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First live birth after uterus transplantation in the Middle East

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Abstract

Background: The first live birth after uterus transplantation took place in Sweden in 2014. It was the first ever cure for absolute uterine factor infertility. We report the surgery, assisted reproduction, and pregnancy behind the first live birth after uterus transplantation in the Middle East, North Africa, and Turkey (MENAT) region.
A 24-year old woman with congenital absence of the uterus underwent transplantation of the uterus donated by her 50-year-old multiparous mother. In vitro fertilization was performed to cryopreserve embryos. Both graft retrieval and transplantation were performed by laparotomy. Donor surgery included isolation of the uterus, together with major uterine arteries and veins on segments of the internal iliac vessels bilaterally, the round ligaments, and the sacrouterine ligaments, as well as with bladder peritoneum. Recipient surgery included preparation of the vaginal vault, end-to-side anastomosis to the external iliac arteries and veins on each side, and then fixation of the uterus.

Results: One in vitro fertilization cycle prior to transplantation resulted in 11 cryopreserved embryos. Surgical time of the donor was 608 min, and blood loss was 900 mL. Cold ischemia time was 85 min. Recipient surgical time was 363 min, and blood loss was 700 mL. Anastomosis time was 105 min. Hospital stay was 7 days for both patients. Ten months after the transplantation, one previously cryopreserved blastocyst was transferred which resulted in viable pregnancy, which proceeded normally (except for one episode of minor vaginal bleeding in the 1st trimester) until cesarean section at 35 + 1 weeks due to premature contractions and shortened cervix. A healthy girl (Apgar 9-10-10) weighing 2620 g was born in January 2020, and her development has been normal during the first 6 months.

Conclusions: This is the first report of a healthy live birth after uterus transplantation in the MENAT region. We hope that this will motivate further progress and additional clinical trials in this area in the Middle East Region, where the first uterus transplantation attempt ever, however unsuccessful, was performed already three decades ago.

Keywords: Human, Infertility, Transplantation, Uterus, Middle East

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Background

Research on uterus transplantation (UTx) dates back to the 1960s and was mostly conducted in dogs. The goal was to establish an animal model of en bloc utero-tubal-ovarian transplantation to further allow the treatment of tubal factor infertility [1]. Due to the lack of effective immunosuppression, and later success of IVF, these projects were abandoned, since IVF became a highly successful treatment option for women with tubal factor infertility [2, 3]. However the group of women with absolute uterine factor infertility (AUFI), due to congenital/surgical absence of a uterus or presence of a non-functional uterus, remained without any treatment options [4].

The Swedish team at the Sahlgrenska Academy, University of Gothenburg, was established in 1998 and during more than 10 years preclinical research on several animal models, including syngeneic UTx in mice, allogeneic UTx in rats, autologous UTx in sheeps, and allogeneic UTx in non-human primates, was conducted [5–12]. Later on, the Swedish team started the first clinical trial on UTx and that was a living donor trial initiated in 2012 [13]. It resulted in the first ever live birth after UTx in 2014 [14]. Thereafter, a restricted number of live births have been reported both after live donor and deceased donor UTx trials, albeit with no successful UTx procedure reported from the Middle East region [15–17]. Since then, a second Swedish trial, including robotically assisted donor surgery has been performed with births achieved [18, 19].

The first two UTx attempts took place in the Middle East, North Africa, and Turkey (MENAT) region. In 2000, a group of Saudi doctors attempted an unrelated living donor UTx, but 99 days after the surgery, hysterectomy was required due to thrombosis in uterine blood vessels [20]. In 2011, a Turkish team performed the second UTx attempt in the MENAT region by a deceased donor UTx procedure. Early miscarriages were initially reported, but no live birth (end-point and definition of success of UTx) has been reported so far [21].

We present the first live birth after UTx in the MENA T region, which was a result of Swedish-Lebanese-Jordanian cooperation.

Methods

Recipient and donor

The 24-year-old recipient (blood group AB+; BMI 26 kg/m^2) had uterine agenesis as part of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. She had bilateral kidneys at typical positions corresponding with MRKH syndrome type 1. Initially, she attempted vaginal lengthening by intercourse obtaining 4 cm vaginal length and then used dilator for 4 months before surgery, obtaining 8-cm long vagina. The recipient was not on any medication. She smokes water-pipe sporadically.

The 50-year-old donating mother (blood group A+; BMI 32 kg/m^2) had six normal pregnancies and vaginal births. Her last menstruation was 4 months before donor hysterectomy. She had no history of miscarriage or extra-uterine pregnancy. She smoked water-pipe sporadically and was not on any medications.

Pre-operative investigations on donor and recipient

Both recipient and donor underwent extensive medical and psychological investigations including imaging, serology, clinical chemistry, HLA typing, and crossmatching as well as psychological evaluation as described previously [14]. Gynecological examination included evaluation of the vagina and cervix (donor) and sampling for chlamydia, gonorrhea, and high-risk human papilloma virus (HPV). Transvaginal ultrasound (TVU) was performed in both recipient and donor. The vascularity of the uterus was studied by a combination of contrast-enhanced MRI and conventional digital subtraction angiography with selective contrast into internal iliac arteries, through a femoral artery catheter.

The recipient underwent MRI of the pelvis and abdomen, with a special focus on vascular anatomy and kidney/ureter positions.

In vitro fertilization

One in vitro fertilization (IVF) cycle to cryopreserve embryos was performed 4 months prior to UTx. The male partner (aged 30) had a normal semen sample. Ovarian stimulation started 5 days after the last combined oral contraceptive pill (COCP) by daily administration of 300 IU of recombinant follicle-stimulating hormone (FSH) s.c. and cetrorelix acetate 0.25 mg s.c. from day 6 of stimulation (fixed antagonist protocol). Ovulation was triggered with gonadotropin-releasing hormone (GnRH) agonist triptorelin 0.2 mg s.c. and urinary human chorionic gonadotropin (hCG) 1500 IU. Cryopreservation was by vitrification.

Surgery—donor

The surgical procedures of donor, recipient, and anesthesia have previously been described in details [13].

Donor surgery entailed isolation of the uterus (excluding oviducts) together with major arteries (uterine and anterior internal iliac branches) and major uterine veins bilaterally and efficaciously without complications. The ovarian vein was obliterated on the left side with atrophic ovary. The graft included parts of the internal iliac veins and arteries as previously described. Substantial parts of the round ligaments and the sacrouterine ligaments, as well as an extensive sheet of the bladder peritoneum, were preserved on the graft side to enable stable fixation of the uterus in the recipient. The major feeding arteries and veins were then clamped and severed,

before the uterus was removed from the pelvis to a back-table setting. Clamping points of the donor's internal iliac vessels were closed with continuous polypropylene (6-0) sutures, and the abdomen was closed in standard three-layered manner.

The uterus was immediately brought to the back-table and initially flushed with 10 mL heparinized saline solution through each artery, followed by flushing for about 20 min with cold preservation solution (Custodiol HTK-solution; Nordmedica), until the organ was blanched and the venous effluent was clear. The graft was kept on ice until transplanted into the recipient.

Surgery—recipient

Recipient surgery started just before the final graft procurement. The abdomen was opened with midline incision, and surgery initially involved dissections of the vaginal vault, ligaments, and the external iliac vessels. The uterine rudiment had to be cleaved to reach the top of the vagina. Sutures (1-0 polypropylene) for subsequent organ fixation were attached to the round ligaments, the sacrouterine ligaments, and the two lateralized parts of the uterine rudiment. The surgery was then directed toward preparation of the external iliac vessels for subsequent anastomosis. The external iliac artery and vein were bilaterally separated from each other and from adjacent tissue. The graft was then positioned inside the pelvis of the recipient. The four vessels including two uterine arteries and two veins were end-to-side anastomosed to the external iliac vessels (one uterine artery and one uterine vein on each side). After completion of the vascular anastomosis, the graft was reperfused. Thereafter, the vagina was anastomosed end-to-end with a continuous absorbable 2-0 suture, and then, the uterus was fixed to the pelvic ligaments bilaterally.

Immunosuppression

The immunosuppression protocol consisted of induction by one dose of 4 mg tacrolimus, 125 mg of azathioprine, 100 mg i.v thymoglobuline, and 500 mg i.v. methylprednisolone. Thymoglobuline was given daily for a total of 5 days: 100 mg daily for 4 days and 75 mg on day 5. Methylprednisolone 500 mg i.v. was given perioperatively, and prednisolone p.o. was given on days 0 to 6 in tapered doses of 80 to 5 mg. Maintenance immunosuppression was by twice daily administration of tacrolimus. Oral azathioprine 2 mg/kg daily was added from day 0 to maintain adequate immunosuppression. Three doses of mycamine 100 mg i.v. were given as antifungal prophylaxis, valganciclovir 450 mg p.o. daily for 6 months was used as CMV prophylaxis, and trimethoprim/sulfamethoxazole as a prevention of pneumocystis pneumonia was given for 3 months.

Post-operative follow-up

Gynecological examinations were performed once a week during the first month and then with gradually reduced frequency. Vaginal cultures and cervical biopsies were taken at routine gynecological examinations and histopathological examination, and grading was according to our published report [22].

Results

Results of preoperative investigations and IVF

The human leukocyte antigen (HLA) mismatch was 1/0, and insignificant anti-HLA antibodies existed but no donor-specific antibodies were detected. Donor and recipient were both seropositive for cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

Examination of donor uterus by TVU showed a normal-sized uterus with a 20 mm subserosal fibroid. The MRI of the donor uterus showed a 7 x 7-mm polyp in the bladder, and she underwent cystoscopy with excision of the polyp. The microscopic examination showed benign inflammatory pseudotumor.

Selective angiography of the uterine arteries showed visible and contrast-enhanced uterine arteries on both sides with a diameter of the lumen of the right and left uterine artery of 2.9–4.4 mm and 3.5–3.9 mm, respectively. Preoperative MRI imaging of the recipient showed a uterine rudiment measuring about 15 x 30 mm; normal ovaries bilaterally, sized 20 × 30 mm; and normal kidneys with normal size, shape, and positions.

Recipient serum level of anti-müllerian hormone (AMH) was 4.2 μg/L. The partner's semen sample was normal (semen volume was 4 ml, total sperm count in ejaculate was 160 million/ejaculate, sperm concentration was 40 million/ml, total motility was 60%, progressive motility was 40%, non-progressive motility was 20%, and non-motile was 20%). Thirteen oocytes were collected in a single stimulation cycle, 11 were mature (M2), and eight grew to blastocyst stage and were cryopreserved.

Surgery—donor

Donor surgery lasted for 608 min, and estimated blood loss (EBL) was 900 ml. Recovery was complicated by lung atelectasis and increased level of c-reactive protein (CRP) 62 mg/L without fever. It was successfully treated with piperacillin/tazobactam i.v. for 6 days. Length of hospital stay for the donor was 7 days. Anti-thrombotic prophylaxis with low molecular weight heparin (LMWH) Lovenox 4000 IU was initiated on preoperative day 1 and continued for 4 weeks after the surgery. After discharge from the hospital, she was healthy and did not present with any symptoms.

One month after the surgery, she underwent a duplex Doppler ultrasound scan of both lower limb veins with no evidence of any deep vein thrombosis and competent

sapheno-femoral junctions on both sides. The urinary tract ultrasound showed a normal urinary tract with normal-sized kidneys on both sides.

Surgery—recipient

Total ischemic time on the back-table was 85 min. Surgical time of the recipient was 363 min (including the anastomosis time 105 min), and EBL was 700 ml. The blood flow of the uterine arteries on both sides was measured before the abdomen was closed. The perioperatively measured (Doppler) blood flow of the uterine artery was 45 ml/min and 46 ml/min on the right and left uterine artery, respectively. The hospital stay was 7 days. No episode of inflammation or rejection has been diagnosed until today. Anti-thrombotic prophylaxis with low molecular weight heparin (LMWH) Lovenox 4000 IU was initiated on preoperative day 1 and continued for 4 weeks after the surgery. She was also treated with 81 mg acetyl salicylic acid (ASA) daily. Two and 4 weeks after UTx, the vaginal culture and urine culture were positive with *Enterococcus faecalis* and *Enterobacter* plus *Klebsiella* pneumoniae, respectively. She was treated with oral antibiotics (levofloxacin 500 mg once a day for 5 days and amoxicillin and clavulanate 1 g twice a day for 7 days) both times with good results. Repeated cultures were normal thereafter.

The first menstrual bleeding occurred 3 weeks after UTx, and menstruations were then regular every 28 to 30 days. The patient developed stenosis over the vaginal-vaginal anastomosis, which tightened gradually after surgery and required manual dilations under sedation three times. Due to persistent anemia, the patient was given erythropoietin 2 times a week 4000 IU s.c. and oral ferrous sulfate with vitamin B12 3 months before embryo transfer due to hemoglobin levels decreasing from 130 g/L before UTx to 95 g/L post UTx and further down to median 77 (77–88) g/L before the treatment. Afterwards, the hemoglobin increased to median level of 95 (88–100) g/L, remained stable during the pregnancy, and declined to 88 g/L at delivery.

Embryo transfer

Ten months after UTx, embryo transfer was performed. A single dose of triptorelin 3 mg was given 7 days before a predicted menstruation. Endometrial thickness of 8.5 mm with triple layers was achieved with a daily administration of estradiol hemihydrate 4 mg per day for 10 days. Embryo transfer was carried out after progesterone supplementation (progesterone in oil 25 mg daily, i.m., and vaginal micronized progesterone 100 mg twice daily) for 6 days. One blastocyst was transferred under abdominal ultrasound guidance. It resulted in a pregnancy confirmed with a positive pregnancy test 14 days after blastocyst transfer. Four weeks later, a viable pregnancy with fetal heartbeat was

Pregnancy

Immunosuppression therapy remained unchanged and consisted of tacrolimus and azathioprine as described above. The concentrations (median (range)) of tacrolimus during pregnancy were 5.5 (3.4–7.9) ng/mL. During the first trimester, anticoagulation prophylaxis consisted of low molecular weight heparin (LMWH) Lovenox 4000 IU once a day and acetyl salicylic acid 81 mg daily which was increased to 160 mg daily from week 12. Progesterone supplementation, both intramuscular injections of progesterone in oil and vaginal micronized progesterone, was gradually tapered by the end of the first trimester. Estradiol 2 mg p.o. once a day was also given during the first trimester. Creatinine levels (median (range)) were normal, with 54.5 (44.2–62.1 μmol/L during the whole pregnancy. Hemoglobin levels (median (range)) were normal to low, with 95 g/L (88–100 g/L) and decreased to 88 g/L at delivery. Hemoglobin increased gradually to 116 (114–118 g/L) after delivery. There were no signs of preeclampsia with normal blood pressure and no significant proteinuria for the duration of pregnancy.

The fetal growth of biparietal diameter, abdominal diameter, femur length, and estimated weight were within the normal range throughout pregnancy as shown in Fig. 1. The pulsatility index (PI) of the umbilical artery and uterine arteries was low to normal, with median PIs of 1.06 (0.7–1.85) and 0.71 (0.7–0.72), of umbilical artery and uterine arteries, respectively.

Cervical length measured on TVU was stable throughout pregnancy with a median length of 30 mm. Cervical biopsies were taken at 16 and 28 weeks. Histology showed no signs of rejection. The patient had minor vaginal bleeding during the 9th week of pregnancy, which led to temporary discontinuation of ASA for 6 days.

The total weight gain was 15 kg. Patient reported perception of fetal movements. Cesarean section was performed at 35 weeks and 1 day due to premature contractions registered on cardiotocography (CTG), and with shortened cervix to 15 mm and dilated at 15 mm. The cesarean section was performed under spinal anesthesia through a midline incision in the abdominal wall and midline incision into the uterus due to big veins in the lower transverse area. The cephalically positioned female fetus was delivered 15 min after skin incision. Apgar score was 9-10-10. Umbilical artery pH was within normal range. Placenta was normal on visual inspection, weighted 472 g and of normal histology. The baby's weight was 2620 g (within the normal range for the gestational age), and she was 47 cm long (Fig. 2). The total surgery time was 45 min.

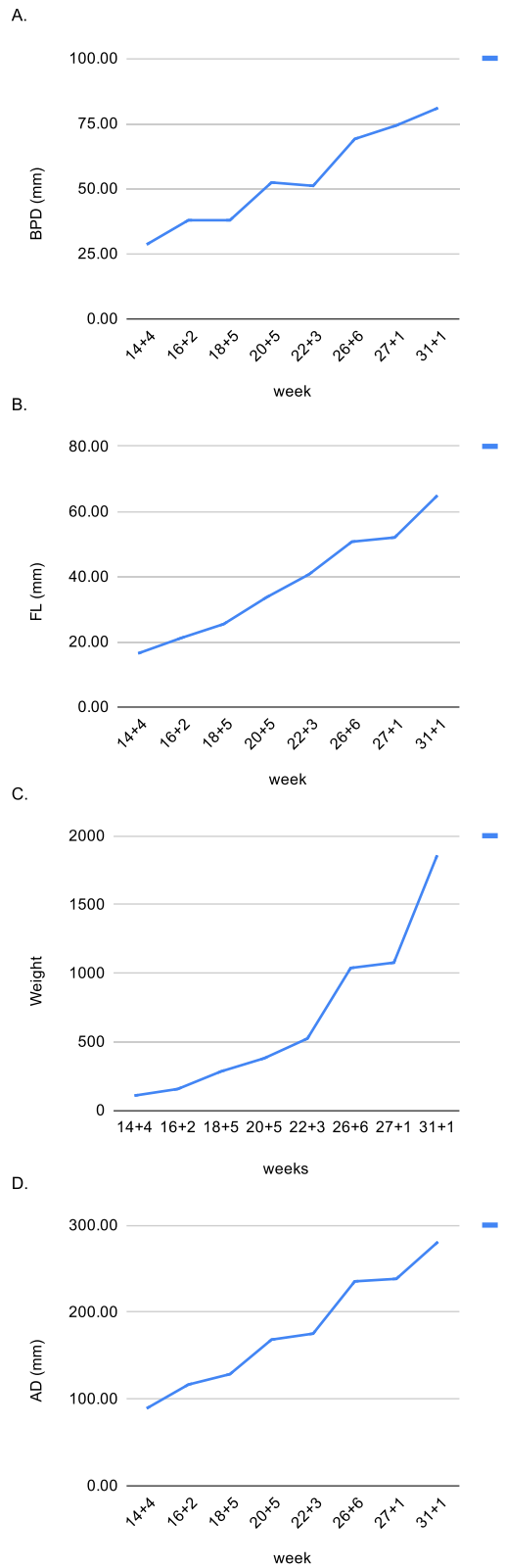

Fig. 1 Estimates by ultrasound of fetal growth. **a** Biparietal diameter (BPD). **b** Femur length (FL). **c** Fetal weight. **d** Abdominal diameter (AD)

No neonatal intensive care was required. The mother and child were discharged from the hospital after 4 days, and breastfeeding was established and continued for 1 month until the patient decided to wean. The baby developed bronchiolitis at the age of 3 weeks and was hospitalized in a neonatal intensive care unit for 2 weeks. Treatment was with i.v. antibiotics and chest physiotherapy. Later development was normal during the 6 months observation, and the weight at 6 months was 7150 g.

Currently, the patient remains on unchanged immunosuppression regime and will undergo another embryo transfer in the upcoming months.

Discussion

Involuntary childlessness due to infertility remains a serious problem globally. Infertility stigma has been well-described in various populations, with ethnic origin and religious affiliation being the most strongly associated factors [23, 24]. While infertility in general causes high levels of stress [25], many women with MRKH syndrome have phobic anxiety and psychoticism (interpersonal alienation), as well as depression and anxiety more often than age-matched controls [26]. It has been demonstrated that UTx has a positive impact on patients' perception of being "a complete woman" [27].

It is important to note that the world's first two uterus transplantations took place in the MENAT region. In 2000, a Saudi team performed unrelated living donor UTx on a previously hysterectomized woman, but 99 days post-op hysterectomy was required due to necrosis [20]. In 2011, the Turkish team attempted the first deceased donor UTx from a young nulliparous woman into a MRKH syndrome patient. Although with long-term graft survival and several early pregnancy losses, no live birth has been reported [28]. We speculate that both of those unsuccessful cases failed due to the lack of proper, structured preclinical and cadaver research. Another important factor which differentiates our success is the so-called "surgical learning curve". It is well described in transplantation of other organs that surgeon's experience defined as caseload plays an important role [29].

In the described case, we have followed the initial Swedish UTx protocol and further confirmed it is an efficient treatment for AUFI, with a live birth being the primary endpoint of UTx. Successful use of a multiparous (G6P6) donor further confirms that women with a history of several pregnancies and births can be suitable uterine donors, although the donated uterus contained a small subserosal myoma which did not affect the surgery nor pregnancy. Perioperative outcomes were comparable with our previous experience [13], donor surgery time was slightly shorter than median in the first Gothenburg trial (608 min vs. 697 min), while recipient surgery took significantly longer, 368 min and 248 min, respectively.

Fig. 2 The newborn baby after birth on January 13, 2020

EBL was nearly identical (900 mL in our donor and median in the trial group, the recipient 700 mL vs 600 mL, respectively). Stenosis on the level of vagina-vagina anastomosis has also been described in other patients, and we believe it might be an effect of electrosurgical bipolar vessel sealing (LigaSure) during organ procurement. Repeated manual dilation was successful. Our patient achieved pregnancy at her first ET, 10 months after UTx, which is a longer waiting period after UTx than in more recently published cases in the USA and Brazil [16, 30]. Our reason to wait for 10 months was to achieve stable levels of immunosuppression and to not initiate ET during the first 10 months after UTx due to a high risk of rejection [22]. ATG was given for 5 days as a precaution due to a low level of anti-HLA antibodies. We suspect that administration of immunosuppressive medications may have been the causative factor of persistent anemia after the surgery which was treated with erythropoietin, iron, and B vitamins. So far (26 months post UTx), no episode of rejection has been diagnosed. Late prematurity (delivery at 35 + 1) is similar with other post-UTx births, while some were delivered as early as 31 weeks due to obstetric complications or by weighting risks and benefits of continuing pregnancy to term [30, 31]. Birth weight of 2620 g was normal for gestational age which is consistent with previous reports [13, 32]. The patient plans to have another baby, so hysterectomy is planned at or after the next delivery.

This success is another confirmation that UTx is a safe and effective treatment for AUFI although still at an exploratory phase, with activities worldwide conducted within scientific trials. In the future, when implemented into standard clinical practice, the procedure should be performed by a multidisciplinary team, including highly experienced gyne-oncology surgeons and transplant surgeons. Further research on cost-effectiveness and safety of different surgical methods including both living and deceased donor UTx trials is needed. Although international cooperation brings unique challenges to patient's management, we proved that a highly experienced surgical team can perform UTx while the local multidisciplinary team can take over the post-transplant care and fertility treatments. This is an especially valuable approach for patients from low- and middle-income countries (LMIC) and disadvantaged populations even in the Western countries when UTx becomes available outside clinical trials.

Conclusions

We present the first live birth after UTx in the Middle Eastern region. Uncomplicated surgery on the donor and the recipient, normal post-operative recovery, absence of rejection, and normal course of pregnancy after the first embryo transfer further confirm that UTx is a safe and successful treatment option for women with absolute uterine factor infertility. This paper outlines a potential first step to spread the UTx to several middle-income countries and to allow thousands of infertile women to bear a child and avoid societal stigmatization of being childless.

Abbreviations

AMH: Anti-müllerian hormone; ASA: Acetyl salicylic acid; AUFI: Absolute uterine factor infertility; BMI: Body mass index; CMV: Cytomegalovirus; CTG: Cardiotocography; EBL: Estimated blood loss; EBV: Epstein-Barr virus; FSH: Follicle-stimulating hormone; GnRh: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; HLA: Human leukocyte antigen; HPV: Human papilloma virus; i.v.: Intravenous; IVF: In vitro fertilization; LMIC: Low- and middle-income country; LMWH: Low molecular weight heparin; MENAT: Middle East, North Africa, and Turkey; MRI: Magnetic resonance imaging; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; PI: Pulsatility index; p.o.: Per os; s.c.: Subcutaneous; TVU: Trans-vaginal ultrasound; UTx: Uterus transplantation

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Authors' contributions
RA, NK, PDK, and MB conceptualized and designed the study. All authors provided patient care, data collection, and approved the final manuscript. RA, CB, LMC, MEK, NK, PDK, and MB performed data analysis and interpretation. RA wrote the draft manuscript.

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Ethics approval and consent to participate
The study (uterus transplantation LD—feasibility study—Sahlgrenska—BMC (GOT-BMC-UTx)) was approved by the Regional Ethics Committee, Bellevue Medical Center, Lebanon, Beirut, and registered as a clinical trial NCT03590405 on July 18, 2018 (https://clinicaltrials.gov/ct2/show/NCT03590405). Written informed consents for trial participation and publication of the results were obtained from the recipient, her partner, and the donating mother.

Consent for publication
Written informed consents for the trial participation and publication of the results were obtained from the recipient, her partner, and the donating mother.

Competing interests
The authors have nothing to disclose.

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