Uterus transplantation trial: 1-year outcome

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Objective: To report the 12-month outcome of seven patients with viable uteri after uterus transplantation (UTx).
Design: Prospective observational study.
Setting: University hospital.
Patient(s): Seven patients with absolute uterine infertility and viable uteri for 12 months after live-donor UTx.
Intervention(s): Predetermined immunosuppression was with tacrolimus and mychophenolate mofetil (MMF) during 6 months, whereupon MMF should be withdrawn. Frequent ultrasound examinations were performed to assess uterine appearance and uterine artery blood flow. Cervical biopsies (for histological detection of rejection) were obtained at preset time points, with temporary adjustments of immunosuppression if there were signs of rejection. Menstruations were systematically recorded.
Main Outcome Measure(s): Menstruation, uterine artery blood flow, histology of cervical biopsies, and blood levels of tacrolimus.
Result(s): All patients showed regular menses after 1–2 months. Uterine artery blood flow was unchanged, with a median pulsatility index of 1.9 (range, 0.5–5.4). Blood levels of tacrolimus were approximately 10, 9, and 8 (μg/L) during months 2, 9, and 12, respectively. Four recipients showed mild inflammation in biopsies after MMF withdrawal and were treated with corticosteroids and azathioprine during the remainder of the 12 months. Subclinical rejection episodes were detected on ectocervical biopsies in five recipients. Histology showed apoptotic bodies and occasional spongiosis in the squamous epithelium. Moderate infiltration of lymphocytes and neutrophils was seen in the epithelial/stromal interface. All rejection episodes were successfully treated for 2 weeks with corticosteroids or dose increments of tacrolimus.
Conclusion(s): We demonstrate long-term uterine viability after UTx, with continued menstruation and unaltered uterine artery blood flow. Subclinical rejection episodes were effectively reversed by temporary increase of immunosuppression.
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Key Words: Infertility, MRKH, rejection, transplantation, uterus

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Absolute uterine factor infertility (AUFI) is considered to be the only major cause of female infertility that remains untreatable. Uterus transplantation (UTx) has been proposed as one possible AUFI treatment. Recently, we initiated the first clinical UTx trial after more than a decade of animal-based research (1, 2). Nine AUFI women were transplanted with uteri from live donors, with the majority of donors being mothers of the recipients. The surgical technique involved isolation of the donor uterus, with substantial vascular pedicles to include parts of the internal iliacs bilaterally, and then transplantation into the recipient by vascular anastomoses to the external iliac vessels. The results of the surgery and postoperative period have been reported in detail (3). The main findings of our previous study included data on unexpectedly long (10–13 hours) surgery times for uterine retrieval with one surgical complication (ureteric-vaginal fistula) in a donor. Furthermore, two of the nine uterine grafts had to be removed during the initial months, with the causes being uterine vessel thrombosis and severe intrauterine infection.

It should be noted that experimental human UTx had been performed

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2 times before our UTx trial, but in both cases in the absence of research preparations by the teams. The first was a live-donor case performed in Saudi Arabia in 2000, with progressive uterine necrosis occurring during the initial months (4). The other experimental case of UTx was performed in Turkey 2011 and involved a uterus from a deceased donor (5). The patient underwent embryo transfer 18 months post UTx, and two early clinical pregnancies, which miscarried, were reported (6).

In the present paper we report on the clinical course during the first 12 months among the seven women of our UTx trial who have kept their transplanted uterus during this first post-transplantation year.

MATERIALS AND METHODS

Patients

The study was approved by the Human Ethics Committee of the University of Gothenburg and was registered in Clinical Trials.gov (NCT01844362). Written informed consent was obtained from all donors, recipients, and their partners. Nine patients, evaluated extensively by a multidisciplinary team, underwent UTx as reported by us in detail in our previous publication (3). Two uterine grafts were removed during the initial 6-month period. One was due to persistent intrauterine infection (recipient 2), and the other was because of bilateral uterine vessel thrombosis (recipient 9).

The characteristics of the patients, their donors, and the surgeries are given in detail in our initial publication (3). In the present report and in all future publications, the original numbering of the patients will be kept to enable the reader to follow the medical, psychological, and quality-of-life outcome of each individual patient. Thus, in the present publication, recipients 2 and 9 are excluded, since their uterine grafts were removed during the initial 6-month period. The remaining seven women who kept their transplanted uterus throughout the first postoperative year had a median age of 28 (range, 27–35) years, had been in a steady relationship with their partners for $\geq$3 years, and had before the transplantation undergone IVF to exclude couples with fertilization failure and also to cryopreserve embryos for transfer, when >12 months had passed after transplantation. Six of the remaining recipients (numbers 3–8), had AUFI because of congenital uterine agenesis, and one (recipient 1) had undergone hysterectomy due to cervical cancer. The transplanted uteri were from the mother in four cases (recipients 1, 4, 6, 7), and in the other cases from a sister (recipient 8), mother's sister (recipient 3), and family friend (recipient 5). The human leukocyte antigen mismatch in the seven cases varied between 1/0 (recipient 7) and 3/2 (recipient 9). Thrombosis prophylaxis was with acetylsalicylic acid (75 mg; Trombyl, Pfizer) once daily, and this continued during the entire 12-month period.

Immunosuppression

Immunosuppression followed a standardized protocol, which is used for kidney transplantation at our transplantation center, and the protocol has been described in detail elsewhere (3). In short, the recipients received induction with methylprednisolone (500 mg; Solu-Medrol, Pfizer) 10 minutes before uterine reperfusion, and depending on local availability, thymocyte antibodies were given as either thymoglobulin (IV, 2.5 mg/kg body weight; Genzyme) or ATG (IV, 5 mg/kg bw; ATG-Fresenius; Fresenius) just before UTx and at a second occasion 12 hours later. All recipients were continuously treated with tacrolimus (Prograf/Advagraf, Astellas) with the aim to lower the trough levels in two steps: 10–15 ng/mL during the first month, followed by 5–10 ng/mL from the second month and onward. Mycophenolate mofetil (MMF; Cellcept, Roche) was given (1 g) preoperatively by the oral route. Starting from postoperative day 1, MMF was administered twice daily, and the aim was to keep the MMF area under the curve (MMF-AUC) trough levels at 40–60 mg $\times$ hour/L. Owing to the potentially teratogenic effects of MMF, this treatment should be discontinued after 6 months, which is a time at least 6 months before the planned initial ET. The aim was to treat the patients with solely tacrolimus from month 7.

Follow-up

All recipients were monitored by regular clinical visits and laboratory examinations. The frequency of these was initially twice weekly, and after a month they were spaced to fortnightly visits during months 2–6 and then monthly visits. The clinical examinations comprised macroscopic inspection of the transplanted uterine cervix and vaginal rim as well as cervical cultures and biopsies. The biopsies were obtained at predetermined time points (1, 2, and 4 weeks and thereafter monthly), and the protocol also included biopsies at suspicion (discoloured cervix, abnormal vaginal discharge, fever, abdominal pain) of any pathological condition, such as infection or graft rejection. The histopathological examination of the cervix was graded according to our proposed rejection classification for the primate uterus (7). In the events of verified rejection on cervical biopsy, the immunosuppression was temporarily elevated. In the event the planned withdrawal of MMF after 6 months resulted in a cervical biopsy that was, per protocol, obtained 2 weeks after withdrawal of MMF or any later biopsy showed signs of accumulation of inflammatory cells, azathioprine (Imurel, Orion Pharma), and prednisolone (Prednisolon, Pfizer) were added as continuous immunosuppression. In the event of cervical intraepithelial neoplasia (CIN) on a cervical biopsy, a real-time polymerase chain reaction assay for typing of human papilloma virus (HPV), which included primers for HPV16, 18, 31, 33, 35, 39, 45, 52, 58, and 67 (8, 9), was used, after DNA had been extracted from cervical brushings by a MagNA Pure LC methodology after isolation with a total nucleic acid kit.

At each clinical visit, transvaginal and abdominal two-dimensional ultrasound (Flex Focus 400, BK Medical AB) were performed to assess the endometrial and myometrial thickness and echogenicity. Doppler ultrasound was used to evaluate the uterine artery blood flow on both sides. Waveform characteristics and measurement of blood flow velocity at peak systole (PSV) and peak diastole were obtained to calculate the resistance index (RI) and pulsatility index (PI).