

Uterus transplantation: Medical breakthrough or surgical folly?

➡ Although uterus transplantation has been proven to be feasible, is it practical or ethical?



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CASE Patient asks for transplantation referral

During an annual ObGyn visit, a 28-year-old G0 with congenital absence of the uterus excitedly tells you about the news report of the first birth following uterus transplantation. She always has dreamed of becoming pregnant, and this medical breakthrough has spurred her imagination of what might be. You ask if she would consider adoption or a gestational carrier. Responding that she prefers to carry her own pregnancy, she asks you to refer her to a uterus transplantation program. You promise to look into this option for her. As she opens the door to leave your office, she mentions that her mother has volunteered to be the uterus donor.

Later, you have misgivings about making a referral for uterus transplantation. You wonder: Is this procedure an appropriate use of health care resources? Do its risks outweigh the benefits?

In September 2014, a 36-year-old Swedish woman gave birth following uterus transplantation. A 61-year-old family friend donated the uterus for the procedure.¹ Prior to this breakthrough, women without a uterus had 3 reproductive alternatives: remain childless, adopt a child, or use a gestational carrier to give

birth to their child. In many countries and some religions there are prohibitions against the use of a gestational carrier, leaving adoption as the only option to parenthood.

The first successful uterus transplantation did not occur by serendipity; a decade of careful work led to this breakthrough.²⁻⁴ Remarkably, it is now proven that this type of transplantation can result in the successful birth of a baby—but at what cost?

The Brännström Uterus Transplantation Program: A medical breakthrough

Dr. Mats Brännström at the University of Gothenburg, Sweden, is the leader of the courageous and innovative team that developed the world's first successful uterus transplantation program. The team required a broad range of expertise and skills and included physicians, scientists, and support staff from Sahlgrenska University Hospital and Stockholm IVF in Sweden; University of Valencia, Spain; Griffith University, Australia; and the Cleveland Clinic, Florida. Two recent publications report on the outcomes of the first 9 uterus transplants.^{5,6}

The successful protocol. The first step in the program is an exhaustive

medical and psychosocial evaluation of the prospective uterus donor and recipient. Among the first 9 uterus recipients, 8 women had congenital absence of the uterus and 1 woman had a hysterectomy for cervical cancer. The uterus donors were mothers (in 5 cases), a mother-in-law, a sister, an aunt, and a friend.

After the recipient is approved for uterus transplantation, she undergoes in vitro fertilization (IVF) with cryopreservation of all embryos. IVF is recommended because it may not be possible to include the fallopian tubes in the uterus transplant or the tubes may not function properly following transplantation. The donor organ is harvested, using a modified radical hysterectomy with extended vascular pedicles, and transplanted into the pelvis of the recipient.

Following transplantation, immunosuppressive medications are prescribed daily to reduce the risk of organ rejection. The recipient is followed on a regular basis with physical examination and cervical biopsy to identify histologic markers of organ rejection. Episodes of rejection are treated with glucocorticoids and adjustment in the dose of immunosuppression medications. Fertility treatment with the recipient's

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previously cryopreserved embryo begins 1 year following transplantation.

A unique feature of uterus transplantation is that the organ can be removed after childbearing is complete, thereby limiting lifetime exposure to immunosuppressive medications.

Uterus transplantation: Surgical folly?

Transplantation of a uterus involves major surgery. The inescapable reality is that the procedure will cause complications in some donors and recipients.

Specific complications faced. In the Brännström series, 1 uterus donor developed a postoperative ureterovaginal fistula, likely caused by extensive dissection of her ureters. This donor needed an additional operation to repair the fistula. Two of the 9 uterus transplants failed. One uterus was removed from the recipient 3 days after transplantation due to vascular occlusion and 1 uterus was removed 105 days after transplantation due to chronic infection resistant to antibiotic treatment. Seven of the transplants were successful and functioning *in situ* 12 months after transplantation as evidenced by regular menstrual bleeding. Five of the 7 recipients had rejection episodes, as demonstrated by the histology of cervix biopsies. Two of the recipients had 3 episodes of rejection. The rejection episodes were treated successfully with glucocorticoids and adjustment of immunosuppression medications.

Pregnancy in women with uterus transplantation is high risk because of the complications caused by immunosuppressive drugs and the high blood flow through the vascular grafts.⁷⁻⁹ In the Brännström series, the agents utilized for immunosuppression included mycophenolate

mofetil, azathioprine, tacrolimus, and glucocorticoids. Mycophenolate mofetil is a potent teratogen and routinely is discontinued prior to initiating attempts at pregnancy. Azathioprine is associated with an increased rate of congenital anomalies, but the benefits of this immunosuppressive are believed to outweigh the risks for most pregnant women with an organ transplant. Tacrolimus increases the risk of developing hypertension, pre-eclampsia, and intrauterine growth restriction during pregnancy.

In the Brännström case report, the woman who became pregnant following uterus transplantation took tacrolimus and azathioprine to prevent organ rejection both before and during her pregnancy. Not unexpectedly, she developed pre-eclampsia with severe features at 31 weeks and 5 days. After admission to the hospital, a worrisome fetal heart rate pattern developed and a cesarean delivery was performed. The newborn male weighed 1,775 g, and no congenital anomalies were observed. During pregnancy, blood flow to the uterus is in the range of 500 mL/min, the equivalent of 1 unit of whole blood per minute.¹⁰ This torrential pulsating flow may increase the risk of a vascular catastrophe such as the rupture of a major artery at one of the graft anastomoses, potentially causing the death of the fetus or mother. Much more experience will be needed to fully characterize the pattern of pregnancy complications that occurs following uterus transplantation.

The cost issue. Uterus transplantation is an extremely expensive medical procedure. In the United States each transplantation is likely to cost hundreds of thousands of dollars. Health care resources used to support uterus transplantation are not available for other pressing

medical needs. Given that it is an experimental procedure, it is unlikely that health insurance will reimburse the costs of the medical care. Transplantation programs will need to seek major donors to support the costs, as was done in the Brännström program, or identify patients capable of paying for the transplant. If programs plan to have most patients pay for the procedure, bioethical concerns of equitable access and fair selection of recipients will need to be addressed.

Ethics. Uterus transplantation raises many bioethical concerns and programs need to engage biomedical ethicists to guide their activities.¹¹⁻¹³ Careful attention to thorough informed consent, risk-benefit analysis, equitable access, and fair selection of participants will be critical to running an ethical program. To reduce the risks of the procedure, programs likely will explore the use of uteri obtained from women who are brain dead or cadavers to spare altruistic living donors from undergoing hysterectomy surgery.

“Group of fools” or Nobel Prize in wait?

On December 23, 1954, the first successful kidney transplant was performed by Dr. Joseph E. Murray and his team at the Peter Bent Brigham Hospital, a predecessor to the Brigham and Women’s Hospital.¹⁴ His small group of physicians worked for years to perfect the kidney transplantation technique in the laboratory prior to attempting the case. A key to their success was the decision to perform the transplant with identical twins as the donor and recipient.

In the 1950s there was great controversy about whether kidney transplantation was a medical

breakthrough or surgical folly. The lead surgical team was referred to as the “group of fools” by some colleagues. But Dr. Murray and his team succeeded in their efforts and opened the field of solid organ transplant. Recognizing the importance of his accomplishment, the Nobel Prize Committee awarded Dr. Murray the 1990 Nobel Prize in Physiology or Medicine. Dr. E. Donnell Thomas, a co-recipient of the award, was simultaneously recognized for developing bone marrow transplantation as a treatment for leukemia.

A medical breakthrough...

Organ transplantation medicine initially focused on the treatment of

life-threatening diseases, including kidney, heart, lung, and liver failure. With recent innovations in composite tissue transplants, including face and limb, transplantation medicine is evolving to expand its focus to the repair of functional deficits that are not life threatening but do significantly impact quality of life. Uterus transplantation is an example of the new era of using transplants to repair functional deficits. The clinicians and patients involved in these innovative programs are courageous pioneers opening new vistas and helping to realize previously impossible dreams. In our time, many stakeholders are likely to conclude that uterus transplantation is a

surgical folly. However, I predict that our children will conclude that uterus transplantation represents a medical breakthrough. ☺

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Instant Poll



You have been assigned to a hospital clinical review board to evaluate potential candidates for uterus transplantation. In the cases below, assume that the women are healthy and psychosocially approved for transplantation. What would you recommend?

A 23-year-old G0 Army sergeant was injured by an improvised explosive device. To save her life, military surgeons removed her uterus, which had been lacerated in the explosion. She requested uterus transplantation to pursue a pregnancy. The Department of Defense has approved her request.

Approve Disapprove

A 30-year-old G0 woman with congenital absence of the uterus is a devout member of a religious community where the tenants of the faith prohibit gestational carriers. Rather than pursue adoption, she is seeking a uterus transplantation to pursue a pregnancy.

Approve Disapprove

A 35-year-old G1P1 had her uterus removed to treat cervical cancer. She has been disease-free for 3 years. She would like a uterus transplant to pursue a pregnancy.

Approve Disapprove

Tell us at rbarbieri@frontlinemedcom.com
Please include your name and city and state.