

Uterine transplantation in an era of successful childbirths from living and deceased donor uteri: Current challenges

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Background and Aims. Uterine transplantation (UTx) is an experimental sterility treatment method in women with absolute uterine factor infertility. This article describes the current trends and risks in UTx and provides an overview of our experience with this method, to date.

Methods. Based on our experience with the Czech UTx trial and the published results of other trials, we describe the possibilities and risks of this perspective method in the treatment of absolute uterine factor infertility (AUI).

Results. Twelve healthy babies were born in 2014-2018 after more than 40 uterine transplantations. There is no general consensus whether it is more suitable to transplant uteri from living or deceased donors, and nulliparous or parous women (with proven obstetrical functionality). Most centers prefer to collect at least ten frozen embryos from in vitro fertilization (IVF) cycles before transplantation. The serious complication of a surgically successful uterine transplantation is posttransplant partial stenosis of the uterine-vaginal anastomosis that may be a technical problem for embryo transfer, outflow of menstrual blood, and sexual satisfaction due to the narrowed and shortened vagina. This paper concludes that, currently, procurement of the uterus and the transplant procedure are surgically feasible and that none of the transplanted uteri have been lost due to rejection but only because of graft thrombosis or infection.

Conclusion. Uterine transplantation, after optimization of surgical methods, selection of suitable donors, standardization of immunosuppressive therapy, adjustment of assisted reproductive technologies and obstetrical proceedings might be an effective therapeutic method for women with AUI who wish to have their own biological child.

Key words: uterus transplantation, absolute uterine factor infertility, deceased donor, living donor

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INTRODUCTION

Uterine transplantation (UTx) is proposed as a sterility treatment method in women with absolute uterine factor infertility (AUI). AUI is an umbrella term covering infertility issues in women who lack a functional uterus because of congenital (e.g., Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS)) or acquired (e.g., hysterectomy, large fibroids, severe intrauterine synechiae) reasons. UTx represents a new level of collaboration of health professionals from different medical specialties: transplant medicine, gynecology, obstetrics, and assisted reproductive technologies (ARTs). The successful introduction of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) has enabled fertility in many women with ovarian or tubal factor infertility since the 1980s, but ARTs are designed to treat difficulties in conception and not gestation as in UTx (ref.¹). Centers specialized in ARTs were focused on IVF methods for a long time; only after 2000 was the idea of UTx revitalized, and research was initiated with animal-based studies²⁻⁵. The first human experimental clinical trial involving nine recipients with UTx from living donors (LD) started in late 2012 in Sweden in Gothenburg under the guidance of

Mats Brännström⁶. AUI remained unresolved until late 2014 when the first healthy baby boy from a transplanted uterus was born in Sweden⁷.

Women willing to undergo experimental UTx want to be mothers in social, genetic, and gestational aspects. UTx is a quality-of-life-improving vascularized composite allograft (VCA) transplantation, and removal of the transplanted uterus is performed after one or two childbirths to avoid the risks resulting from prolonged immunosuppressive therapy. Adoption and gestational surrogacy are the other available options to attain parenthood, and both have their specific pitfalls^{8,9}. Among other things, surrogacy is currently forbidden by laws or effectively prohibited by restrictive regulations in many countries, and adoption is usually a demanding and long administrative procedure with an unpredictable result. UTx also raises several ethical questions because it is still in an experimental phase and involves at least three parties – donor, recipient and future child – whose risks of harms should be considered and assessed in clinical trials. A positive attitude toward UTx, following strict criteria for the recipient, donor and health care team, was declared in 2013 by the Montreal criteria for the ethical feasibility of uterine transplantation¹⁰. Regarding the health care team, Montreal criteria

require that it must be a part of an institution that meets Moore's third criterion because it pertains to institutional stability¹¹. The ethical issues surrounding UTx are complex and related particularly to the principles of autonomy, beneficence, nonmaleficence, justice and dignity¹².

Worldwide, over 40 uterine transplantations have been performed in more than 10 centers in four continents. Unfortunately, only some have been described in detail^{6,13-19}. Altogether, 12 children were born from transplanted wombs, 11 in recipients with a uterus from LD (8 in Sweden, two in the United States and one in Italy) and one recently announced birth from a deceased donor (DD) uterus (Brazil) (ref.²⁰). Some ethical aspects of UTx have been discussed, particularly those relating to the ethical preference for living or deceased donation of the uterus, on the ethicality of UTx versus gestational surrogacy, and on the risks to the LD, recipient and born child resulting from surgeries and immunosuppressive therapy²¹⁻²⁶.

The purpose of this paper is to provide information gleaned from Czech experience with ten UTx cases (five from LD and five from DD) and the published results of other trials and case reports, on the possibilities and risks of this so far experimental but perspective method of treatment of AUI that enables delivery of a biological child to women without uteri whose only options available so far were adoption and gestational surrogacy.

Interest of potential recipients in UTx

The attitude and interest of women with AUI toward UTx, and the methods of recipients and donor selection, were described by the Czech team (more than 62% of women with MRKHS with surgically created neovaginas were interested in the uterus transplantation) and some others to date²⁷⁻³⁰. As a contribution to the discussion of this aspect, the Dallas team published recently their experience regarding the interest of 179 potential recipients and 62 donors (74% of them altruistic) in UTx and development of a five-step screening protocol³¹. Although the existing literature posits that women with MRKHS are the most eligible patients for the experimental uterus transplantations and most of the UTx procedures were performed on MRKHS women to date, there is a lack of research regarding their real interest in this experimental method of attaining motherhood. The interest of the whole group of women with AUI (1:500 women of child-bearing age) wanting to be mothers through UTx was not studied to date in detail because the method itself is still in the era of clinical trials²³. If the experimental phase will change into clinical treatment in the future, such studies should be of utmost importance because of various reasons - e.g., to plan health insurance treatment costs in countries where it exists, to guarantee a sufficient number of donors and to ensure the availability of treatment to all potential infertile patients. ARTs are expensive, but UTx should have by far a higher price, and it is ethically problematic if only those with funds and/or access to specialized clinics would be able to undergo AUI treatment through UTx in the future^{22,26}. When considering UTx, the possibility of this operation in genetically XY transgender women with a neovagina is discussed as well³².

Risk for recipients related to ART

Non-life-saving transplantations (VCA) have been ethically justified based on the quality of life improvement. The main difference between UTx and other VCA transplants is based on the major abdominal surgery and temporary nature of UTx without the need for lifetime use of immunosuppressive agents. There is a lower surgical risk but the need for permanent use of immunosuppressive therapy in the other VCAs such as the hand and face²². The uterus recipients are exposed to several risks in the pre- and posttransplant periods. Ovarian stimulation for IVF (to obtain cryopreserved embryos for the posttransplant frozen embryo transfers) might result in ovarian hyperstimulation syndrome³³. After oocyte pick-up (OPU), there is a risk of ovarian bleeding and hemoperitoneum that needs to be solved by laparoscopy¹⁹.

Risk for recipients related to transplant surgery

The first human UTx was performed by a Saudi Arabian team from non-relative LD in 2000. Hysterectomy because of graft necrosis was performed three months later¹³. Similarly, inevitable posttransplant hysterectomy, both early and late, was performed because of graft thrombosis and vascular complications in several centers, including Swedish, United States (US), and Czech trial centers^{6,15,19,34}, and because of uterine infectious complications in one Swedish (intrauterine abscess) and one Czech case (herpes simplex virus infection)^{6,19}. Surgical success (uterus more than three months in situ) was achieved in most recipients in published data from Sweden (8 out of 9) and Czech Republic (7 out of 9) to date, but further data from larger studies are needed and it is too soon to promise this relatively high surgical success rate to further recipients worldwide^{19,35}. The transplanted uterus of the Cleveland (US) group did not survive because of fungal infection of the graft¹⁵. One vesicovaginal fistula in the first ever Czech recipient had developed during transvaginal incision of the firm partial vaginal stenosis of the uterine-vaginal anastomosis¹⁹. The detailed analysis of the risks in the recipients of uterus should be performed when the uniformly reported data from all or at least from most of the UTxs will be published.

Risk for recipients related to antirejection therapy

Induction antirejection therapy is used to prevent the acute rejection in the first posttransplant month, and maintenance immunosuppressive therapy is administered later to maximize its antirejection effect and minimize the potential side effects. Because there is no blood marker today (as in kidney and liver transplants) that could reveal impaired uterine function or incipient rejection, the effect of immunosuppressants is monitored by regular biopsies from the uterine ectocervix to reveal the episodes of obviously subclinical rejection with borderline changes or mild, moderate and severe grades³⁶. When borderline changes are detected, a wait-and-see approach without the administration of antirejection treatment should be used with a control cervical biopsy performed 2-3 weeks later: borderline changes could resolve spontaneously. Mild and moderate rejection episodes are reversed with three days

of methylprednisolone intravenously, and a rare severe rejection is obviously reversed with thymoglobulin intravenously and with subsequent elevation of tacrolimus doses or the addition of azathioprine¹⁹.

As living donation in kidney and partial liver transplantations lead to better long-term graft survival rates and a decreased need for strong immunosuppressive regimens, the preference of LDs in UTx has been suggested in the era of animal Swedish studies³⁷. The Czech UTx experience, thus far, does not fully support this suggestion in humans¹⁹. The antirejection treatment in pregnancy is based on tacrolimus and on azathioprine in recipients where it was added because of the episodes of rejection during the posttransplant and pre-pregnancy periods^{7,16}. A ceased intake of mycophenolate mofetil is recommended prior to the embryo transfer attempts because of its teratogenic effect³⁸.

Potential risk for living donors

LDs of the uterus must be informed about perioperative and long-term risks of procurement surgery, including psychological consequences. The ethical dilemmas in living donation of uterus are related to the issue of subjecting a healthy woman to harm for the benefit of another, although relative, and transforming her into a patient. Determining all risks and their rates to LDs is difficult because only a limited number of procurement surgeries have been performed, but some of the described complications appeared more frequently than in total abdominal hysterectomies - e.g., the usual risk of ureteral injury during hysterectomy is 0.1-0.5%; in more invasive recovery of the uterus for UTx, it is significantly higher to date. The donor from Saudi Arabia's first UTx case developed laceration of the ureteral wall in the pelvis with intraoperative suture, and postoperative recovery was uneventful¹³. The Czech team had an experience with a similar complication, but partial laceration of the right ureter upon its crossing with common iliac vessels occurred during the dissection of the ovarian vein, and suture was performed immediately¹⁹. The second LD from the Swedish trial developed ureterovaginal fistula two weeks postoperatively, and successful reimplantation of the ureter was performed four months later⁶. These three urological complications of the graft recovery surgery in LDs together with one prolonged hypotonia of the urinary bladder with the normal voiding time achieved three months postoperatively¹⁹, were described in the literature regarding UTx to date. Although sexual dysfunction may occur in a minority of women after hysterectomy (and had not been described in donors after uterus recovery for UTx yet), this must be included in the informed consent for living donors³⁹. As a low percentage of LDs of life-saving solid organs may feel guilty or depressed when the donated organ fails, the psychological consequences of living donation of uterus should be considered as well⁴⁰. On the other hand, LDs of the uterus may feel psychological and emotional benefits from helping another person, although these subjective benefits resulting from donation of the organs such as kidney or a part of liver might be higher. The psychological risk/benefit ratio for uterus donors should be assessed

postoperatively, as well. The reduction of the risks of procurement procedure to LD depends on the surgical team with previous experience on repeated graft procurements in human multiorgan donors or in animal-based studies¹⁹.

Options of venous outflow

The dissection of the fragile and varicose uterine veins is obviously the most complex and time-consuming part of the uterus recovery in LDs because of their anatomical variations and close relation to the ureters in parametria. In a report of a first live birth after UTx in the USA, utero-ovarian veins were used solely for uterine outflow because the uterine veins were not usable¹⁶. This case provided the proof of concept of this technique of venous outflow even in pregnancy. Others have used the ovarian instead of uterine veins in their uterine transplants as well^{17,19,35}. Since the beginning, the researchers in UTx were focused on the idea of simplification of the procurement and transplant procedures to increase the availability and success rate: the use of two ovarian veins was among the first realized ideas. The utilization of ovarian veins would require the removal of one or both ovaries, depending on how many ovarian veins should be used in an individual case. In LD UTx, postmenopausal donors should be preferred to prevent harm to potential premenopausal donors due to the lack of endogenous estrogens after bilateral oophorectomy in premenopausal donors with intraoperatively detected poor quality of uterine veins and the need of both ovarian veins for good quality of graft venous outflow.

Utilization of living or deceased donors

The question of the source of the uterine graft remains relevant because both approaches have advantages and disadvantages. Because the uterus is not a vital organ, living donation of the uterus poses a lower ethical dilemma than living donation of kidney or a part of a liver⁴¹. Because the birth of a first child has occurred from a DD uterus recently, the ultimate goal of AUFI treatment was therefore achieved with both LD and DD concepts²⁰. When the numbers of UTx through deceased and living donations are completed in the future, and more children will be born from DD wombs, more precise comparison of the efficiency and safety in both concepts should be performed. The ongoing Czech trial is the first comparing the feasibility, success rate and safety of LD and DD UTx concepts¹⁹. To date, only the US group from Dallas initiated the trial with both LD and DD UTx similar to the Czech team³⁴.

Both relative and altruistic LDs of the uterus probably cannot provide a sufficient supply of uteri for the potential recipients. DDs should be a source of them as well. Therefore, it might be possible to use either of the two options in the future⁴². The main advantages of deceased donation of the uterus are the avoidance of harm to LDs associated with the recovery surgery, and anonymity of donation. DD anonymity should have a positive impact on the recipient's psychological comfort because it eliminates the long-term feeling of a debt to the LD. Moreover, procurement surgery in DD is less time-consuming, and wider uterine vessels with patches of internal iliac arteries

and veins (as well as ovarian veins) should be retrieved and used for anastomosis to the recipient's external iliacs. The main advantage to utilize LDs is pragmatic. There is a sufficient time for all necessary donor graft examination, planning of the surgeries to suit all members of the multidisciplinary team, as well as the recipient. Because UTx is ephemeral, longer viability of the graft from the LD (compared with the DD) proven in kidney transplantation should not be an important issue in UTx, which is proposed for a maximum of 5 years posttransplantation to attain motherhood, and then hysterectomy should be performed. The researchers should be wary of potential living donors (both relatives and altruistic) with a history of preterm deliveries, deliveries of newborns with intra-uterine fetal growth restriction, and repeated abortions, which might have a negative impact on reproductive success and may be kept secret by over-motivated donors.

Embryo collection, embryo transfer and reproductive success

A minimum of 10 frozen embryos from IVF cycles need to be obtained prior to inclusion into the Czech UTx trial, but the number of frozen embryos may vary according to the habits of a particular center and legal conditions of the individual countries. After the consumption of all frozen embryos for ETs without reproductive success, further IVF should be performed and OPU after hormonal stimulation could be performed transvaginally or transabdominally according to the individual anatomical disposition of each recipient. Posttransplant partial stenosis of the uterine-vaginal anastomosis could be a technical problem for frozen-thawed ET. Because this complication after UTx was published only by the Czech team in several uterine recipients with MRKHS, there is a need to describe the occurrence of this abnormal finding in all transplanted recipients because it should affect the technique of embryo transfer, outflow of menstrual blood, and sexual satisfaction due to the narrowed and shortened vagina¹⁹. Because the embryo collection through the IVF procedure, including ICSI, is performed very similarly everywhere, a single embryo is transferred in all centers, and preimplantation genetic testing of the embryo is neither mandatory nor routinely performed, and there is a lack of published information on aspects such as the timing of the ETs and use or non-use of endometrial receptivity analysis before ET. The purpose of this test is to identify the optimum day of receptivity to perform personalized ET. Further information should be provided as well: ET performed during the natural cycle or on hormonal replacement therapy (particularly in women with anovulation) and the daily dose and length of vaginally administered progesterone after ET. Each of these steps may have an impact on the reproductive success rate. It should be of utmost importance to report the average number of ETs to achieve pregnancy per uterus recipient (and to compare it to the infertile women with their own wombs) because it is difficult to predict it now. Because most of the UTx procedures have been performed in MRKHS women to date, the types of

neovaginas in the recipients have differed between the centers. Although German and Czech uterine recipients had the neovaginas created using a Vecchiotti-based surgical technique^{17,19}, the recipient's neovaginas in the USA were created through self-dilation^{15,34}, and the Swedish team had recipients with both nonsurgically (self-dilation) and surgically (skin graft) created neovaginas⁶. The comparison of the different methods of neovagina creation regarding the occurrence of posttransplant vaginal stenosis and the reproductive success rate will be of interest when the detailed data of most of the performed cases are available. Because there is a lack of existing experience, potentially different resorption of vaginally administered progesterone before and after ET in neovaginas created through different techniques should be studied as well.

Children born from UTx worldwide

The ultimate aim of UTx in the treatment of AUI is the birth of a healthy child. Pregnancy was achieved in both living and deceased donor concepts^{7,16,20,43}. Since September 2014, in total, 12 healthy children have been born after UTx at four centers prematurely or near-to-term due to different reasons (e.g., preeclampsia, cholestasis, and premature rupture of membranes) through Cesarean section. The first ever child was born after UTx in the 32nd week of pregnancy due to preeclampsia with a neonate birth-weight of 1,775 grams⁷. There is no evidence of an increased risk for children born from UTx, and, although the deliveries occurred prior to term, no intrauterine growth restriction had been recorded^{7,16}. Potential harms to the fetus may include the impact of immunosuppressive agents, risk of compromised blood flow to and from the uterus during pregnancy, and risk of preeclampsia that could impact both the fetus and future mother.

Experimental uterine transplantation trials

In total, more than 10 cases of UTx from LD and DD were performed at a few centers worldwide usually once or twice, and only some of them were described in the literature^{13-15,17}. The Swedish, USA (Dallas) and Czech centers have performed more than 30 UTxs to date^{6,19,34}. Current clinical experience has shown that some of the initial transplants are associated with surgical failure^{6,19,34}. We believe that a minimum of 10 procedures should be performed at each center to reveal the real success rate of the treatment of AUI through UTx.

Only some surgical aspects of UTx have already been published and discussed (e.g., the type of venous outflow from the uterus), but some other non-surgical aspects of the experimental treatment process have not yet been shared and discussed. Among others, there remains a lack of complete information on the occurrence of posttransplant partial vaginal stenosis in recipients, the detailed realization of IVF, ET and preimplantation genetic testing of the embryos. The unification of the steps for successful fertilization should be important for the realistic assessment of the reproductive success rate of UTx. Additionally, the UTx trials should be registered in ClinicalTrials.gov.

Creation of an international registry

Although the method of UTx is still developing, only a few dozen of transplants have been performed thus far. Given the experimental nature of UTx, an international registry of all recipients, donors and born children should be developed to monitor and share the outcomes in all involved centers worldwide. Procurement of the organ is not an easy and fast procedure, and the basic condition of success is a trained team comprising transplant surgeons and gynecologists. Because the total number of performed UTx procedures is low, sharing the experience among the research teams through the registry should be helpful for everybody. The detailed outcomes of the Czech UTx trial were published recently, as well as the outcomes of other trials^{6,15-17,19}. Sharing the nature and number of complications between the centers will help to inform others about possible pitfalls associated with different aspects of the experimental treatment process. The question remains whether to create the register retrospectively (our suggestion) or insert the data only prospectively from future transplants.

CONCLUSIONS

The aim of UTx is the delivery of a healthy child. To secure a safe childbirth, it is essential to select the most suitable recipient with a compatible donor, to maintain appropriate surgical procedures and immunosuppressive treatment, and to ensure high-quality ART and obstetrical care using the interdisciplinary cooperation of a stable team of expertise. In the future, all medical, legal, religious, ethical and financial aspects must be resolved before UTx could become a standard treatment for AUFI.

ABBREVIATIONS

ART, assisted reproductive technology; AUFI, absolute uterine factor infertility; DD, deceased donor; ET, embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LD, living donor; MRKHS, Mayer-Rokitansky-Küster-Hauser syndrome; OPU, oocyte pick up; UTx, uterus transplantation; VCA, vascularized composite allograft.

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