One uterus bridging three generations: first live birth after mother-to-daughter uterus transplantation

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Objective: To determine whether a uterus from the mother of a woman with absolute uterine factor infertility can be transplanted to daughter and carry a pregnancy with delivery of a healthy child.
Design: Part of an observational study.
Setting: University teaching hospital.
Patient(s): Twenty eight-year-old woman with uterine agenesis, her male partner, and her 50-year-old mother.
Intervention(s): In vitro fertilization with embryo cryopreservation before live donor uterus transplantation (UTx). Induction immunosuppression. Embryo transfer 12 months after UTx, pregnancy controls, delivery, and hysterectomy.
Main Outcome Measure(s): Results of IVF-ET, parameters of pregnancy/birth, and surgical data of transplantation/cesarean section/hysterectomy.
Result(s): Two IVF cycles before UTx resulted in 10 cryopreserved embryos. Donor surgery included hysterectomy with vascular pedicles of uterine vessels and proximal vessels up to and including parts of internal iliacs. Recipient surgery was by bilateral vascular connections to external iliacs, vaginal–vaginal anastomosis, and uterine fixation. Pregnancy occurred at the first single ET, and the pregnancy proceeded uneventfully until gestational week 34, when the patient developed cholestasis with intense pruritus. Cesarean section was performed at 34+6, with delivery of a healthy boy (weight 2,335 g). Hysterectomy was performed 3.5 months after delivery. The weight of the healthy child at 12 months was 9.3 kg. Grandmother (uterus donor) and mother are in good health 3 years after UTx.
Conclusion(s): This is the first report of a live birth after mother-to-daughter UTx, and it also represents the second birth ever after human UTx.
Clinical Trial Registration: NCT01844362. (Fertil Steril® 2016;106:261–6. ©2016 by American Society for Reproductive Medicine.)
Key Words: Human, infertility, pregnancy, transplantation, uterus

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More than a decade ago we initiated a translational research program with the aim to develop uterus transplantation (UTx) toward a clinical treatment for women with absolute uterine factor infertility.

We reported in 2002 the first pregnancy in a truly transplanted uterus, as demonstrated in the syngeneic mouse UTx model (1) with follow-up studies demonstrating live offspring with normal postnatal development (2), also when the uterus had been exposed to 24 hours of cold ischemia between procurement and grafting (3). Our subsequent studies included large domestic species such as the pig (4) and sheep (5), as well as experimental studies in nonhuman primates including autologous (6, 7) and allogeneic (8, 9) UTx. Thus, the initiation of the first clinical UTx trial in 2013 (10) followed the guidelines of the innovation, development, exploration, assessment, and long term follow-up (IDEAL) concept for introduction of surgical innovations (11).

Uterus transplantation can be performed either as a live (12) or a deceased donor (13) procedure. The advantages of a live donor UTx procedure, as in the present study, is that the quality of the transplanted organ is superior, because of a relatively short ischemic time and because only organs with good function are chosen. However, in all live donor situations there is the additional risk of donor surgery. This and other ethical aspects of live donor UTx were recently reviewed by us (14). To date, 11 human UTx attempts have been reported in the scientific literature, with 10 of these using the live donor concept (10, 12) and 1 with the deceased donor concept (13). There is only one live birth reported so far, and this was with a family friend, of postmenopausal age, as a live donor (15). The present study reports the second live birth after human UTx, with this also being the first birth with the uterine graft from a close relative, in this specific case the grandmother of the baby that was delivered.

MATERIALS AND METHODS

Recipient and Donor

In 2013, a patient with uterine agenesis (Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome) underwent UTx in a trial (NCT01844362) including nine women. Written informed consents from the recipient, her partner, and the donating mother were obtained, and the study was approved by the Ethics Committee, Sahlgrenska Academy, Gothenburg, Sweden. The outcomes of the total cohort after 6 and 12 months have been reported (10, 16). In short, two grafts were removed within 4 months. The causes were intrauterine infection (hysterectomy 3.5 months after UTx) and bilateral uterine vessel thrombosis (hysterectomy 3 days after UTx). Seven patients initiated ET attempts after 12–15 months, with the first birth from this cohort occurring in September 2014 (15). That uterus was from an unrelated live donor.

The 28-year-old recipient (blood group A+; body mass index 24 kg/m^2) of the present study had skin-graft neovagina surgery at age 16 years. The 50-year-old donating mother (blood group A+; body mass index 25 kg/m^2) had three normal vaginal births (at age 22 years, uterus recipient [body weight (bw) 3,650 g] in gestational week 41; at age 25 years, healthy girl [bw 3,630 g] in gestational week 40; at age 29 years, healthy girl [bw 3,385 g] in gestational week 42]. During the years before UTx, she had regular menstruations. We performed serial ultrasound examinations during the months before UTx to ascertain normal changes of the endometrial thickness and echogenicity. We did not perform any hysteroscopy or endometrial biopsy. The human leukocyte antigen mismatch was 1/0 and human leukocyte antigen antibodies were negative. Donor and recipient were both seropositive for cytomegalovirus and Epstein Barr virus.

IVF Procedure

In vitro fertilization to cryopreserve embryos was performed approximately 1 year before planned UTx by two GnRH agonist cycles. Serum level of antimüllerian hormone was 3.3 μg/L, and the antral follicle count was 13. Results of semen analysis of the male partner were normal. Serum P at her first visit indicated luteal phase, and from that day 400 μg GnRH agonist (nafarelin; Synarela, Pfizer) was administered twice daily and after down-regulation reduced to 200 μg for 14 days. Ovarian stimulation was with FSH (Puregon, MSD) 175 IU daily for 11 days. Oocyte maturation was triggered by 250 μg hCG (Ovitrelle, Merck Serono). Eight oocytes were retrieved in this first cycle and fertilized by standard IVF. After culture for 5 days, four blastocysts were vitrified.

A second IVF procedure, with identical protocol as above, was performed 8 weeks later, and this resulted in seven fertilized oocytes. Because the semen sample on this occasion was suboptimal, intracytoplasmic sperm injection was performed. Four day-2 embryos were cryopreserved, and extended culture of remaining embryos resulted in two additional day-5 embryos, which were vitrified. Thus, the patient had six blastocysts and four day-2 embryos cryopreserved before UTx.

Surgery

The general technique of live donor UTx has previously been described in detail (10). Donor surgery entailed isolation of the uterus (excluding oviducts) together with major arteries (uterine and anterior internal iliac branches) and major uterine veins plus proximal branches of utero-ovarian veins. In this specific case the uterus was removed with two large uterine veins on the right side and one major uterine vein on the left side (Fig. 1), including bilateral segments of the internal iliac veins. Thus, there were major differences in the venous outflow of this case, as compared with the initial successful UTx case (15). Donor surgery lasted for 10 hours, 17 minutes, and blood loss was 400 mL. Hospital stay for the donor was 6 days. She has had no medical or psychological complications after surgery, which took place approximately 3 years ago.

Recipient surgery started before final graft procurement and initially involved dissections of the vaginal vault and the external iliac vessels. The uterus was flushed with preservation solution (Custodiol, NordMedica), and during back-table preparation (cold ischemic time 56 minutes), the right lower uterine vein and the proximal 5 to 6 cm of the left utero-ovarian vein were anastomosed end-to-end to endings of the internal iliac segments (Fig. 1). The graft was positioned