would increase the chances of successful transplantation.
- Techniques such as laparoscopic-assisted robotic surgery will facilitate deep uterine dissection in live donors easier and could also reduce surgery-related morbidity to a considerable extent.

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Supplementary material

The online video (Real time gray scale ultrasonographic video view of the intrauterine pregnancy at 7 References) is available at http://whe.sagepub.com/supplemental-data

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