Current status of uterus transplantation in primates and issues for clinical application

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Objective: To clarify the current status of uterus transplantation (UT) and the medical, ethical, and social problems surrounding UT.
Design: Systematic review.
Setting: Not applicable.
Patient(s): Mainly nonhuman primates and humans.
Intervention(s): Not applicable.
Main Outcome Measure(s): A systematic search of Pubmed with the terms "uterus/uterine transplantation" was performed for English-language articles to review the current status of UT and issues associated with its clinical application, with a focus on nonhuman primate and human studies on UT.
Result(s): The first UT procedure in humans was conducted for a patient with absolute uterine infertility in Saudi Arabia in 2000. The transplanted uterus was removed after 99 days owing to prolapse and necrosis. That attempt led to a greater focus on basic UT experiments in animal models, including nonhuman primates. The subsequent accumulation of basic data has led to performance of UT in humans by groups in Turkey and Sweden. However, there has yet to be a pregnancy or delivery after allo-UT in primates. Moreover, there are many medical, ethical, and social problems that require examination before clinical application.
Conclusion(s): Clinical application of UT has just begun, but more basic data are needed and medical, ethical, and social problems require thorough discussion before clinical application. (Fertil Steril® 2013;100:280–94. ©2013 by American Society for Reproductive Medicine.)
Key Words: Uterus transplantation, surrogacy, uterine factor infertility, Mayer-Rokitansky-Küster-Hauser syndrome

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In 1978, Robert G. Edwards, Patrick Steptoe, and coworkers produced the world's first child (Louise J. Brown) by in vitro fertilization (IVF) (1). Subsequently, many infertile patients have had children using assisted reproductive technology (ART). The International Committee for Monitoring Assisted Reproduction Technology of the European Society of Human Reproduction and Embryology estimated that ~5 million children were born with the use of ART up to 2011. The first birth in Japan by IVF occurred in 1983, and 2.7% (~30,000) of all births were due to IVF in 2010 (2), indicating that many infertile patients have received benefits from ART. However, patients with uterine-factor infertility (UFI) are unable to conceive a child because their uterus is absent or nonfunctional. Such women may have options of gestational surrogacy and adoption; however, gestational surrogacy is not

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approved in many countries (3–6). Therefore, uterine transplantation (UT) is an important potential option for women with UFI (7–13). This approach has been studied in animal models (14–17), including nonhuman primates, and in humans (18, 19). Here, we summarize the current status of UT and the tasks required to promote its clinical application.

SEARCH STRATEGY

A systematic literature search in Pubmed was performed with the keywords "uterus transplantation" OR "uterine transplantation." A manual search of the bibliographies of relevant papers was carried out to identify additional studies for possible inclusion. Articles written in a language other than English were excluded from this review.

CURRENT CONDITIONS OF PATIENTS WITH UTERINE-FACTOR INFERTILITY

The World Health Organization defines infertility as a disease resulting in a failure to conceive after ≥ 1 year of unprotected intercourse (20). There are various causes of infertility and many are treatable with the use of ART; however, the prevalence of UFI is 3%–5% in the general population (21), and this condition remains untreatable. UFI is classified into congenital and acquired UFI. The congenital type includes Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, uterine hypoplasia, and uterine malformation; the incidence of MRKH syndrome is 1 per 4,500 women (22, 23). Acquired UFI is caused by hysterectomy due to malignant uterine tumor, benign disease (including leiomyoma and adenomyosis), postpartum hemorrhage, and loss of fertility due to adhesion in the uterus in Asherman syndrome. The major cause of absolute UFI is hysterectomy due to uterine fibroids (17). In the United States, one-half of patients in IVF surrogate programs are women who have undergone hysterectomy (24). There has also been an increase in juvenile malignant uterine tumor, and patients aged ≤ 40 years old now account for $>30\%$ of cases (25, 26). Uterine malignancy frequently requires hysterectomy, but it may be treatable with trachelectomy and high-dose medroxyprogesterone acetate therapy for fertility preservation (27–29). These women can not deliver a child and have limited options of adoption and gestational surrogacy. Furthermore, UFI may cause decreased mental, physical, and social quality of life (QOL) because the patient can not have a baby herself (30), which may result in loss of female identity.

CURRENT CONDITIONS OF UTERUS TRANSPLANTATION

First Uterus Transplantation with a Live Donor

Gestational surrogacy is the only option for a woman with UFI to have a genetically linked child. However, there are several problems with gestational surrogacy and the procedure is not permitted in Japan and other countries for similar reasons (3–6). UT may allow women with UFI to deliver a child based on recent advances in organ transplantation, microvascular anastomosis and tissue preservation, improved understanding of the mechanism of immune rejection, and development of immunosuppressive agents. In 2000, the first UT procedure between humans was conducted in Saudi Arabia (18). The recipient was a woman aged 26 years who had undergone hysterectomy 6 years earlier because of postpartum hemorrhage, and the donor was a woman aged 46 years with bilateral ovarian cysts. Menstruation was observed twice after transplantation, but the transplanted uterus was removed after 99 days because of uterine prolapse with signs of necrosis and vascular thrombosis. After the study, it was shown that the donor did not give full informed consent for UT, which has led to criticism of the study (31–33). The group in Saudi Arabia conducted experiments of orthotopic uterine autotransplantation in 16 baboons and 2 goats, but they evaluated only survival of the uterine graft and mid- and long-term vessel patency, which may not represent sufficient data in animal experiments (18).

Basic Studies of Uterus Transplantation

The first transplantation study of female organs was tubal/uterotubal transplantation to treat tubal factor infertility in the 1960s (34). Tubal transplantation achieved pregnancy in animal models (35–37) but resulted in failure to achieve pregnancy in humans (38–40). After that, grafts with the oviduct and uterus, not the oviduct alone, were proposed to maintain blood flow in the oviduct, and basic experiments on UT started (41, 42). The first procedure for surgical isolation of the uterus followed by reanastomosis was developed in dogs (41, 43). Autografts (42, 44–46) and allografts (46–49) were conducted; however, the only immunosuppressive drugs available were azathioprine and cortisone, which were insufficient to prevent rejection. Although appendiceal UT using the appendix for tubal transplantation (50–52) was also tried, tubal transplantation was not required after the birth of Louise J. Brown by IVF in 1978 (1) and studies in this field were no longer conducted. After that, tubal infertility was treatable; however, uterine infertility remained untreatable, and the report of UT in humans in 2000 promoted an immediate worldwide increase in UT studies in animal models (53).

UT studies have been performed in many countries, including Sweden, Turkey, Japan, United States, United Kingdom, China, France, Spain, Germany, Romania, and Australia, in mice (54–59), rats (60–67), rabbits (68, 69), pigs (70–74), sheep (75–82), rhesus monkeys (83, 84), cynomolgus monkeys (85–87), and baboon (88–90) (Table 1). Pregnancy and delivery after allograft with the use of immunosuppressive agents have been shown in some animals (63, 81). The objective of UT differs from reconstruction of organ function in other solid organ transplantation, because the goal is to have a healthy child. The ethical guidelines of the International Federation of Gynecology and Obstetrics indicate that adequate studies in large animals, including primates, should be conducted before clinical application of UT in humans (21). UT studies in primates provide important information for clinical