Clinical pregnancy after uterus transplantation

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Objective: To present the first clinical pregnancy after uterus transplantation.
Design: Case study.
Setting: Tertiary center.
Patient(s): A 23-year-old Mayer-Rokitansky-Kuster-Hauser syndrome patient with previous vaginal reconstruction and uterus transplantation.
Intervention(s): Eighteen months after the transplant, the endometrium was prepared for transfer of the thawed embryos.
Main Outcome Measure(s): Implantation of embryo in an allografted human uterus.
Result(s): The first ET cycle with one day 3 thawed embryo resulted in a biochemical pregnancy. The second ET cycle resulted in a clinical pregnancy confirmed with transvaginal ultrasound visualization of an intrauterine gestational sac with decidualization.
Conclusion(s): We have presented the first clinical pregnancy in a patient with absolute uterine infertility after uterus allotransplantation. Although the real success is the delivery of a healthy near-term baby, this clinical pregnancy is a great step forward and a proof of concept that the implantation phase works. (Fertil Steril® 2013;100:1358–63. ©2013 by American Society for Reproductive Medicine.)
Key Words: Uterus transplantation, clinical pregnancy, uterine factor infertility

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Absolute uterine factor infertility (UFI) is one of the devastating causes of infertility (1). Currently, gestational surrogacy is the sole option for having a genetic offspring in these patients (2). Despite the progress in assisted reproductive technologies in the last decades, no current approach has been able to treat the problem of UFI. UFI may result from congenital (complete Müllerian agenesis, uterine hypoplasia) or acquired causes such as hysterectomy due to malignant and benign reasons (myoma, adenomyosis, postpartum hemorrhage) or due to intrauterine adhesions, which affect approximately 3%–5% of the general population (1, 3–8). Uterus transplantation research has been carried out in different animal models including nonhuman primates to define the optimum surgical technique and clarify the immunological and technical aspects (8–13). As a result of the tremendous work of these researchers, pregnancy after allo- and auto- uterus transplantation has been documented in some animal species including nonhuman primates (14–17).

Here we report the first clinical pregnancy in a human after uterus allotransplantation.

MATERIALS AND METHODS

Patient Information

The patient was a 23-year-old woman with complete Müllerian agenesis previously operated for vaginal reconstruction with jejunum. She was selected as one of the candidates for uterus transplantation after 6 months of counseling and discussion of the surgical, immunosuppression treatment and pregnancy-related risks. Local transplantation committee and

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This study is scheduled to be presented at the Conjoint Meeting of the International Federation of Fertility Societies and the American Society for Reproduction Medicine in October 2013.
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Institutional Review Board approval was obtained for this study. She and her husband were examined for infertility by measurement of basal hormone levels and antral follicle reserve, ovarian reserve tests (anti-Müllerian hormone, 1.95 ng/mL; thyroid-stimulating hormone, 5.9 μIU/mL; PRL, 44.3 ng/mL), and sperm analysis. Sperm analysis was evaluated with World Health Organization 2010 criteria (total progressive sperm count, 64 million/mL) (18).

Testing for lupus anticoagulant and anticardiolipin antibodies, factor V Leiden deficiency, activated protein C resistance, prothrombin G20210A, polymorphism at position 677 for methyl tetrahydrofolate reductase (MTHFR) gene, and protein S were performed to rule out thrombophilia and hyperhomocysteinemia. The patient was homozygoous for polymorphism at position 677 for the MTHFR gene. Low molecular weight (LMW) heparin (4000 IU, Clexane, Enoxaparine Na, Sanofı Pasteur As.) and levothyroxine (50 mg Euthyrox, Merck Ilac) were administered daily. Cabergoline (0.5 mg, Dostinex, Pfızer Pharmacia Saglik Urunleri) was administered weekly.

IVF Procedure

Multiple-dose flexible GnRH antagonist protocol (0.25 mg daily when leading follicle is 14–15 mm) was used in the first IVF cycle (19). E_2 and P levels were 2,421 pg/mL and 0.7 ng/mL on the day of hCG administration. Ten oocytes were picked up yielding six metaphase II (MII) oocytes and three grade 1 embryos. Pituitary down-regulation with daily GnRH agonist (long protocol) was commenced in the second IVF cycle (20). E_2 and P levels were 3,700 pg/mL and 1.1 ng/mL at hCG day. Twelve oocytes were collected yielding nine MII oocytes and five grade 1 embryos. Both oocyte pick-up procedures were performed transvaginally 36 hours after 250 hCG injection (Ovitrelle, Merck Serono).

Embryo Vitrification

Irvine Scientific brand was used in the first, and Vitrolife brand was used in the second IVF cycle. Retrieved oocytes were prepared for intracytoplasmic sperm injection (ICSI) (21). Polyvinylpyrrolidon was used for sperm selection and immobilization. ICSI was performed in HEPES-buffered medium (22). Injected oocytes were transferred to a fertilization medium (P-1 Irvine Scientific; G-IVF, Vitrolife) supplemented with 10% human serum albumin. After pronuclear evaluation on the next day after ICSI, zygotes bearing both two pronuclei and a second polar body were transferred to the fresh cleavage medium (Early Cleavage Medium with gentamicin, Irvine Scientific; G1, Vitrolife), supplemented by 10% human serum albumin for culture until day 3.

On day 3, embryos were evaluated according to the Istanbul Consensus Workshop of the Alpha Scientists (23). A day 3 embryo with <10% fragmentation, without multinucleation, and a stage-specific cell size was rated as good and scored as a grade 1 embryo. The number of blastomeres and the percentage of fragmentation were also counted and recorded.

All day 3 embryos were vitrified one by one, using cryotop (Kitazato Biopharma) and cryotip (Irvine Scientific) in the first IVF procedure and the cryoloop device (Vitroloop, Vitrolife) in the second IVF procedure (24–27).

Uterus Transplantation

Uterus allotransplantation has been performed from a 22-year-old deceased donor after pretests of HLA matching and screening for TORCH (28). Vascular anastomoses were performed between the recipient's external iliac vessels and the donor's internal iliac vessels.

Immunosuppression Protocol and Infection Prophylaxis

Induction immunosuppression with a 2.0 mg/dL daily dose of antithymocyte globulin and 1,000 mg of prednisolone was started initially. Maintanence immunosuppression was with 0.2 mg/kg tacrolimus, mycophenolate mofetil (MMF; 2 g/day), and 20 mg prednisolone for the first 12 months. After studying the data on the teratogenic effects of MMF, we discontinued it and replaced it with azathioprine starting from postoperative month 12 (29).

Immunosuppressant doses with respect to future pregnancy were prednisone <15 mg/day, azathioprine <2 mg/kg, and tacrolimus at therapeutic levels (5–15 ng/mL) monitored biweekly (29). The dose for prednisone and azathioprine was adjusted based on clinical or laboratory findings of infection, rejection, or leukopenia (30). Complete blood cell count, liver, and kidney function tests were also performed weekly to monitor the safety of treatment. Fluconazole, piperacillin/tazobactam, cotrimoxazole, oral nystatin drops, and oral valacyclovir tablets were administered for prophylaxis. SC heparin was performed for antithrombotic prophylaxis (MTHFR C677T homozygote mutant and protein S, 28.3%).

Follow-up Examinations

During follow-up, bilateral uterine artery Doppler ultrasound was performed twice a day for the first 10 days, every day for the next 20 days, and then biweekly. Vaginal biopsies were taken every 2 weeks in the first 3 months. Cervical biopsies were taken every month, and endometrial biopsies were performed every 3 months to monitor findings of thromboses or rejection. Uterine blood flow was assessed using color Doppler ultrasound (Voluson E8, General Electric) with a 9.0 MHz transvaginal transducer (RIC5-9-D endocavity probe, General Electric). Three-dimensional ultrasound demonstrated normal uterine cavity (Fig. 1). We performed color Doppler ultrasound of the uterine arteries at the cervicocorporeal level lateral to the cervix as suggested by Kupesic-Plavsik et al. (31). We defined the cutoff point for the Doppler resistance index as 0.80 on the basis of the present data for renal transplantation evaluation (32). Speculum examination of the cervix was performed once a week.

Endometrial Preparation

Eighteen months after uterus allotransplantation and confirmation of the graft stability, the endometrium was prepared with a standard artificial E_2 replacement protocol and

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