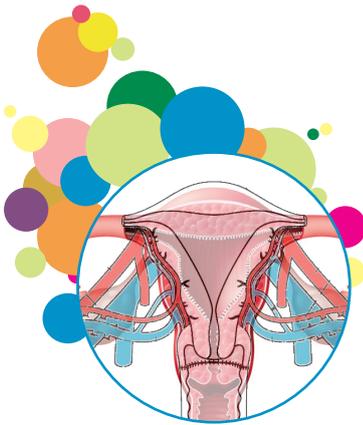


Pioneering uterus transplantation: Breaking new ground in human reproduction



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The first successful uterine transplant is a groundbreaking medical advance that constitutes a milestone in the field of human reproduction. The surgical procedure, which involves the transplantation of a healthy uterus into a female, is considered a viable option for women whose uterus is congenitally absent or after hysterectomy, or is severely diseased. This form of infertility is known as AEFI (absolute uterine factor infertility), for which the uterine transplant procedure constitutes a treatment with a high likelihood of success.

Although there are cases of infertility that can be addressed in various ways with ART (assisted reproductive techniques), in cases such as total absence of uterus or failure of implantation or nourishing a fetus to term, all of which are considered forms of UFI (uterine factor infertility), ART may prove unsuccessful. UFI causes are divided into a) congenital, such as uterine agenesis (Rokitansky-Kuster-Hausner syndrome) or uterine hypoplasia and b) acquired, such as fibroids, intrauterine adhesions or previous hysterectomy due to genital tract malignancy, benign diseases or uncontrollable postpartum hemorrhage. These conditions can lead to lifelong infertility, leaving women with surrogacy or adoption as their only options, which nevertheless may often prove unsatisfactory for numerous reasons. Thus, UFI women seem to be the ideal candidates for this cutting-edge surgical procedure.

The number of potential candidates for uterine transplantation is extremely high. In the United States alone in 2005 there were 12,000 women in the reproductive age group of 15-44 years with congenital absence of the uterus (1 / 5,000 newborns). Moreover, 1,000 hysterectomies for every 1 million births were performed immediately postpartum: cesarean hysterectomies are estimated to be performed in 1 out of every 198 cesareans and in 1 out of every 938 deliveries. Furthermore, in 2005 there were over 12,000 women aged 15-44 years with congenital absence of the uterus, at least 8,000 of whom are likely to be interested in conceiving. Moreover, 5,000 hysterectomies are performed every year in women in the age group of 15-24 years due to cancer or benign indications (0.2 / 1,000 women / year), which means that 4,000 women in this age group each year may be interested in conception and therefore in uterine transplant. Radical hysterectomy is considered the only treatment for early invasive cancer, while world-

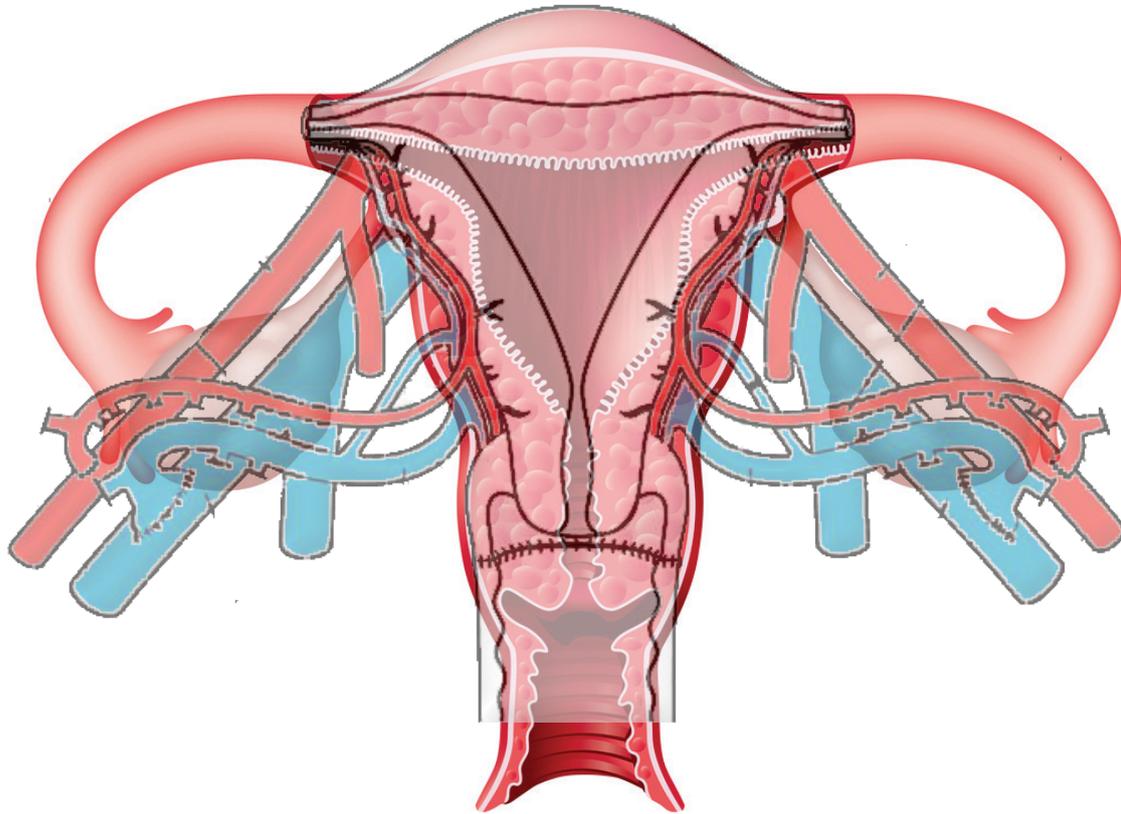


Figure. The uterus transplantation is a complex surgical procedure including extensive vascular dissections in the donor and anastomoses in the recipient

wide almost 70,000 new cases of cervical cancer are diagnosed in the childbearing age group. Currently, over 62 million women in the United States are in the reproductive age range and more than 10 million of these women may have absolute UFI. Even when restricted to women aged 15-34 years, in the United States there are currently about 7 million women who have lost their uteruses due to benign causes or obstetric complications.

Investigation into uterine transplantation began as early as in 1918. In 1964-1966, Eraslan, Hamernik and Hardy at the University of Mississippi Medical Center in Jackson for the first time performed an animal (dog) autotransplantation of the uterus and delivered a pregnancy from that same uterus. However, with the availability of in vit-

ro fertilization starting from 1978, uterine transplantation research was deferred. In 2000, in Saudi Arabia, Wafa Fagee performed a uterine transplant from a 46-year-old hysterectomy patient into a 26-year-old recipient who had undergone obstetric hysterectomy after childbirth; however, the transplanted uterus functioned for just 99 days and ultimately needed to be removed after failure due to blood clotting. In 2010, Diaz-Garcia and co-workers at the Department of Obstetrics and Gynecology, University of Gothenburg in Sweden executed the world's first successful allogenic uterus transplantation in a rat the offspring of which were healthy. In 2011, in Turkey, a team of doctors led by Ömer Özkan at Akdeniz University Hospital in Antalya conducted the world's first uterus transplant from

a deceased donor into a 21-year-old Turkish woman, Derya Sert, who had been born without a uterus. The patient had six menstrual periods post-surgery, a sign of a fully functioning uterus, and became pregnant in April 2013. However, in May 2013 her pregnancy was terminated in its 8th week when doctors failed to detect a fetal heartbeat.

Finally, success came in October 2014 when the first healthy baby was born to a uterine transplant recipient in Sweden and was reported in *The Lancet* by Mats Brännström, Professor of Obstetrics and Gynecology at the University of Gothenburg, and colleagues. The baby boy was born prematurely by cesarean section, at 31 weeks and 5 days, after the mother had developed preeclampsia, and had normal weight for gestational age (1775 gr). The Swedish mother, 36 years old, was born with Rokitansky syndrome (Müllerian agenesis) and had had a uterus transplant performed in 2013 from a live 61-year-old donor. One year after transplantation, the recipient underwent a single embryo transfer, which resulted in pregnancy. She was then given triple immunosuppression (tacrolimus, azathioprine and corticosteroids), which was continued throughout pregnancy. There were three mild rejection episodes, one during the pregnancy, but they were all successfully treated with medication.

The procedure of uterine transplantation starts with the uterus retrieval surgery on the donor followed by three major surgeries on the recipient. First is the transplantation surgery, then in the event of a successful full term pregnancy a cesarean section is performed, and eventually, after completion of childbearing, a hysterectomy needs to be

performed so that the immuno-suppressive treatment can be terminated.

There are certain basic criteria that need to be met for the recipient, the donor and the medical team. First, the recipient should be a genetic female with no medical contraindications to transplantation, have uterine absence and have failed other therapy. She should want a child, be physically and psychologically fit to be a mother and be compliant with treatment and understand the risks of the procedure. As far as the donor is concerned, she should ideally have completed childbearing, have no contraindication to the procedure and be fully responsible and competent to make informed decisions without any kind of coercion. Last but not least, the medical team should belong to an established institution and have provided informed consent to both parties. It is requested that there be no conflict of interests and that anonymity can be protected unless recipient or donor waive this right.

The uterine transplantation procedure is still considered to be in an experimental stage but remains the last resort in cases of AUF1, the only major type of female infertility that is still considered untreatable. However, a number of specialists find the entire procedure ethically questionable bringing to light major clinical and ethical considerations that need to be addressed. The unique aspects of uterine transplantation, which is unlike any other transplantation of organs, call for meticulous analysis and deliberation regarding the clinical and ethical issues raised for the donor, the recipient, the offspring and all other stakeholders involved in this innovative and groundbreaking procedure. ■