

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.

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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/m²) 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/m²) 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.

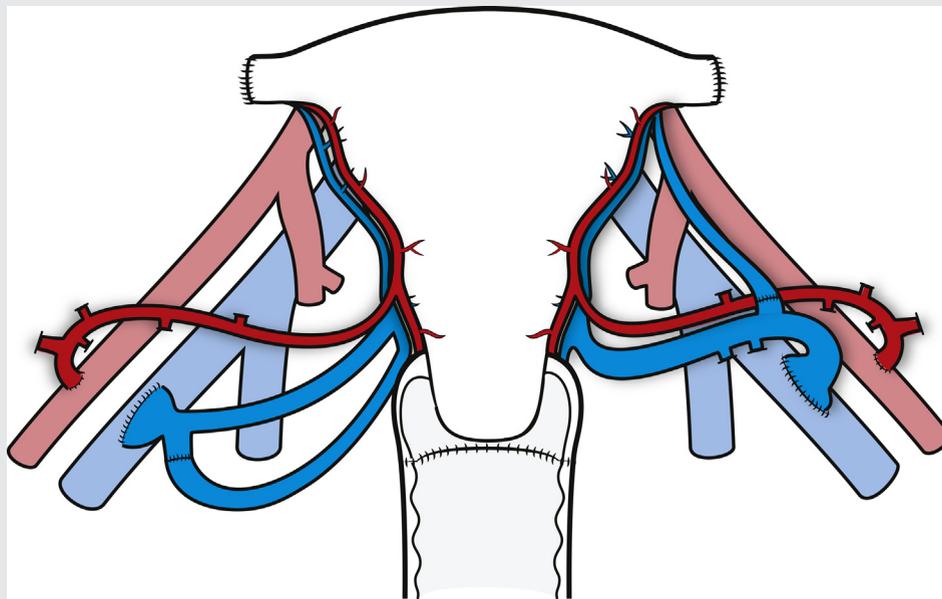
A second IVF procedure, with identical protocol as above, was performed 8 weeks later, and this resulted in seven fertilized oocytes. Because the semen sample on this occasion was suboptimal, intracytoplasmic sperm injection was performed. Four day-2 embryos were cryopreserved, and extended culture of 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

FIGURE 1



Schematic overview of the arteries (red) and veins (blue) of the graft and that of the recipient (lighter tones). Anastomosis sites are marked by suture lines.

Brännström. Mother-to-daughter uterus transplantation. *Fertil Steril* 2016.

inside the pelvis of the recipient, and four end-to-side anastomoses (total duration 74 minutes) were completed on the external iliac vessels (Fig. 1). The vagina was anastomosed end-to-end, and then the uterus was fixed to the pelvic ligaments. The measured (Doppler) blood flow of the major uterine artery was 30 mL/min. The duration of recipient surgery was 4 hour, 44 minutes, and blood loss was 300 mL. The hospital stay of the recipient was 7 days.

Immunosuppression and Follow-up of Prepregnancy

The recipient received induction therapy with IV methylprednisolone (500 mg; Solu-Medrol, Pfizer) and anti-thymocyte globulin (2.5 mg/kg bw; Thymoglobulin, Genzyme) on the day of surgery, with anti-thymocyte globulin repeated day 1 and 5 mg twice daily of oral prednisolone (Prednisolone, Pfizer) for the initial 4 postoperative days. Double maintenance therapy, from the day of surgery and for 10 months, was with oral tacrolimus (Prograf/Advagraf, Astellas) and oral mycophenolate mofetil (Cellcept, Roche). The aim was to then only treat with tacrolimus, however, because of repeated rejection episodes mycophenolate mofetil was replaced by oral azathioprine (2mg/kg/d; Imurel, Orion Pharm).

Examinations (gynecologic, ultrasonographic) with standard blood and urinary tests were performed twice weekly during the first month and then with gradually reduced frequency (14-day intervals months 2–6; monthly intervals months 6–12). To detect rejection, cervical biopsies were taken at weeks 1, 2, and 4 and then once monthly. Determination and grading of rejection was according to a uterine rejection scale, developed for the nonhuman primate (8, 9) and applied to human (16).

The median trough levels of tacrolimus were 9.1 (range, 3.7–20.0) ng/mL and 8.25 (4.8–13.0) during months 1–3 and 4–12, respectively. The patient had two asymptomatic episodes of mild rejection (weeks 3 and 12 after UTx), both detected by cervical biopsy. Both episodes were treated with IV methylprednisolone (500 mg, 3 days), followed by oral prednisolone (initially 20 mg daily) in 5-week-tapered protocols. The control biopsy, 2 weeks after the second rejection episode, still showed mild inflammation and consequently tacrolimus was increased (30%) and prednisolone maintained at 5 mg daily from the last week of the 5-week-tapered protocol. A follow-up cervical biopsy, taken some weeks after the 5-mg prednisolone period, was normal. Blood pressure was normal during the initial 12 months, and hemoglobin levels varied between 93 and 127 g/L.

Evaluation of Uterine Functionality Previously to Pregnancy Attempt

The first menstruation occurred 33 days after UTx. Menstruations were then with regular intervals but with somewhat long (median 36 days [range, 31–39 days]) intervals. Uterine artery pulsatility index (PI) was stable during the first 12 months (median of 2.07 [1.47–8.17] and 2.19 [1.54–3.42] on left and right side, respectively).

RESULTS

Embryo Transfer

One year after UTx, a single blastocyst was transferred on day LH+6 of the natural cycle, according to Swedish routines, with approximately 70% of frozen embryo transfers

performed in the natural cycle. Supplementary luteal-phase support was given by daily IM P (25 mg) for 2 weeks. A pregnancy test was positive 20 days after single blastocyst transfer and ultrasound 4 weeks later showed fetal heartbeat.

Pregnancy

The recipient continued with triple immunosuppression therapy (tacrolimus, azathioprine, and prednisolone) during pregnancy, with tacrolimus trough levels of 6.1 (range 2.3–9.2) ng/mL during pregnancy. Creatinine increased around gestational week 16, from a median of 94 $\mu\text{mol/L}$ (range, 89–110 $\mu\text{mol/L}$) during the initial pregnancy period to 137 $\mu\text{mol/L}$ (127–151 $\mu\text{mol/L}$) from gestational week 18 and onward during pregnancy. Ultrasound (gestational week 23) showed moderate bilateral hydronephrosis. The patient did not have any symptoms related to hydronephrosis, and the ultrasound examination over the kidneys was performed because of the creatinine rise.

Hemoglobin declined to 79 g/L in gestational week 18, from a median of 101 g/L (100–112 g/L) during the months before. Initial oral ferrous sulfate treatment caused major gastrointestinal side effects and instead 2 single doses (500 mg) of IV ferric carboxymaltose (Ferinject, Orifarm) was given, and treatment with darbepoetinalfa (60 μg weekly SC; Aranesp, Amgen) was initiated. Hemoglobin levels were subsequently around 95 g/L (median). Blood pressure and glucose levels were normal, and proteinuria was not detected.

Fetal growth parameters and umbilical artery PI were normal (Fig. 2). The PIs of the uterine arteries were low to normal (Fig. 2).

The pregnancy proceeded normally (weight gain 7 kg, cervix 37–51 mm) until gestational week 33, when intense pruritus developed. Elevated serum levels of bile acid indicated intrahepatic cholestasis. An elective cesarean section had been planned to gestational week 35+0, but this was now brought forward to 34+4, to relieve the patient from her pruritus.

At cesarean section, through a midline incision, a cephalically positioned male baby was delivered 29 minutes after skin incision. The long time from skin incision to delivery was due to a necessary dissection and visualization of the uterine arteries that curled up on the frontal-lateral aspect of the lower uterine segment. This was done to avoid injury to the arteries at the uterine incision. The total surgical duration was 2 hours, 5 minutes. Perioperative bleeding was 900 mL. Apgar scores were 9–10–10. Umbilical artery pH was 7.37. The histologically normal placenta was of normal weight (495 g). The birth weight (2,335 g) was within the normal range (–7%) for gestational age. The length and head circumferences were 44 cm and 33 cm, respectively.

Postpartum Period and Hysterectomy

The baby showed signs of mild respiratory distress, which was treated for 2 days with continuous positive airway pressure ventilation with surfactant (Curosurf, Chiesi Farmaceutici). Owing to postoperative maternal hemoglobin of 78 g/L, 2

units of erythrocyte concentrate were given the day after delivery. Levels of bile acids normalized within 5 days. The tacrolimus dose was lowered by 45% on the day after delivery. The mother and child were discharged from hospital after 8 days. Breastfeeding was initiated after 2 weeks and continued for 3 months. The baby developed fully normally, with weights (kg) of 4.0, 6.2, 7.4, and 9.3 at ages 2, 4, 6, and 12 months, respectively.

Azathioprine and prednisolone medication intake was terminated 2.5 months after delivery, when the patient made her final decision that she did not want to keep her uterus for attempts to achieve a second pregnancy. We recommend delaying such a decision for 1 to 2 months after delivery, to ascertain that the baby was in good health and to allow for the uterus to reverse to the nonpregnant size and thereby simplify the hysterectomy procedure. Hysterectomy, by a midline incision, was performed 3.5 months after delivery. There were few adhesions around the uterine fundus, but extensive paracervical adhesions were present. Double-J ureteric stents were applied to aid in the dissection. The anastomosis sites were fully patent, and Doppler-estimated blood flow of uterine arteries was 50 and 35 mL/min on the left and right side, respectively. Surgical duration was 4 hours, 35 minutes, with a blood loss of 600 mL. The patient was discharged on postoperative day 4. Tacrolimus medication was stopped the day before surgery, and oral prednisolone was lowered from 5 mg to 2.5 mg daily and kept for 2 weeks. One month after hysterectomy, the patient developed signs of infected vaginal vault hematoma, which was treated by transvaginal drainage and oral antibiotics, after which complete recovery was established. The patient was in good health 12 months after childbirth.

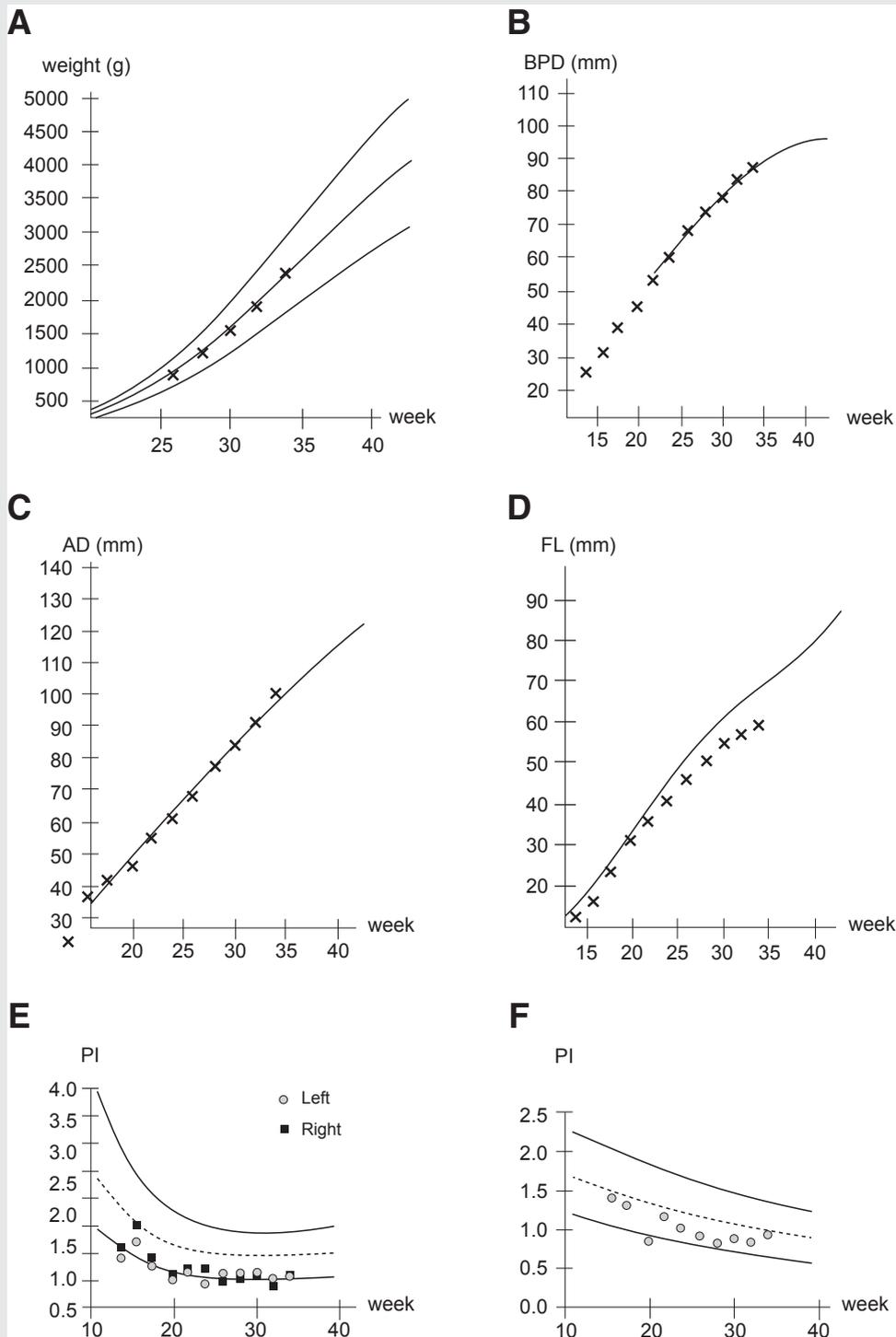
DISCUSSION

We report the second live birth after UTx, which is the first with the uterus donated from a close relative, in this case the grandmother of the baby. Thus, this three-generation-bridging uterus has harbored both the pregnancy of the newborn baby but also its mother.

The surgery of this specific case was uneventful, both for the donor and the recipient, despite surgical durations of approximately 10 and 5 hours, respectively. It is recognized that the operating time in the donor was long, but the duration of the complex donor surgery is likely to be substantially shortened in the future by surgical training, as in all novel surgical procedures, including live donor kidney and live donor liver transplantation.

The duration of recipient surgery of approximately 5 hours is acceptable. We do not presently foresee the need for any major modification of this procedure. Each specific case will, however, be treated differently concerning the venous outflow, because large inter-individual variation exists. Thus, this second successful UTx case had a somewhat different venous outflow compared with the primary live birth case (15). In the present case, we also included full segments of the internal iliac veins to facilitate venous drainage. In the first, albeit unsuccessful, human case performed in year 2000 (12), saphenous extensions of 6–8 cm were anastomosed

FIGURE 2



Estimates by (A–D) ultrasound of fetal growth and (E, F) blood flow during pregnancy. (A) Weight; (B) biparietal diameter (BPD); (C) abdominal diameter (AD); (D) femur length (FL); (E) pulsatility index (PI) of uterine arteries; and (F) PI of umbilical artery.

Brännström. Mother-to-daughter uterus transplantation. *Fertil Steril* 2016.

end-to-end to short ends of the uterine arteries and veins to enable bilateral end-to-side anastomosis to the external iliacs. They also used up to three uterine veins on each side

for anastomosis. Our approach was to dissect the largest uterine vein all the way down to the internal iliac vein to be able to perform direct anastomosis on the external iliacs of this

large internal iliac vein that also has a reasonably thick vessel wall, which would facilitate anastomosis surgery.

The source of a uterus in UTx can be either a living or a deceased donor, the latter also referred to as a brain-dead, heart-beating donor. In our series of nine UTx procedures we used live uterus donor, and a majority of the donors were mothers, as in the present report. We think that a mother is a natural first choice as a uterus donor. She is past her fertile period, shares at least half of the histocompatibility antigens with the recipient, and has proven functionality of the uterus, by giving birth to the recipient. In the present case, the mother had three term vaginal deliveries and no miscarriages or obstetric complications. Thus, although the uterus was within some few years of predicted menopause state, the functionality was likely to be good. The world's second UTx attempt, performed in 2011, used a uterus from a nulliparous deceased donor (13). Despite multiple attempts of IVF with fresh and frozen embryo transfers, only two very early miscarriages were reported (17). The cause of this pregnancy failure is unknown, but it should be noted that the uterus was from a young woman who had never been pregnant, and it had never demonstrated its functionality in terms of pregnancy capacity. We suggest that only uteri that have carried at least one normal pregnancy to term and with no history of pre/post-term birth, repeated miscarriage, or pre-eclampsia should be transplanted. In the present case there had not been any fertility problems, and the uterus had been through three normal deliveries.

Importantly, the pregnancy was fully normally in terms of fetal growth and umbilical blood flow. Noteworthy is that pre-eclampsia, which occurred in the pregnancy of the first UTx-baby (15), where the mother had unilateral renal agenesis, did not develop in this MRKH patient with double kidneys. Although immunosuppression, IVF, and pregnancy in an aged uterus may all predispose to pre-eclampsia, we postulate that a single kidney in MRKH patients is an additional risk factor for pre-eclampsia after UTx (18).

The patient of the present study achieved pregnancy at her first ET, using elective single blastocyst transfer to minimize the risk of a multiple pregnancy. Blastocyst transfer, as compared with transfer of a cleavage-stage embryo, may also contribute to a higher probability of success (19).

The patient desired uterine removal 3 months after childbirth. This hysterectomy was, because of extensive adhesions, complicated and with a surgical duration similar to transplantation. The measured uterine artery blood flow at hysterectomy (50 and 35 mL/min on each side) was in the similar range as the blood flow (30 mL/min) at transplantation (10). It is important to note that UTx does not only involve the primary surgery but always this subsequent hysterectomy and in the successful cases also cesarean section. Although a hysterectomy is associated with a surgical risk, the graft removal enables discontinuation of immunosuppression, hence long-term side effects of these drugs can be avoided.

In conclusion, we report the first live birth from a mother-to-daughter UTx, which also represents the second successful

human UTx. The repeated success of UTx shows that this is a feasible future treatment for women with absolute uterine factor infertility.

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