Uterine Transplantation: Surgical Innovation in the Treatment of Uterine Factor Infertility

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Abstract

Uterine factor infertility (UFI) is a condition that affects thousands of women and is estimated to have a prevalence as high as one in five hundred reproductive-aged women. A wide range of circumstances can lead to UFI and include women with congenital absence of a uterus (Mayer Rokitansky Kuster Hauser or MRKH syndrome), women who have undergone iatrogenic removal of the uterus, or women who have uteri that are in situ but have been damaged by infection or surgical instrumentation. There have been 17 published reports of human uterine transplantation in the world. This article will summarize the history of human uterine transplantation and discuss our current understanding of the medical, surgical, and ethical considerations surrounding this innovative procedure.

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INTRODUCTION

Since the first birth reported after uterus transplantation in 2015, numerous centres have reported initiating a uterus transplantation program for uterine factor infertility (UFI).[1] UFI is a condition that affects thousands of women and is estimated to have a prevalence as high as one in five hundred reproductive-aged women.[2] A wide range of circumstances can lead to UFI and include women with congenital absence of a uterus (Mayer Rokitansky Kuster Hauser or MRKH syndrome), women who have undergone iatrogenic removal of the uterus, or women who have uteri that are in situ but have been damaged by infection or surgical instrumentation. Absolute UFI is a challenging infertility problem as there are currently no treatments despite the fact that most women with UFI have functioning ovaries that can produce viable oocytes. While advances in assisted reproductive technologies are significant, women with UFI cannot carry pregnancy, which leaves adoption and the use of in vitro fertilization (IVF) with gestational carriers as the only methods for parenting. While many patients find these alternatives to be satisfactory, adoption and surrogacy may be impossible for some patients due to personal, religious, legal, financial or ethical reasons.[3] Uterine transplantation, however, represents a novel treatment option for UFI. Uterine transplantation has been performed successfully in rodent, swine, and nonhuman primate models.[4,5] At the time of this review, there have been 17 published reports of human uterine transplantation in the world. This article will summarize the history of human uterine transplantation and discuss our current understanding of the medical, surgical, and ethical considerations surrounding this innovative procedure.

Key Words: Uterine transplantation, uterine factor infertility, deceased donor uterus transplant, reproductive transplant

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A BRIEF HISTORY OF UTERINE TRANSPLANTATION

The first human uterine transplantation procedure was reported in 2002 by physicians in Saudi Arabia and involved a 26-year-old recipient with UFI due to a prior hysterectomy.[6] The donor was a living 46-year-old female undergoing hysterectomy for benign indications. The donor sustained a ureteral injury as a complication of the surgery. The recovered uterine vessels were short and were extended by use of segments of the saphenous veins. These were reportedly anastomosed end-to-side with the external iliac vessels. The failure of the graft has since been attributed to poor structural support for the uterus with subsequent thrombosis of the vascular supply and prolapse. The uterus was removed three months postoperatively and found to be necrotic. This transplant was not performed as part of a clinical trial and there have been no subsequent attempts by this group.

The next human uterine transplant did not take place until nine years later, in 2011. During this time, research in animal models was performed to demonstrate promise in swine, rodent and non-human primates.[7] The 2011 transplant was performed by a Turkish team, and was novel in the first-ever use of a deceased donor. The recipient was a 21 year-old patient with MRKH who received a uterus from a brain-dead multi-organ donor of similar age.[8] In this attempt, the common iliac vessels of the graft were anastomosed end-to-side with the recipient external iliac vessels. This transplanted uterus remains in situ as of the time of this publication and has shown evidence of menstrual function. However, despite several early failed pregnancies, no successful live births have resulted from the graft to date.[9]

Dr. Mats Brännström performed the first clinical trial of human uterine transplantation in Sweden, with a six-month follow-up report published in 2014.[10] Dr. Brännström's team had previously built successful animal models in multiple species, including small mammals and non-human primates.[11–13] This work is in contrast to prior human attempts, which were not preceded by any formal research in uterine transplantation. Dr. Brännström's living donor trial included nine women, eight of whom had UFI due to MRKH. In addition, most of these women received transplants from family members with an average donor age of 53 ± 7 years. The donor uteri were recovered along with segments of the internal iliac arteries below the branching of the gluteal artery along with the uterine veins to the level of the internal iliac vein. The anastomosis was then completed using bilateral end-to-side anastomoses to the external iliac arteries.[10] In some cases, the ovarian vein was used if the uterine vein was felt to be suboptimal. Of the nine transplants performed, two were removed within several months of the transplant, one for vascular thrombosis and one for a severe infection of the graft. In addition, one donor developed a uretero-vaginal fistula postoperatively which required surgical repair.[10] The seven remaining grafts continued to prove viable and recovered menstrual function within months of the transplant without any need for hormonal support. Multiple live births have since been reported from Dr. Brännström's group.[2] As planned, all births have been via Cesarean section and, aside from a reported preterm delivery at 31.5 weeks due to severe preeclampsia in one patient, obstetric outcomes appear to be favorable. This clinical trial is the first and only trial thus far to demonstrate proof of concept that uterine transplantation can achieve the ultimate endpoint of a healthy live birth.

Currently, multiple academic centres throughout the world are developing uterine transplantation protocols as the result of the encouraging findings reported by the Swedish group. Our centre has performed one transplant on February 24th, 2016; ten total transplants for UFI are planned under an IRB-approved deceased donor clinical trial.[14] Unfortunately, the graft required removal on postoperative day 12 due to a severe fungal infection, which disrupted one of the vascular anastomoses and led to graft failure. A series of living donor uterine transplants in the United States have recently been reported from another U.S.-based team.[15] Of their five initial attempts, three were removed within two weeks of transplant for graft thrombosis, likely related to venous congestion and insufficient graft outflow. Therefore, of the 17 reported transplants reported by five groups internationally thus far, eight have required graft removal due to complications.

Although uterine transplantation is still an evolving and highly experimental surgical procedure with a known risk of failure, there is widespread interest from both patients burdened by UFI as well as surgical teams around the globe. Both medical and surgical considerations will be reviewed in the following two sections. In addition, current topics of interest in the uterus transplant community will be addressed throughout the manuscript, including donor selection (living versus deceased donor), surgical considerations related to uterus procurement, post-transplant management, and ethical concerns surrounding surgical management of UFI.

MEDICAL FACTORS

Although the causes of UFI are diverse, typically patients will either present with a diagnosis of MRKH or a prior hysterectomy for a gynecological indication. Hysterectomies are frequently performed for cancer or pre-cancer, pelvic pain, endometriosis or abnormal uterine bleeding, or more rarely for obstetrical complications. In the Turkish study, only 17% of applicants had undergone hysterectomy and the remainder had a diagnosis of MRKH. In the Swedish trial, only one of the nine transplant recipients had a prior hysterectomy (for cervical cancer) and eight were MRKH patients.[10] In contrast, our experience interviewing 250 candidates from the United States revealed a very high percentage (64%) with prior hysterectomy, half of whom had undergone hysterectomy for benign indications.[16] To date, all reported uterine transplants have been restricted to reproductive-aged recipients.

ABBREVIATIONS

UFI	Uterine factor infertility
MRKH	Mayer-Rokitansky-Kuster-Hauser