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SPECIAL ARTICLE

Medical and ethical considerations in uterus transplantation

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ABSTRACT

Transplanting a uterus has unique characteristics, since a successful outcome is represented only by the birth of a viable healthy child. For this reason, critical issues in this type of transplantation differ profoundly from those of other solid organs and, beside a functioning uterus, involve 3 additional steps. First, at the time of implantation, the quality of embryo is tested by specialized decidual cells surrounding the implanting embryo; such testing is aimed at allowing the development of a normal embryo. Second, from early gestation onward, blood supply to the uterus increases from 45 to 750 mL per minute. Vascular anastomoses should support such a marked increase in blood flow. Third, full transformation of spiral arterioles in the placental bed is required to direct 75% of the uterine blood flow to the intervillous space. Unfortunately, no suitable animal model is available for experimentation. Three overarching ethical issues must be considered. Should organ transplant be conducted when it is not absolutely necessary as a life-saving or quality-of-life-saving measure? To what extent should medicine delimit its potential in spite of societal desires? Should society demand from medicine the application of whichever technology can be developed and, if so, to what extent?

1. Introduction

The science of transplantation started with the first successful human organ transplant—a kidney—by Murray [1] in 1954, followed by the transplant of a pancreas by Lillehei [2] in 1966, a liver by Starzl [3] and a heart by Barnard [4] in 1967, and bone marrow by Good [5] in 1968.

Since this pioneering work, much knowledge has been acquired and the practice of transplantation today involves cell lines, tissues, organs, and structures [6]. Progress in immunosuppressive treatment reduced the incidence of acute rejection but not the frequency of chronic immune damage [7]. Further progress requires clarification of elusive mechanisms involved in organ and bone marrow cell engraftment, rather than the development of ever-more potent immunosuppressive agents [8]. Recently, it was proposed that the same mechanisms exist for both types of transplant, consisting of a response of "donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion" [9]. In other words, reciprocal tolerance induction is the reason human leukocyte antigen matching is not essential for organ transplantation [8].

Today, the main goal of researchers in transplantation is to induce the type of specific unresponsiveness labeled "full tolerance" toward the donor. This is usually not obtained at the clinical level; only some patients who have discontinued their medication appear to have developed tolerance and any challenge to the immune system—such as a mild infection—can easily break the equilibrium and cause major problems [7]. For the time being, it seems realistic to aim for a state of "almost tolerance," where minimal immunosuppression will be required [10].

Given the present situation, organ transplantation should not be conducted when it is not absolutely necessary as a life-saving or quality-of-life-saving measure. Clearly, transplanting a uterus does not fall into either category, making it mandatory to discuss its advisability before and apart from its feasibility.

In the field of transplants, there are specific ethical considerations to take into account, especially in uterus transplantation: the extent to which medicine should facilitate risky surgery for non-life-threatening purposes; patient autonomy and individual/social acceptance of involuntary childlessness; informed consent and the limits of its application; the existence and ethical acceptability of alternative solutions such as surrogate mothers or adoption; and issues of personal identity of both the donor and the recipient.

2. Transplanting a uterus

In a climate of increasing popularity and feasibility of transplants, it was inevitable that attention would focus on the reproductive tract. Allotransplant of ovaries poses almost unchallengeable obstacles, and successful attempts have been obtained only with frozen [11] or fresh [12] autotransplants, whereas replacing a muscular structure such as the uterus has been deemed possible for years.

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At present, 3 reports on uterus transplantation in humans have been published. The first was on the partially successful (medically speaking) uterus transplantation from a living donor carried out in 2000 by a team led by Wafa Fageeh. The recipient, a 26-year-old woman, had lost her uterus at age 20 owing to postpartum hemorrhage; the donor, a 46-year-old woman, had undergone surgery for multiloculated ovarian cysts. The transplant patient had 2 episodes of withdrawal bleeding upon cessation of hormonal therapy, then developed acute vascular thrombosis 99 days after transplantation, when hysterectomy became necessary.

The intervention received much media attention, including harsh criticism. In *The Lancet*, a negative comment focused on the alleged official complaint lodged by the donor's family against the medical team [13]. Following an investigation, accusations were deemed unfounded and the journal issued a formal apology [14]. This led to the publication of the results in 2002 [15].

This case highlighted some of the major technical and ethical issues involved in transplanting a uterus. The presence of acute thrombosis in uterine vessels, with resulting infarction, at macroscopic and microscopic histopathologic examination is of paramount importance. This seemed to have been caused by inadequate uterine structure support, possibly leading to tension, torsion, or kinking of the connected vascular uterine grafts [13].

The second report involved 2 postmenopausal donors and their respective daughters (both in their 30s) as recipients [16]. One of the recipients was born without a uterus and the other had her uterus removed because of cervical cancer. Surgery was carried out without complications and the medical team plans to follow the patients closely for a year, during which time they will be given immunosuppressive therapy. The plan afterwards is for the 2 recipients to attempt conception via in vitro fertilization (IVF); after 1 or 2 pregnancies, the uteruses will be removed so that the women will no longer require immunosuppressive treatment.

The third attempt was reported by a team led by Omer Ozkan [17] who, over a 2-year period, selected 3 candidates from 10 women with Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome; the women previously underwent vaginal reconstruction surgery and were informed of available treatment choices, including gestational surrogacy.

Patients and their families received detailed information on the possibility that pregnancy may not be achieved; on risks and complications of transplantation surgery and immunosuppressive treatment; on possible pregnancy complications under immunosuppression; and on the potential need for subsequent hysterectomy. With full approval from local transplantation and institutional review boards, a 21-year-old woman with MRKH syndrome who had undergone vaginal reconstruction with jejunal segment was selected for the first attempt. Formal consent included legal contracts explaining possible complications of the non-life-saving, potentially life-threatening procedure; the immunosuppressive protocol; and possible pregnancy-related risks. Before surgery, the woman underwent 2 IVF cycles, which yielded 8 grade-1 embryos. The donor was a 22-year-old brain-dead nullipara. The transplantation procedure consisted of orthotopic replacement and fixation of the retrieved uterus, and revascularization via end-to-site anastomoses of both hypogastric arteries and veins to bilateral external iliac arteries and veins. During the recipient procedure, bilateral salpingectomy was performed to prevent possible ectopic pregnancy. The patient had menses 20 days after transplant surgery and has had 12 menstrual cycles since the operation. So far, no pregnancy has been achieved [17].

3. Pregnancy following transplantation

For young women who have undergone transplant of a solid organ, pregnancy represents a relatively common event [18], although only limited information on pregnancy outcome and on guidelines for optimal counseling and clinical management is available [19].

3.1. Pregnancy in recipients of solid-organ transplants

Systematic reviews and meta-analyses [20,21] of pregnancy outcomes in kidney transplant and liver transplant recipients revealed that live birth rates were higher and spontaneous abortion rates were lower among post-kidney transplant patients than among the general US population. Incidences of pre-eclampsia, gestational diabetes, preterm delivery, and cesarean delivery were also higher than among the general US population (Table 1). Pregnancy outcomes were more favorable among women with lower mean maternal ages, and obstetric complications were more common when there were shorter mean intervals between kidney transplant and pregnancy.

The post-liver transplant live birth rate was higher than that of the general US population and similar to the post-kidney transplant live birth rate. The post-liver transplant spontaneous abortion rate was lower than that of the general US population and similar to the rate among kidney transplant recipients. The incidences of pre-eclampsia, cesarean delivery, and preterm delivery were higher than in the general US population and lower than among kidney transplant recipients; mean gestational age and birth weight were significantly higher ($P < 0.001$) for liver transplant recipients versus kidney transplant recipients. These systematic reviews show that successful pregnancies can occur in kidney and liver transplant recipients in the setting of multiple medication exposures. Major risks for the neonate are prematurity and severe growth retardation [22] (Table 2).

3.2. Pregnancy in uterus transplant recipients

In view of preliminary attempts at uterus transplantation where success is measured exclusively by the birth of a healthy child, it is timely to discuss potential risk factors for impaired maternal and fetal outcome in the event of a pregnancy. The topic has already been the subject of discussion [23–25] but several issues require further elaboration.

Selecting the best immunosuppression therapy (i.e. utilizing modern induction therapy) is of paramount importance [26]. Brännström et al. [27] propose using anti-thymocyte globulin to lower the numbers of circulating T-cells, followed by standard triple immunosuppression (tacrolimus/cyclosporine, corticosteroids, and antiproliferative agent). This type of protocol results in 100% graft survival of highly immunogenic composite tissues such as the hand and the face [28].

Several other specific problems exist. First, the quality and plasticity of the vascular anastomoses required for the vital perfusion of the uterus must be severely tested because, in contrast to other solid organs, uterine arteries during pregnancy have to accommodate an increase in blood supply from 45 to 750 mL per minute, representing approximately 25% of the cardiac output at term. Without vascular anastomoses of the highest quality—capable of accommodating such a significant increase in blood flow in a short time—fatal placental ischemia during pregnancy may be unavoidable.

Second, in terms of organ function, Brännström's group [29] demonstrated that successful pregnancies are possible following allogeneic uterus transplantation in rats, yielding normal pregnancy rates, birth

Table 1
Outcome of pregnancy after kidney versus liver transplantation.

	Kidney transplantation[a]	Liver transplantation[b]
No. of recipients	3570	306
No. of pregnancies	4806	450
Live birth, %	73.5 (95% CI, 72.1–74.9)	76.9 (95% CI, 72.7–80.7)
Spontaneous abortion, %	14.0 (95% CI, 12.9–15.1)	15.6 (95% CI, 12.3–19.2)
Pre-eclampsia, %	27.0 (95% CI, 25.2–28.9)	21.9 (95% CI, 17.7–26.4)
Cesarean delivery, %	56.9 (95% CI, 54.9–58.9)	44.6 (95% CI, 39.2–50.1)
Preterm birth, %	45.6 (95% CI, 43.7–47.5)	39.4 (95% CI, 33.1–46.0)

Abbreviation: CI, confidence interval.
[a] Data from Ref. [20].
[b] Data from Ref. [21].