



Uterine Transplantation: An Option beyond Surrogacy

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ABSTRACT

Over the years, a lot has developed in the field of infertility and artificial reproductive techniques worldwide, but the uterine factor infertility still remains an unresolved issue in reproductive medicine. Absolute uterine factor infertility is synonymous with congenital absence of uterus or a physiologically nonfunctioning uterus. Very few options including surrogacy and adoption are available for these patients. Both surrogacy and adoption are associated with legal, ethical, financial, religious, and psychological issues. For some of these patients, uterine transplant could be a viable option in future. However, the ability of uterus to carry the pregnancy to the period of viability and the effect of immunosuppressant on the fetus make the uterine transplant a more complex operation than any other transplants. From the earliest uterine transplant tried in 1931 in Germany to the first successful child birth following transplant in Sweden in 2014, uterine transplantation has come a long way. Among the countries that have tried this till now, Sweden has reported five cases of successful births posttransplant. Behind these successful cases, there is dedication and perseverance of few individuals who continued their efforts in spite of repeated failures. At the moment, the uterine transplant can be considered experimental at the best. However, considering the large number of hysterectomies done all over the world and uteruses available for transplantation, uterine transplant has potential to surpass, in numbers, the other transplant in near future.

Keywords: Artificial reproduction techniques, Reproductive medicine, Uterine factor infertility, Uterine transplant.

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INTRODUCTION

Organ transplantation has been popular in many fields as a lifesaving procedure. Considering the higher rate of hysterectomy in our country for both gynecological and obstetric causes, uterine transplant would have been an expectedly popular surgery. However, unlike the other

organ transplants uterine transplantation is rather a life-enhancing but not a lifesaving procedure, done only for absolute uterine factor infertility. Uterine factor infertility is the most unresolved issue in reproductive medicine. It includes congenital absence or a physiologically nonfunctioning uterus. Surrogacy and adoption are the options for these patients, but both are associated with moral and ethical difficulties. For some of these patients, who have been born without uterus or who have lost their uterus through illness, uterine transplant is a viable option.

History

Trials on Animals

In 1964 and 1966, at the University of Mississippi Medical Center the first autotransplantation of the uterus was performed on animal (dog) and subsequently delivered a pregnancy from that uterus.¹ In 2010 Diaz-Garcia and coworkers, at the University of Gothenburg in Sweden, did the world's first successful allogenic uterus transplantation, in a rat, with healthy offspring.²

Trials on Humans

In 1931 in Germany, a Danish transgender woman, died from organ rejection 3 months after receiving one of the world's earliest uterine transplants.³ With the availability of *in vitro* fertilization in 1978, uterine transplantation research was deferred.⁴ In Saudi Arabia in 2000, a uterine transplant was performed, from a 46-year-old hysterectomy patient into a 26-year-old recipient⁵ whose own uterus was removed due to postpartum hemorrhage. The transplanted uterus functioned for 99 days, but ultimately needed to be removed due to thrombosis. In Turkey, in 2011, the world's first uterus transplant from a deceased donor was conducted by a team of doctors at Akdeniz University Hospital.⁶ The patient was a 21-year-old Turkish woman, Derya Sert, who was born without a uterus. She had menses for 6 cycles posttransplant and also got pregnant, however, abortion took place at 8 weeks of gestation. In Sweden in 2012, the first mother-to-daughter womb transplant was done by Swedish doctors at Sahlgrenska University Hospital at Gothenburg University led by Mats Brannstrom.⁷⁻⁹

First Successful Pregnancy

A Swedish woman of 36 years of age had received a uterus in 2013, from a live 61-year-old donor. In October 2014,

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it was announced that, for the first time, a healthy baby had been born to a uterine transplant recipient. First menstruation occurred 43 days after transplantation and she continued to menstruate at regular intervals. After 1 year of transplantation, first single embryo was transferred, which resulted in pregnancy. She was then given triple immunosuppression with tacrolimus, azathioprine, and corticosteroids, which was continued throughout pregnancy. She had three episodes of mild rejection, one of which occurred during pregnancy which were all reversed by corticosteroid treatment. Fetal growth was monitored by ultrasound and color Doppler all throughout the pregnancy. The patient was admitted with preeclampsia at 31 full weeks and 5 days, and a cesarean section was done because of abnormal cardiotocography. A male baby with a normal birth weight for gestational age (1775 gm) was born.¹⁰ In Sweden, totally nine uterine transplantations have been done till today, out of which five resulted in successful pregnancies. The first uterine transplant performed in the United States took place on 24 February 2016 at the Cleveland Clinic but failed due to infection by *Candida albicans*, which caused damage to the local artery compromising the blood support of the uterus and necessitating its removal.¹¹

Need for Uterine Transplant

Absolute uterine factor infertility is the indication for uterine transplant. That includes congenital absence (Mayer Rokitensky Kuster Hauser syndrome) and acquired due to Asherman syndrome or hysterectomy performed due to obstetric cause in the treatment of postpartum hemorrhage or gynecological cause, such as malignancy. Surrogacy and adoption are options for these patients but both approaches, unfortunately, deprive them of the maternal experience of pregnancy and birth. There are some psychological, ethical, religious, legal, and financial issues also associated with it. In fact, surrogacy is prohibited in some countries.

DONORS

Donor selection is done by two approaches. In Sweden, they used live-donor approach whereas in Cleveland clinic trial they used deceased-donor approach. Each approach has pros and cons. The live-donor approach gives control over the timing of the transplant and allows a far more thorough assessment of the donor's medical profile and suitability. But, it also puts a healthy individual at risk, particularly, since pelvic surgeries are performed near so many vital organs. The deceased-donor approach dramatically reduces the pool of available organs. It also offers technical advantages because we are able to recover the uterus with larger vessels.

PROCEDURE

Candidates for transplant are generally chosen from age 18 to 36 years with absolute uterine factor infertility. Counseling regarding procedure and risks is essential. *In vitro* fertilization procedure starts before transplantation. Patients ovaries are stimulated, eggs are retrieved and fertilized *in vitro* with partner's sperms. Six to ten embryos are selected and frozen. Patient is started on immunosuppressant therapy before surgery. The procedure involves suturing the uterine vessels – a pair on each side of the organ – to the recipient's vessels, after which the vaginal tissues are connected to the recipient's gynecological anatomy. The graft is then securely sewn into the pelvis to stabilize the uterus for future pregnancies.

Originally, it was believed that four of the following six blood vessels (two uterine, two ovarian and also a collateral supply from two vaginal vessels) were necessary to maintain a viable uterus. But subsequent studies showed that the uterus remains viable when supplied by ovarian vessels alone and is capable of pregnancy and delivery. A "microvascular technique" for uterine auto transplantation was developed and used in eight pigs. This technique proved unsuccessful as the subjects failed to achieve a normal menstrual cycle. Postmortem examinations revealed thrombosis of the small uterine blood vessels. To overcome this, a large vessel patch technique or "macrovascular" technique was utilized with limited success. The study involved taking part of the aorta, inferior vena cava, common and internal iliac vessels coupled with the uterine arteriovenous tree, together with the uterus en bloc as a large vessel patch. This "method" was supported by evidence demonstrating that the uterus resected en bloc is probably less likely to undergo blood vessel thrombosis.

After 6 to 8 weeks of transplantation, the patients attain menstrual function. Around 1 year after transplantation the uterus fully heals and frozen embryos can be transferred one at a time. Immunosuppressant drugs are continued throughout pregnancy and monthly biopsies are done to rule out rejection. Delivery is done by cesarean section. Women in the trial who achieve a successful delivery can keep the uterus for further pregnancy – number of pregnancies can be limited up to two, for safety reasons – or the uterus can be surgically removed after the delivery to avoid continued immunosuppression. We can also offer to stop immunosuppressant drugs and let the immune system reject the uterus, which in many cases is absorbed by the body without need for intervention.

Shortcomings of Uterine Transplants

Uterine transplant carries some legal and ethical issues. The patient is kept on immunosuppressant therapy for very

long time which is harmful. And in live-donor approach, a total of four major surgeries are required. First surgery is done on the donor to remove the uterus. Second surgery is transplantation of the uterus. When the patient becomes pregnant, cesarean section (3rd surgery) is done and when childbearing is over then hysterectomy (4th surgery).

CONCLUSION

The uterus is the newest organ to be transplanted. Considering millions of hysterectomies being performed worldwide and enormous number of uteruses are available for transplant, it is surprising that the story of successful uterine transplant has just begun. With the availability of artificial reproductive techniques and surrogacy, the indications for uterine transplant will remain very few. However, when we look at it as a scientific breakthrough, it is a pioneering work by some of the dedicated professionals.

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