REVIEW

Uterine Transplant: a New Option to Restore Fertility

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Abstract

The uterine transplant has been thought of as a treatment for women with absolute uterine factor infertility, allowing them to procreate, carry a pregnancy and give birth to genetic children not intended for lifelong use. In recent years, surgical techniques for donor sampling and uterine transplant have evolved, reducing complications that, along with proper immunosuppressive treatment, reduce the chances of rejection and improve obstetric outcomes, leading to increased live births. Pregnancy can be obtained by embryo transfer after ensuring that the graft is stable. Not being a life-saving transplant, after birth, the uterus can be kept for a new pregnancy, or a hysterectomy can be performed.

Keywords: uterus transplant, solid organ transplant, absolute uterine factor infertility, immunosuppressive reatment.

Rezumat

Transplantul uterin a fost conceput ca un tratament pentru femeile cu infertilitate absolută a factorului uterin, permițând să procreeze, să aibă o sarcină și să dea naștere copiilor genetici, nefiind destinat utilizării pe tot parcursul vieții. În ultimii ani, tehnicile chirurgicale de prelevare a donatorilor și transplantul uterin au evoluat, reducând complicațiile care, împreună cu tratamentul imunosupresor adecvat, reduc șansele de respingere și îmbunătățesc rezultatele obstetricale, ducând la creșterea ratei de nou-născuți vii. Sarcina poate fi obținută prin transfer de embrioni după ce ne asigurăm că grefa este stabilă. Nefiind un transplant vital, uterul poate fi păstrat după naștere pentru o nouă sarcină sau poate fi efectuată histerectomia.

Cuvinte cheie: transplant uterin, transplant de organe solide, infertilitate absolută a factorului uterin, tratament imunosupresor.

INTRODUCTION

The uterus is the female reproductive organ in which the implantation of the developing embryo (blastocyst) and the development of the fetus until birth takes place. Conception and pregnancy are affected by uterine factors in 1 in 500 women of reproductive age and may be secondary to the uterus's absence or anatomically and physiologically dysfunction. Absolute uterine factors infertility is caused by either congenital factors (Mayer Rokitansky-Küster-Hauser syndrome, complete androgen insensitivity syndrome, uterine malformations) or acquired factors (hysterectomy, Asherman syndrome, radiation damage)[1,2]. In patients with cervical and endometrial cancer, uterine infertility may occur as a result of hysterectomy or radiation therapy that causes endometrial atrophy and prevents embryo implantation[3,4]. This diagnosis affects a woman's quality of life, causing depression, loss of identity, and low self-esteem[1].

If until recently, women with absolute uterine infertility could become parents only through surrogacy or adoption, they can have genetic children through uterine transplant. Uterine transplant restores anatomical and reproductive function and thus gives women the opportunity to conceive, experience pregnancy, and give birth[1,5].

The first birth of a human fetus following a uterine transplant was in 2014 in Sweden[6]. To date, at least 80

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uterine transplants with over 40 newborns have been reported worldwide[7].

Regarding uterine transplants, there are raised ethical issues such as the values of reproductive autonomy, gestational parenting, non-maleficence, dignity, benefice, justice, and the health of newborns. It is recommended that surrogate adoption and motherhood be more valued, but taking into account personal, religious, and cultural values. In some countries, there are legal issues, with surrogacy being banned by law. Although a high-risk procedure, 97.5% of women prefer to have a uterine transplant to become a parent at the expense of surrogacy or adoption[1,6].

Before transplantation, the correct selection of donors and recipients is important in evaluating the risk-benefit ratio of uterine transplants. Psychological evaluation is also performed, and complex information about the surgery and possible complications is provided. Donor approval is required by applicable law in each country[8,9]. Thus, their health is assessed, including blood group compatibility and human leukocyte antigen (HLA) testing for HLA mismatch and the presence of HLA antibodies. A multidisciplinary team of specialists in gynecological and transplant surgery, anesthesia, internal medicine, immunology, reproductive medicine, psychosomatic medicine, radiology, and pathology are required to perform the transplant and postoperative follow-up[10].

Surgery for both the donor and the recipient is complex and prone to complications, but in most cases, the evolution is good[11].

Pregnancy is obtained by embryo transfer, a high risk of complications burdens the evolution, and the birth is recommended by cesarean section. After the birth, depending on the woman's reproductive desire, the immunosuppressive treatment can be continued for a new pregnancy, or the hysterectomy can be performed with the removal of the graft and the cessation of the immunosuppressive treatment[5,11]. Uterine transplant is not a transplant to save a woman's life but only to restore anatomical and functional normalcy, and its success is measured by the birth of a healthy child[5,12] and the quality of life experienced by those involved[13]. In the future, the success rate of uterine transplant could be improved by creating a bioengineered uterus with the ability to self-regenerate and repair, thus eliminating the inherent risks of extensive surgery and immunosuppressive therapy[14].

In this article, we wanted to present the surgical technique for both the donor and the recipient, the post-transplant management with immunosuppressive treatment, the therapeutic attitude towards the complications that may occur, the patient's supervision, and the evolution of the pregnancy.

UTERUS DONOR

After knowing the risks and benefits involved, the donor must decide to donate voluntarily[10]. Uterine donors can be living or deceased, young or menopausal women who gave birth or not. In the case of the deceased donor, a brain-dead donor with cardiac activity, the donation decreases the complexity of the surgical procedure and the general risks without any psychological implications[6,15,16,17]. Instead, the inconveniences in the case of the deceased donor are related to the limited preoperative evaluation with an incomplete medical history, lack of intervention planning, and the appearance of ischemia-reperfusion[15,18]. Better results have been shown for living donors[19].

In the case of menopausal women, before surgery, an essential condition is the initiation of regular menstruation through hormone replacement therapy to highlight menstrual function and increase blood flow through the uterine arteries[6,20,21].

Preoperatively, it is recommended to evaluate the uterus by ultrasound, high-resolution magnetic resonance imaging, and computed tomography angiography. These are necessary to assess the diameters of the uterine arteries and veins and rule out stenoses or vascular calcifications that would decrease the procedure's success[10]. Likewise, it is essential to exclude precancerous lesions of the uterus, pathologies that can affect fertility (endometrial polyp, adenomyosis), or uterine surgery[6,18].

The surgical technique involves harvesting the uterus, cervix, supporting ligaments, cutting the vagina 10-15 cm below the vaginal fornix, and carefully dissecting the uterine vessels and internal iliac arteries to the origin to avoid injury. Thus, the deep uterine arteries and veins, the distal portion of the internal iliac arteries and veins, and sometimes the utero-ovarian veins are removed along with the uterus. In addition, the fallopian tubes will be removed but will not be transplanted to avoid a possible occurrence of ectopic pregnancy. The ovaries are left in situ to the donor. The removed graft is treated with heparinized saline, then with a special solution for organ preservation instead; the inconveniences in the case of the deceased donor are related to the limited preoperative evaluation with an incomplete

medical history, lack of intervention planning, and the appearance of ischemia-reperfusion. The duration of the uterine removal operation is between 9 and 13 hours, usually without intraoperative complications and with low blood loss (100 ml)[10,20,21]. If the ovarian vein is removed, it may be necessary to perform unilateral ovariectomy[10].

Due to extensive surgery, postoperative complications are found in one in ten donors and are often secondary to genitourinary tract lesions (ureteric lacerations or thermal injuries, ureterovaginal fistula) or vaginal cuff dehiscence and may require surgical repair[10,20,21].

To reduce donor morbidity, the surgical technique has evolved, with the use of robotic surgery and removal of the ovarian vein instead of the uterine vein, the dissection being less risky[22].

UTERUS RECIPIENT

Preoperatively it is recommended to evaluate the pelvis by computed tomography to exclude calcifications in the iliac arteries[10].

The surgical technique initially involves bilateral dissection of the external iliac pedicles followed by an end to side vascular anastomoses with the internal iliac pedicles of the graft, placed in an orthotopic position, ensuring an adequate uterine infusion. After performing the vascular anastomoses intraoperatively, the blood flow is checked by Doppler ultrasound and the flow meter with transit time. If no flow is present, vascular reanastomosis is required. Subsequently, the vaginal arch of the bladder and rectum is dissected. A vagino-vaginal anastomosis is performed, and the uterus is fixed on the round and sacrouterine ligaments and paravaginal connective tissue. The peritoneum of the bladder on the uterine graft is sutured to that of the recipient to supplement the structural support[5,10,20]. The recipient's fallopian tubes, if present, are not anastomosed to the uterus due to the increased risk of necrosis and abscess[23]. In patients with Mayer Rokitansky-Kuster-Hauser syndrome, neovaginoplasty is required a few years before uterine transplant. Uterine transplant is not recommended for patients with intestinal neovaginoplasty due to the risk of infection during immunosuppressive treatment[10].

The duration of the operation for transplanting the uterus is between 4 and 8 hours, with an average blood loss of 150-500 ml[10,20]. The most common intraoperative complications are acute blood loss, anemia, and bladder damage[5].

It is important to monitor blood flow through the vessels in the first days postoperatively to identify immediate complications such as thrombosis of the uterine pedicles that require removal of the graft[10,20]. Sometimes, at 1-3 months postoperatively, uterine infection with uterine or pelvic abscess and even sepsis can occur. These complications require a hysterectomy to remove the graft[20,24]. Clinical signs suggestive of uterine infection or graft rejection are fever, pelvic, abdominal pain, abnormal vaginal discharge, or discolored cervix[6].

In most cases, the uterus is viable, the postoperative evolution is good, the endometrial function returns to normal, and menstruation resumes after 3-6 weeks, becoming regular after about 6 months[20,24].

IMMUNOSUPPRESSIVE TREATMENT

After uterine transplantation, immunosuppressive therapy is required to prevent graft rejection. Induction of immunosuppression with anti-thymocyte globulin (ATG) is preferred, followed by regimens with drug combinations such as tacrolimus, mycophenolate mofetil, and prednisolone. Cyclosporine may be used instead of tacrolimus for better tolerability of treatment[10,12].

Monitoring during treatment is important to identify immunodepression-related complications. In the first 6 months after transplantation, there are more frequent infections associated with Cytomegalovirus (CMV), Pneumocystis carinii or jirovecii, Toxoplasma gondii, Listeria or Aspergillus[25,26,27]. Thus, during immunosuppression, infectious prophylaxis for Pneumocystis is recommended by administration of cotrimoxazole for 6 months, and CMV infection is prevented by the administration of valganciclovir for 3-6 months in the absence of antibodies[10].

After transplantation, the recipient should have a frequent gynecological examination, a transvaginal and Doppler ultrasound, eosinophil count, CMV DNA monitoring, cervical bacterial culture, and ectocervical biopsy with histopathological examination to detect rejection of the transplanted uterus. An abundant watery vaginal discharge is the main manifestation that can occur. It is important to monitor the number of eosinophils every 1-2 weeks, as their growth means immune activation and early cell rejection. Histological signs of rejection are the identification of ulceration and infiltrate of mixed inflammatory cells rich in plasma cells, In these cases, an endometrial biopsy can be performed with the evidence of a diffuse necrotic endometrium. Thus, in the first month postoperatively,

the evaluation is done twice a week, then every 2 weeks until six months after the transplant, later monthly[1,6,10,18]. During pregnancy, one to three cervical biopsies are recommended in the first and second trimesters to show signs of rejection[5,10]. CMV DNA monitoring is mandatory because CMV infection in solid organ transplant patients is associated with high rejection rates, graft loss, and even patient death[28].

When planning a pregnancy, mycophenolate mofetil is replaced 6 months before embryo transfer with azathioprine which is non-teratogenic[1,10]. During pregnancy, immunosuppressive therapy consists of taking tacrolimus alone or combined with azathioprine and prednisolone. They are safe without causing fetal malformations, but with the risk of premature birth and low birth weight pregnancy, the risk is also determined by maternal status[10,29]. The duration of immunosuppressive therapy should not be prolonged to reduce the side effects[20]. Potential side effects include tacrolimus nephrotoxicity, bone marrow toxicity secondary to azathioprine, diabetogenic effect in tacrolimus treatment, and corticosteroids. Patients are monitored clinically and biologically for potential adverse effects of immunosuppressive therapy, including determining tacrolimus and mycophenolate mofetil concentrations in the blood[6].

Even in pregnancy, episodes of light rejection of transplantation can be treated with corticosteroid boluses. The treatment of severe episodes of rejection outside of pregnancy is managed with aggressive immunosuppressive regimens that act at the cellular and humoral level, while in pregnancy, the only option is the administration of corticosteroids in high doses[10,18,20]. After the birth of one or two children, a hysterectomy can be performed, with cessation of immunosuppressive therapy, thus reducing the secondary risks of infection or neoplasia[1].

OBSTETRIC OUTCOMES

To prevent the negative effect of hormonal treatment on graft function, it is recommended that ovarian stimulation, oocyte retrieval, and embryo cryopreservation be performed before uterine transplantation[1,10].

At least 3 months after transplantation, when the patient is physically recovered, vascular anastomoses are healed, normal menstruation is established, complete CMV prophylaxis is administered, in the absence of histopathological evidence of uterine rejection, and under non-teratogenic immunosuppressive therapy, embryo transfer can be performed[6,30,31]. IVF procedures with a single euploid blastocyst implantation are preferred to avoid additional risks inherent in multiple pregnancies[1,10]. Pre-gestational testing for aneuploidy may also be considered to reduce the risk of miscarriage[32,33]. If endometrial preparation is required for embryo transfer, transdermal administration of estrogen is preferred because oral bioavailability may be decreased due to hepatic enzyme induction secondary to immunosuppressive therapy[23].

Pregnancy is considered high risk and requires close monitoring every 2-3 weeks by experienced obstetricians, maternal-fetal, and transplant specialists to assess fetal growth, biophysical profile, uterine and umbilical arterial Doppler, as well as to identify acute rejection and measure the levels of immunosuppressive drugs[1,5,30].

Patients with kidney, liver, or heart transplants are not at increased risk of allograft rejection during pregnancy[34]. Blood flow through the uterine arteries is usually normal to low range throughout pregnancy, which may be secondary to the absence of constricting mechanisms of the denervated uterine graft[6]. Miscarriage can also occur, with the main cause being obstruction of blood flow leading to venous congestion and enlargement of the uterus[35,36]. Ozkan et al. reported the premature birth of a live fetus after 5 miscarriages after performing an anastomosis between the utero-ovarian vein and the left ovarian vein with the saphenous vein graft to remove the vascular obstruction[35].

Spontaneous or iatrogenic prematurity and its implicit effects on the fetus may occur more frequently in women with uterine transplantation[1]. Solid-organ transplantation and IVF increase the risk of complications such as preterm birth, small for gestational age or low birth-weight fetuses, perinatal mortality, and oligohydramnios[10,23,35]. Also, an increased risk of hypertension in pregnancy or preeclampsia is most likely in women with uterus transplants due to IVF, immunosuppressive therapy, and old age of the uterus[6]. A complicated pregnancy with a central placenta with abnormal adhesion (accreta) has also been reported[18]. Cases of cervical incompetence, gestational diabetes, fetal intrauterine demise, and placental abruption have also been reported[5].

The delivery is performed by low-transverse cesarean section after midline skin incision at 37 weeks in the absence of maternal or fetal complications. Cesarean section is preferred because the effects of uterine contractions on vascular anastomoses are unknown[1,5,16].

After birth, depending on the patient's reproductive desire and the condition of the graft, a hysterectomy

can be performed, or immunosuppressive treatment can be continued for a new embryo transfer in the future, after at least 6 months[1,5,6].

TRANSGENDER WOMEN AND UTERINE TRANSPLANTATION

Although uterine transplantation is currently used only in women with female infertility, it may be a fertility option in transgender health care in the future. Jones et al. in a cross-sectional study of 182 transgender women in uterine transplant, found that 88% would like to menstruate, 94% want to be able to conceive and give birth in the future, and 99% they would be happier if they did this intervention, which would make them more feminine and improve their quality of life. In addition, 90% would consider a vaginal transplant to improve their sexual experience[21].

In the case of transgender women from male to female, hormonal variations, pelvic anatomy, and lack of vaginal mucosa can complicate the evolution of uterine transplantation[21,37]. This has legal barriers, with embryo transfer and pregnancy being prohibited for a person who is not born a woman[38]. Uterine transplant in transgender patients is currently theoretical, with no reported cases in the literature, so the success of a pregnancy and fetal outcome is unknown.

CONCLUSIONS

Uterine transplant is a breakthrough in medicine and aims to restore fertility in women with uterine infertility, allowing them to conceive and give birth. It currently involves extensive surgical technique, appropriate immunosuppressive therapy, and careful monitoring to successfully achieve a pregnancy and improve quality of life. In the future, the goals for uterine transplant are to perform a uterus by bioengineering, transplant in cancer patients with post-therapeutic uterine lesions, and transgender patients.

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