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## Uterine transplantation: A step towards creating a nest for future

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### Abstract

Infertility due to the inability of the uterus to carry a pregnancy ranks among the most unresolved issues in reproductive medicine. It affects millions of women worldwide who have congenital or acquired uterine affections, often requiring hysterectomy, and potentially represents a considerable fraction of general infertile population. Patients suffering from severe uterine infertility are currently compelled to go through gestational surrogacy or adoption; both the approaches unfortunately deprive them of the maternal experience of pregnancy and childbirth. Infertility due to the inability of the uterus to carry a pregnancy ranks among the most unresolved issues in Reproductive medicine. It affects millions of women worldwide who have congenital or acquired uterine affections, often requiring hysterectomy, and potentially represents a considerable fraction of the general infertile population.

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Patients suffering from severe uterine infertility are currently compelled to go through gestational surrogacy or adoption; both approaches, unfortunately, deprive them of the maternal experience of pregnancy and birth. Uterus transplantation (UTx) is the only available treatment for absolute uterine factor infertility (AUI), which is caused by either absence (congenital or after hysterectomy) or presence of a non-functioning uterus. Uterus transplantation became a clinical reality after more than 10 years of structured animal-based research. Aside from gestational surrogacy, this procedure is the only alternative for women with AUI to attain genetic motherhood. In the Middle East, North Africa and Turkey (MENAT) region, out of a population of around 470 million, more than 100,000 women of fertile age are estimated to suffer from AUI. Introduction of UTx as an infertility treatment in this region will certainly differ in specific countries from ethical, religious and legal standpoints depending on culture and religion. The aim of this article is to give an overview of the research-based development of UTx and its clinical results up until today as well as to explore how UTx would fit into current infertility treatments, with its existing multifaceted religious perspectives.

**Keywords:** Human, infertility, transplantation, uterus, congenital, hysterectomy, gestational surrogacy, AUI, immunosuppression, amenorrhea

### Introduction

Up to 15% of the reproductive population is infertile, and 3 to 5% of these cases are caused by uterine dysfunction. This abnormality generally leads women to consider surrogacy or adoption. Uterine transplantation, although still experimental, may be an option in these cases. Uterus transplantation is a highly experimental procedure for the treatment of absolute uterine factor infertility (AUI). AUI refers to infertility that is completely attributable to uterine absence (congenital or surgical) or an abnormality (anatomic or functional) that prevents embryo implantation or completion of pregnancy to term. This topic will review the surgeries for the donor and recipient, immunosuppression, and obstetric issues involved in uterus transplantation.

### Cases of Transplants

In 1931 in Germany, Lili Elbe, a Danish transgender woman, died from organ rejection three months after receiving one of the world's earliest uterine transplants.

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With the availability of *in vitro* fertilization in 1978, uterine transplantation research was deferred. In Saudi Arabia in 2000, a uterine transplant was performed by Dr. Wafa Fagee, from a 46-year-old hysterectomy patient into a 26-year-old recipient whose own uterus had hemorrhaged after childbirth. The transplanted uterus functioned for 99 days, but ultimately needed to be removed after failure due to blood clotting. Within the medical community there was some debate as to whether or not the transplant could truly be considered to have been successful. Post-operatively, the patient had two spontaneous menstrual cycles, followed by amenorrhoea; exploratory laparotomy confirmed uterine necrosis. The procedure has raised some moral and ethical concerns, which have been addressed in the literature.

In Turkey, on 9 August 2011, the world's first uterus transplant from a deceased donor was conducted by a team of doctors at Akdeniz University Hospital in Antalya. The 21-year-old Turkish woman, Derya Sert, who had been born without a uterus, was the first woman in history to receive a womb from a deceased donor. The operation, performed by Dr. Ömer Özkan, Dr. Munire Erman Akar and their team, was the world's first uterus transplant surgery gaining long-term function, as evident by the fact that Ms. Sert has had six menstrual periods post-surgery and is said to have a fully functioning uterus. The Turkish medical team who performed the delicate surgery, however, is still cautious about declaring the operation a complete success. "The surgery was a success. But we will be successful when she has her baby", Ozkan said. "For now, we are happy that the tissue is living. On 12 April 2013, Akdeniz University announced that Derya Sert was pregnant. The statement made by the university hospital also added that Ms Sert would give birth by C-section to prevent any complications. On 14 May 2013, it was announced that Ms Sert had terminated her pregnancy in its 8th week following a routine examination where doctors failed to detect a fetal heartbeat.

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 Brännström

The first uterine transplant performed in the United States took place on 24 February 2016 at the Cleveland Clinic. The transplant failed due to a complication on 8 March and the uterus was removed. In April it was disclosed that a yeast infection by *Candida albicans* had caused damage to the local artery compromising the blood support of the uterus and necessitating its removal.

The first uterine transplant performed in India took place on 18 May 2017 at the Galaxy Care Hospital in Pune, Maharashtra. The 26-year old patient had been born without a uterus, and received her mother's womb in the transplant

### First successful pregnancy

In October 2014 it was announced that, for the first time, a healthy baby had been born to a uterine transplant recipient, at an undisclosed location in Sweden. The British medical journal *The Lancet* reported that the baby boy had been born in September, weighing 1.8 kg (3.9 lb) and that the father had said his son was "amazing". The baby had been delivered prematurely at about 32 weeks, by cesarean section, after the mother had developed pre-eclampsia. The Swedish woman, aged 36, had received a uterus in 2013, from a live 61-year-old donor, in an operation led by Dr.

Brännström, Professor of Obstetrics and Gynaecology at the University of Gothenburg

The woman had healthy ovaries but was born without a uterus, a condition that affects about one in 4,500 women. The procedure used an embryo from a laboratory, created using the woman's ovum and her husband's sperm, which was then implanted into the transplanted uterus. The uterus may have been damaged in the course of the caesarian delivery and it may or may not be suitable for future pregnancies. A regimen of triple immuno-suppression was used with tacrolimus, azathioprine, and corticosteroids. Three mild rejection episodes occurred, one during the pregnancy, but were all successfully suppressed with medication. Some other women were also reported to be pregnant at that time using transplanted uteri. The unnamed mother, who received a donated womb from a friend, said that she hoped the treatment would be refined to help others in the future. The transplant is intended to be temporary – the recipient will undergo a hysterectomy after one or two successful pregnancies. This is to avoid the need for her to take immunosuppressive drugs for life with a consequent increased risk of infection

The uterus transplantation research project at the University of Gothenburg, which started in 1999, has been evaluated in over 40 scientific articles. The procedure remains the last resort – it is expensive and not likely to be covered by insurance and, unlike other methods of fertility assistance and treatment, is a relatively new and somewhat experimental procedure, performed only by certain specialist surgeons in select centers, in which the attendant risks of a relatively invasive organ transplant operation, including infection and organ rejection. Some ethics specialists regard the risks to a live donor, as opposed to a post-mortem donor, as being too great, and some find the entire procedure ethically questionable, especially since the transplant is not a life-saving procedure.

### Uterine Transplantation in India

Doctors at a Pune hospital conducted India's first womb transplant on 18<sup>th</sup> May 2017 where they transfer a mother's uterus to her 21-year-old daughter, who is unable to conceive a child. The second transplant was also conducted on the very next day on a 24-year-old woman from Baroda who suffers from Asher man's Syndrome (scar tissue in the uterus) and have receive her mother's womb.

A team of 12 doctors at Pune's Galaxy Care Laparoscopy Institute (GCLI) conducted the procedure on a Solapur resident, who does not have a uterus. The doctors retrieve the uterus at around from the donor and transplant it in recipient. The procedure took 9 hours to do the first uterine transplantation, while the second one took only 7 hours. The surgeons retrieved the uterus using a laparoscopic technique, which was expected to shorten the duration of the procedure.

The hospital has been preparing for womb transplants over the past few months and recipients were made to undergo ovulation stimulation through IVF. Frozen embryos are implanted in the womb after transplantation for the couple to conceive. The first two womb transplants were done free although the cost of the procedure is around Rs 7-8 lakhs. According to the doctors the transplantation is not known to harm the recipient or the baby despite the use of anti-rejection drugs (immuno-suppressants) and the multiple surgeries involved.

Both the recipients will be able to conceive using in-vitro fertilization (IVF) and have children. Both donor and recipients undergo screening procedure post which the uterus is retrieved and transplanted in the recipient, who undergoes three surgeries. If the recipient conceives, she will deliver the baby through Caesarean-section and has to take immuno-suppressants for the rest of her life to prevent rejection of the donor uterus.

The Maharashtra directorate of health services granted Galaxy Care Laparoscopy Institute (GCLI) the license to carry out womb transplantation for five years after inspecting its facilities in April 2017. The hospital decided to go ahead for the procedure after they obtained final approval from district level committee at government run Sassoon hospital.

Besides GCLI, Bangalore-based Milann International Institute for Training and Research in Reproductive Health has also received approval from Indian Council of Medical Research for womb transplantation on two women, but no dates have been announced yet. The surgical team who conducted the transplant went to Sweden to learn about the transplantation procedure before practicing on human cadavers in Germany and the US.

### Procedure

Uterine transplantation starts with the uterus retrieval surgery on the donor. Working techniques for this exist for animals, including primates and more recently humans. The recovered uterus may need to be stored, for example for transportation to the location of the recipient. Studies on cold-ischemia/perfusion indicate an ischemic tolerance of more than 24 hours

The recipient has to look at potentially three major surgeries. First of all, there is the transplantation surgery. If a pregnancy is established and carried to viability a cesarean section is performed. As the recipient is treated with immuno-suppressive therapy, eventually, after completion of childbearing, a hysterectomy needs to be done so that the immuno-suppressive therapy can be terminated.

The uterine transplant is the surgical procedure whereby a healthy uterus is transplanted into an organism of which the uterus is absent or diseased. As part of normal mammalian sexual reproduction, a diseased or absent uterus does not allow normal embryonic implantation, effectively rendering the female infertile. This phenomenon is known as absolute uterine factor infertility (AUI). Uterine transplant is a potential treatment for this form of infertility.

### Ethical consideration

Aside from considerations of costs uterine transplantation involves complex ethical issues. The principle of autonomy supports the procedure, while the principle of non-maleficence argues against it. In regard to the principles of beneficence and justice the procedure appears equivocal<sup>[9]</sup>. To address this dilemma the "Montreal Criteria for the Ethical Feasibility of Uterine Transplantation" were developed at McGill University and published in *Transplant International* in 2012<sup>[9]</sup>. The Montreal Criteria are a set of criteria deemed to be required for the ethical execution of the uterine transplant in humans. These findings were presented at the International Federation of Gynecology and Obstetrics' 20th World Congress in Rome in October 2012. In 2013 an update to "The Montreal Criteria for the Ethical Feasibility of Uterine Transplantation" was

published in *Fertility and Sterility* and has been proposed as the international standard for the ethical execution of the procedure

The criteria set conditions for the recipient, the donor, and the health care team, specifically:

1. The recipient is a genetic female with no medical contraindications to transplantation, has uterine absence that has failed other therapy, has "a personal or legal contraindication" to other options (surrogacy, adoption). It is asked that she wants a child, is suitable for motherhood, psychologically fit, likely to be compliant with treatment, and understand the risks of the procedure.
2. The donor is a female of reproductive age with no contraindication to the procedure who has concluded her childbearing or consented donating her uterus after her death. It is asked that there is no coercion and the donor is responsible and sound to make informed decisions.
3. The health care team belongs to an institution that meets Moore's third criterion regarding institutional stability and has provided informed consent to both parties. It is asked that there is no conflict of interests, and anonymity can be protected unless recipient or donor waives this right.

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