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Case report

Transplantation of the human uterus

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Abstract

Human uterine transplantation was performed on 6 April 2000 on a 26-year-old female who lost her uterus 6 years earlier due to post-partum hemorrhage. The donor, a 46-year-old patient with multiloculated ovarian cysts, underwent a hysterectomy modified to preserve tissue and vascular integrity. The donor uterus was connected in the orthotopic position to the recipient's vaginal vault and additional fixation was achieved by shortening the uterosacral ligament. The uterine arteries and veins were extended using reversed segments of the great saphenous vein, then connected to the external iliac arteries and veins, respectively. Immunosuppression was maintained by oral cyclosporine A (4 mg/kg/body wt.), azathioprine (1 mg/kg/body wt.) and prednisolone (0.2 mg/kg/body wt.). Allograft rejection was monitored by Echo–Doppler studies, magnetic resonance imaging (MRI), and measurement of the CD4/CD8 ratio in peripheral blood by fluorescence activated cell sorter (FACS scan). An episode of acute rejection was treated and controlled on the ninth day with anti-thymocytic globulin (ATG). The transplanted uterus responded well to combined estrogen–progesterone therapy, with endometrial proliferation up to 18 mm. The patient had two episodes of withdrawal bleeding upon cessation of the hormonal therapy. Unfortunately, she developed acute vascular thrombosis 99 days after transplantation, and hysterectomy was necessary. Macro- and microscopic histopathological examination revealed acute thrombosis in the vessels of the uterine body, with resulting infarction. Both fallopian tubes remained viable, however, with no evidence of rejection. The acute vascular occlusion appeared to be caused by inadequate uterine structure support, which led to probable tension, torsion, or kinking of the connected vascular uterine grafts. © 2002 International Federation of Gynecology and Obstetrics. Published by Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

During the past three decades, scientists have made tremendous efforts to solve infertility problems; indeed, the achievements and developments that have occurred in this field have had a considerable clinical impact [1]. Infertility due to the absence of a uterus, or to a congenitally malformed uterus with normally functioning ovaries, has remained an obstacle to pregnancy, however, especially in communities where surrogate gestational carriers are approved by neither religious nor ethical authorities.

Uterine transplantation could provide a solution to this problem, but its feasibility, safety and reproducibility remain to be proven. To evaluate the potential for safe, successful uterine transplantation in humans, we reviewed earlier animal experiments and clinical trials. The main difficulty was the vascular anastomosis between the uterine vessels of donor and recipient [2]. Unlike other organs, where large vessels are the source of blood supply, in the uterus, the blood supply and drainage occur through a net of tiny vessels. Most earlier animal experiments were performed with avascular techniques that led to failure and the formation of pelvic abscesses [3]. Human trials were limited to transplantation of endometrial tissue [4], and no documentation of successful uterine transplantation was available in the English literature.

The Islamic religious position on uterine transplantation was clarified in March 1990, before initiation of this project, when the Islamic Jurisprudence Council approved the transplantation of reproductive organs that do not transfer genetic coding.

2. Experimental animal studies

The present project conformed with the 'Guiding Principles in the Care and Use of Laboratory Animals' approved by the authorities of the King Fahad Research Center. Previous experiments had proven the feasibility of uterine transplantation in animals, with successful pregnancy [5]. As the main difficulties lay in the uterine vascular connections, some researchers performed avascular uterine transplantation in the animals, which resulted in failure and in the formation of pelvic abscesses. We, therefore, decided to concentrate our animal studies on uterine reimplantation rather than transplantation. We focused on the vascular surgical anatomy and its variations [6], the physiology of the uterine blood flow, and mastery of the microvascular techniques of uterine arterial and venous anastomosis.

Autologous orthotopic uterine reimplantation was performed on 18 virgin female animals (16 baboons and two goats). The baboons' average age, weight and height were 2–4 years, 15.6 kg and 37 cm; the goats' average age, weight and height were 2–3 years, 20–30 kg and 60–71 cm. Surgery was performed with the animals under general anesthesia without muscle relaxation. Prophylactic antibiotics (Tetracycline, 20 mg/kg/body wt.) were given for 5 days. In each animal, a midline abdominal incision was made. Hysterectomy was modified to preserve tissue and vascular integrity. The extirpated uterus was flushed in both the antegrade and retrograde manner with 60 cm^3 of cold Euro–Collins solution, then reimplanted orthotopically in the same animal by doing cervico-vaginal anastomosis. The first eight animals underwent end-to-end uterine vascular anastomosis, but anastomotic occlusion and pelvic abscesses occurred due to graft failure and vascular thrombosis in 12 of the 16 (75%) vascular connections. Therefore, the technique was modified, so that the anastomosis was performed between the uterine vessel and the internal iliac vessels in an end-to-side fashion using monofilament non-absorbable polypropylene sutures. This modification was technically easier to accomplish; it also provided wider anastomotic stoma and a higher success rate in the remaining 10 animals, with proven vascular patency in 18 of 20 (90%) vascular connections. All animals underwent abdominal exploration after 6–12 weeks to evaluate the survival of the reimplanted uterus, and the following steps were taken: (1) assessment of vascular patency by visualizing emptying and refilling of veins and pulsatility of arteries, and by palpation of the arteries for presence or absence of thrill; (2) assessment of uterine and

fallopian tube viability by evaluation of their color and texture; (3) observation of bright red fresh bleeding from the tissue on abrasion or puncture; and (4) determination of pelvic infection.

Our animal studies demonstrated survival of the uterine graft and indicated that good mid- and long-term vessel patency could be achieved using skillful microvascular techniques for uterine arterial and venous anastomosis in an end-to-side fashion.

After reviewing the earlier reported experimental work by other researchers [5] and our satisfactory results, we decided to prepare for a human trial. Protocols for human uterine transplantation were designed, detailing indications, contraindications, selection criteria, surgical techniques, immunosuppression regimen, and clinical follow-up. Detailed informed consent forms were prepared for the donor and recipient according to the guidelines and regulations of the Food and Drug Administration (FDA).

3. Material and methods

The potential recipient was a 26-year-old female who had undergone a hysterectomy in 1994 because of massive bleeding following a cesarean section. She had consulted us concerning the possibility of uterine transplantation and after thorough evaluation was found to be eligible.

The donor was a 46-year-old female who presented with bilateral multiloculated ovarian cysts measuring 8×6 cm on the right side and 3×2 cm on the left side. Hysterectomy with bilateral salpingo-oophorectomy was planned, as this patient agreed to donate her uterus. ABO compatibility, HLA tissue matching, and negative cytotoxic antibodies in the recipient were confirmed.

4. The procedure

4.1. The donor

On 6 April, 2000 uterine extirpation was carried out with the patient under general anesthesia. The donor's abdomen was opened through a midline incision; bilateral en-block oophorectomy was performed and the ovaries were sent for frozen section, which confirmed the benign nature of the cyst. Uterine removal was accomplished using a technique modified so as to maintain the vascular pedicle of the uterus as long as possible, and thus maintain tissue integrity. The long vascular pedicle was maintained by transecting the round ligaments as far laterally as possible. The ureters were identified and protected. The infundibulopelvic ligaments were clamped, divided, and sutured. The pararectal and paravesical spaces were developed with care to avoid traumatizing the numerous small veins in the broad ligaments and paravesical space. The uterine arteries were then encircled with vessel loops. The uterosacral ligaments were serially divided and sutured. The uterovesical peritoneum was incised and the bladder was separated from the cervix and the vagina. At that stage, methyl prednisolone (500 mg) and heparin (20 000 i.u.) were given i.v. The uterine arteries were clamped 1 inch away from the uterine body. The vagina was entered by circumferential incision and the extirpated uterus immersed in cold saline for topical hypothermia. The graft was flushed with modified cold (4 °C) Euro–Collins solution, antegrade through uterine arteries and retrograde through uterine veins, to ensure removal of all white blood cells and fibrin and to induce central core cooling for tissue preservation during the ischemia period. The uterosalpingeal graft was additionally trimmed to ensure removal of any remnants of unwanted tissue. A 6-cm long segment of the great saphenous vein and an 8-cm long reversed segment were anastomosed to each uterine vein and artery, respectively, with 6×0 non-absorbable polypropylene suture (prolene-Ethicon) on a sterile side bench to extend the length of the vascular pedicles (Fig. 1). The eight vascular grafts were flushed again with Euro–Collins solution to check for any anastomotic leaks. A small laceration of the anterior wall of the donor's left ureter was found and was splinted with a double J tube and sutured by the urologist.

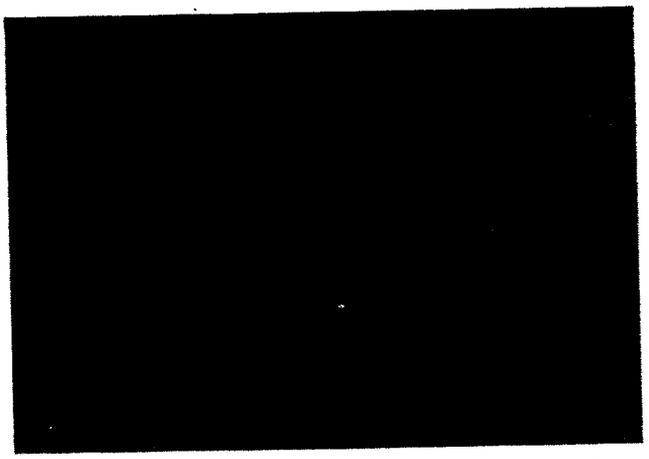

Fig. 1. The end-to-end vascular anastomosis of the uterine artery (U.A.) to the saphenous vein (S.V.) segment. (A) Line of division of the saphenous vein. (B) Continuous micro-anastomosis. (C) Posterior wall completed. (D) Anterior wall completed.

4.2. The recipient

A pre-operative oral dose of cyclosporine (4 mg/kg/body wt.) was administered 6 h prior to surgery and methyl prednisolone (500 mg i.v.), was administered to the patient at induction of anesthesia.

The recipient's laparotomy was started when donor uterine extirpation was imminent. A midline sub-umbilical incision was selected and intra- and retroperitoneal adhesions were lysed. The internal and external iliac vessels were dissected bilaterally. The bladder and rectum were dissected from the cervical stump and the latter was excised. The donor uterus was placed in orthotopic position and the cervix was then sutured to the recipient vaginal vault by single interrupted non-absorbable 2×0 Ti-cron (Ethicon) sutures. Uterosacral shortening was accomplished using two non-absorbable 2×0 Ti-cron sutures. The extended uterine veins and arteries were then anastomosed to the external iliac veins and arteries, respectively, with 6×0 prolene. No ovarian arterial or venous anastomosis was performed. Five hundred milligrams of methyl prednisolone was given i.v. on releasing the iliac clamps and re-establishing uterine perfusion. The abdomen was closed in layers after complete homeostasis. The recipient made an uneventful recovery with good wound healing. White blood count, cyclosporine level, and creatinine phosphokinase enzyme levels were checked twice a week. The immunosuppression consisted of oral cyclosporine (4 mg/kg/body wt.) divided into two doses to assure a serum trough level of 200 ng%, azathioprine (Immuran) (1 mg/kg/body wt.) and prednisolone, with a maintenance dose of 0.2 mg/kg/body wt. The adequacy of immunosuppression was monitored by measuring the lymphocyte subpopulation (CD4/CD8 = helper/suppressor) cell ratio by cyto-immunological cytometer (FACS Scan) and Doppler ultrasound to study flow volume, pulsatility and resistance index [7]. On the ninth post-operative day, the patient complained of low abdominal and back pain, general fatigue, malaise, and body ache. She had minimal serosanguinous vaginal discharge, low-grade fever, and tachycardia, indicating acute rejection. The CD4/CD8 ratio was found to be reversed to 3.4. Abdominal Doppler ultrasound showed increased brightness due to myometrial edema. The patient was treated by increasing the oral doses of cyclosporine and azathioprine and administering an intravenous pulse of methyl prednisolone. The rejection did not resolve, however. Antithymocytic globulin (ATG) (2.5 mg/kg/body wt.) was given, controlling and resolving the rejection phenomenon. Cervical in-

spection on the 12th day revealed good healing of the cerviovaginal anastomosis, with some venostasis of the lower 1/3 of the ectocervix. Biopsy was not attempted, so as to avoid anastomotic disruption. The symptoms of rejection disappeared after 2 days and the CD4/CD8 ratio was 1.3. Doppler ultrasound revealed excellent bilateral uterine arterial perfusion, with low resistance indices (Fig. 2). Hormonal therapy with estrogen and progesterone (Progyluton) was given for the first 3 months to build up the atrophic endometrium. Two withdrawal bleedings occurred promptly after cessation of the hormonal therapy. These were considered to reflect good blood perfusion and viability of the transplanted uterus.

4.3. Removal of the transplanted uterus

On the 99th day, the patient experienced a sudden feeling of heaviness, with a foul-smelling vaginal discharge on straining. Speculum examination revealed a dusky-colored cervix prolapsing into the vagina. Immediate Doppler ultrasound confirmed cessation of the uterine blood flow. A diagnosis of mechanical occlusion of the uterine vessels with resulting uterine infarction was made, and the need to perform a hysterectomy became obvious. At surgery, the uterus was found to be infarcted and the uterine arteries, veins, and their supplying grafts were thrombosed. Both fallopian tubes remained pink and viable, however. Histopathologic microscopic examination confirmed the above findings as well as the viability of both tubes and absence of any rejection (Fig. 3).

5. Discussion

Advances in immunology make organ transplantation for end-stage organ failure a clinical reality [8]. Advances in microvascular surgery and tissue preservation as practiced in ovarian transplantation [9] provide support for major steps in the new era of the surgical management of infertility [10]. Such advances can be applied successfully in uterine transplantation, and indeed, our experimental work with microvascular uterine

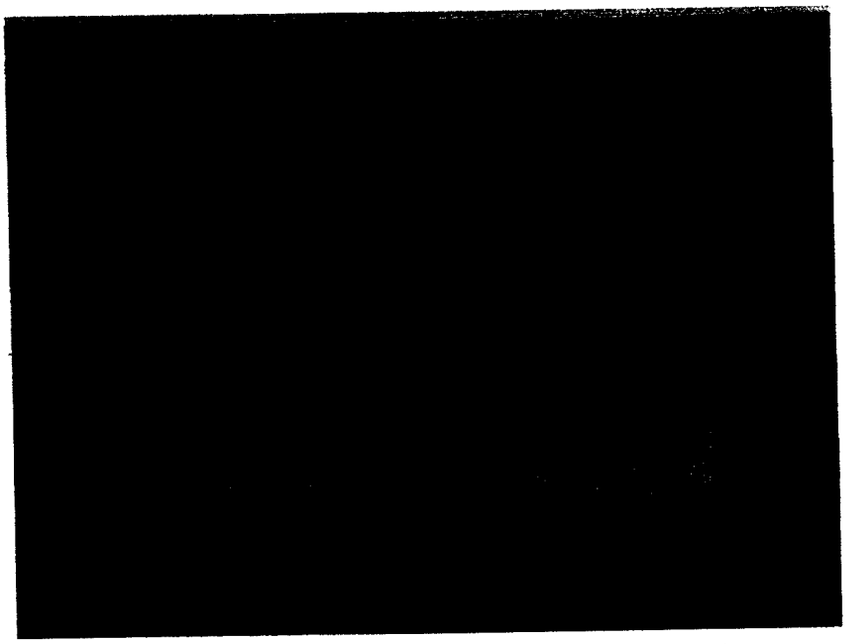

Fig. 2. Doppler ultrasound showing normal blood flow and velocity in the uterine artery.

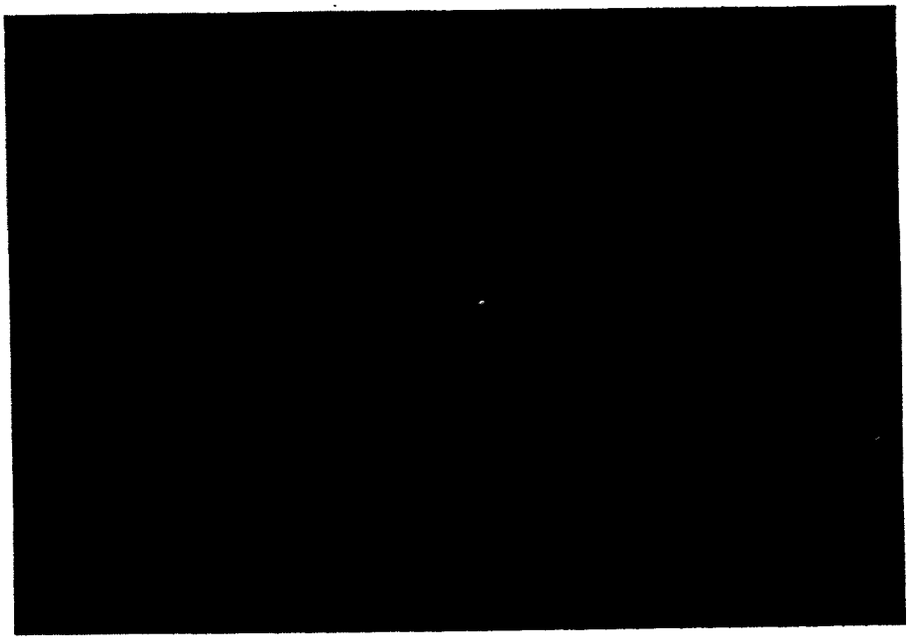

Fig. 3. Histopathological view (10× magnification) hematoxylin eosin coloration. The fallopian tubes of normal anatomical pattern and vascularity.

vessel anastomosis provides ample clinical evidence of good mid- and long-term vascular patency and graft survival.

Simple non-invasive techniques such as Doppler ultrasound to monitor and detect early rejection are essential. Cytoimmunological monitoring for activated lymphocyte sub-population (CD3/CD4 = helper/suppressor) cell ratio using monoclonal antibodies is a simple non-invasive technique to monitor rejection, with a sensitivity and specificity approaching 96% and 88%, respectively [11]. Punch biopsy from the endocervix, to detect and histopathologically grade rejection seen as myocyte necrosis and perivascular infiltration of lymphocytes, is an invasive procedure that could be associated with certain risks. It was, therefore, not applied in our patient.

Modification of the hysterectomy technique in the donor is essential to promote the preservation of a longer vascular pedicle and application of gentle atraumatic technique to preserve the uterus, and differs from conventional hysterectomy. Extension of the vascular pedicle for a required length using a conduit such as the great saphenous vein or the radial artery may be advantageous in selected patients, and the application of microvascular techniques by an experienced vascular surgeon is mandatory. The use of fine polypropylene monofilament non-absorbable sutures is required. Suspension of the uterus to the anterior abdominal wall (ventrouteropexy) and by uterosacral shortening is essential, to avoid displacement of the uterus with consequent tension, torsion, or kinking on the vascular pedicle, and anastomosis, with obstruction of blood flow and vascular thrombosis.

6. Conclusion

Our clinical results with the first human uterine transplantation confirm the surgical technical feasibility and safety of this procedure in gynecologic, surgical, and vascular terms. Acceptable short- and mid-term outcomes were documented by good endometrial proliferation on hormonal

therapy and the occurrence of two withdrawal bleedings in the transplanted menopausal donor uterus.

An understanding of the surgical vascular anatomy and physiology of the uterine blood flow, and the application of microvascular techniques in uterine vessel anastomosis, solved the earlier reported difficulties encountered in that aspect. Cytochemical and cytoimmunological non-invasive techniques for monitoring graft rejection are useful and reliable. Preservation of the tissue and vascular integrity during uterine extirpation is essential. A vascular pedicle of good length with the possible use of an extension conduit, such as the radial artery or the great saphenous vein, could be required. Strong fixation of the transplanted uterus to the anterior abdominal wall and the sacral promontory is required, as the uterus lacks the support of the uterosacral ligaments and could develop slow progressive or acute prolapse with consecutive thrombosis, infarction, and loss of the uterus.

Further clinical experience and additional development of the surgical techniques could make uterine transplantation useful in the treatment of infertility, especially in communities where the surrogate mother concept is unacceptable from a religious or ethical point of view.

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References

[1] Hunt RB. Complications of infertility surgery. In: Hunt RB, editor. Atlas of female infertility surgery. 2nd edition, Mosby Year Book, St Louis MO, 1992:485–495.
[2] Denjean R, Boeck W, Gordts S, Brosens I. Ovarian transplantation by selective microvascular anastomosis in the rabbit. Br J Obstet Gynaecol 1982;89:652–656.
[3] Confino E, Vermesh M, Thomas Jr. W, Gleicher N. Non-vascular transplantation of the rabbit uterus. Int J Obstet 1986;24:321–325.
[4] Turunen A. On traumatic amenorrhea, 2 cases of endometrium transplantation which led to the birth of a full term infant. Gynecologia 1967;164:12–23.
[5] Eraslan S, Hamermik RJ, Hardy JD. Replantation of uterus and ovaries in dogs with successful pregnancy. Arch Surg 1966;92:9–12.
[6] Gary G. Anatomic exposure in vascular surgery. Philadelphia, PA: Williams and Wilkins, 1991:446–448.
[7] Hall TS, Baumgardner WA, Borkon AM et al. Diagnosis of acute cardiac rejection with antimyosin monoclonal antibodies, phosphorus nuclear magnetic resonance imaging, two-dimensional echocardiography and endomyocardial biopsy. J Heart Transpl 1980;5:419–424.
[8] Organ transplantation: an update. Archives of the XVI International Congress of the Transplant Society 1996; 1–6.
[9] Von Theobold F, Roffe JL, Berrocal J, Le Porrier M, Muller G. Heterotopic autotransplantation of the ovary in women. Presse Med 1987;16:1239–1241.
[10] Carmona F, Ballash J, Gonzales MJ. Ovarian function and tubal viability and pregnancy after tubo-ovarian transplantation in the rabbit. Human Reprod 1993; 8:929–931.
[11] Baughman L. Monitoring of allograft rejection. Heart and heart-lung transplantation. Philadelphia, PA: W.B. Saunders, 1990:157–164.