Uterus transplantation in the human: a complex surgical, medical and ethical challenge

Ivo Brosens1,2,* Sadaf Ghaem-Maghami3, and Robert Pijnenborg4

1Catholic University Leuven, Leuven, Belgium 2Leuven Institute of Fertility and Embryology, Leuven, Belgium 3Faculty of Medicine, Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK 4Department of Woman & Child, University Hospital Leuven, Leuven, Belgium

*Correspondence address. E-mail: ivo.brosens@med.kuleuven.ac.be

As discussed in the current issue of this journal, uterine transplantation in the human is becoming a real possibility, and a range of research and ethical criteria have been proposed to regulate its introduction (Del Priore et al., 2012). However, the need to ensure a normal pregnancy outcome will become a major clinical challenge for several reasons. First, the vascular anastomoses of the transplanted uterus will be severely tested during pregnancy. The uterus is indeed not a steady-state organ, such as the liver or kidney, but an organ requiring exceptional vascular plasticity to accommodate a growing fetus. During gestation, blood supply to the uterus increases from 45 to 750 ml/min, representing ~25% of the cardiac output at term. Furthermore, deep placentation in humans involves transformation of a relative small number of spiral arteries into large vessels that provide 90% of uterine blood flow to the intervillous space of the placenta by midpregnancy. Without high-quality vascular anastomoses that can accommodate such a dramatic increase in blood flow in a short space of time, fatal placental ischemia during pregnancy may be unavoidable.

Achieving an adequate level of vascular plasticity in the transplanted uterus remains a major challenge. Autotransplantation in the porcine model using a microvascular anastomotic technique failed because of gradual vessel thromboses (Sieunarine et al., 2006). The sheep appears to be a more successful model as the uterus in this species is relatively small compared to the size of pelvic blood vessels (Dahmkahler et al., 2008). Clearly, it is important to distinguish ischemia-reperfusion and surgical trauma from immunological rejection in the case of allogeneic transplant rejection. Autologous, syngeneic and allogeneic animal models have been very informative in understanding these two major reasons underpinning transplant failure and have enabled the development of surgical techniques that minimize the risk of surgical damage and subsequent thrombosis.

In terms of organ function, Brännström’s group has demonstrated that successful pregnancies are possible following allogeneic uterine transplantation in the rat (Wranning et al., 2011). They reported normal pregnancy rates, birthweights and growth in the offspring of rats with transplanted uteri. Although reassuring, it is prudent not to extrapolate too much from an animal model with a gestation of only 3 weeks (Brännström et al., 2012). Recent studies on primates, including a series of cynomolgus macaques and baboons, have also reported successful transplantations, although no successful pregnancies as yet (Enskog et al., 2010; Mihara et al., 2011; Johannesson et al., 2012; Kisu et al., 2012). It is unfortunate that the animals selected for these studies do not exhibit the same type of deep placentation as humans.

In the previous reported case of human uterine transplantation (Fageeh et al., 2002), T-lymphocyte ratios in peripheral blood and uterine Doppler flow studies were used to monitor organ rejection. Initially, the transplanted uterus appeared viable and well perfused and the patient had two withdrawal bleeds after hormonal treatment. However, ~3 months after transplantation, Doppler ultrasonography demonstrated cessation of uterine blood flow, suggesting occlusion of the uterine arteries. Hysterectomy was inevitable, and histopathologic examination revealed acute thrombosis in the vessels of the uterine body, with resulting infarction. Immunosuppressants were administered pre-, peri- and post-operatively. Taking everything in account, vascular occlusion rather than immune rejection was the cause of graft failure in this case (Fageeh et al., 2002).

In recent cases from Sweden (Hansen, 2012), the donors were the mothers of the recipients, but this does not negate the need for immunosuppressants. A key ethical issue is whether a desire to bear a child outweighs the potentially harmful effects of these drugs on the mother and unborn child. Immunosuppressive drugs have been shown to be deleterious for fetal development in several experimental animal models. In humans, they are associated with an increased risk of miscarriage, prematurity, intrauterine growth retardation and low birthweight, but not with a significant increase in fetal malformation rates (Tordon et al., 2002).

The clinical data on immunosuppressive drugs in pregnancy are often viewed as reassuring, although they do suggest a significant impact on placental formation. Specialist immune cells, including uterine uNK cells, dendritic cells and regulatory T-cells, are essential at the feto-maternal interface, especially for remodeling of the spiral...
arteries. Interference with this process is bound to compromise endovascular trophoblast invasion and transformation of the spiral arteries in the myometrial junctional zone, which in turn predisposes for a spectrum of pregnancy complications, ranging from late abortion, preterm birth, pre-eclampsia, fetal growth restriction and placental abruption (Pijnenborg et al., 1983; Brosens et al., 2011). However, pregnancy is an immune privileged state. With increasing understanding of the mechanism that confers maternal tolerance to placental antigens, it may be possible to reduce or altogether stop immunosuppressive agents during pregnancy.

The method by which a pregnancy is to be achieved is also a point to be considered. It is difficult to know to what extent tubal function will be maintained in the transplanted uterus, and the risk of an ectopic pregnancy may well be high. If IVF is planned, this should probably take place prior to uterine transplantation. Finally, there is a need to define criteria for the quality of the donor uterus (e.g. exclusion of adenomyosis, submucous fibroids, HPV infection or cervical dysplasia) and the health of the receiver (e.g. hypertensive disease and diabetes).

From an ethical perspective, uterine transplantation is intended to enable the birth of a healthy child (Del Priore et al., 2012). Pregnancy and neonatal complications may arguably be less acceptable in uterine transplantation patients than in women who have become pregnant after life-saving organ (e.g. kidney or heart) transplantation. Like any surgical innovation, uterine transplantation must be rigorously assessed. However, clinical application and acceptability will equally lie in obtaining solid evidence of safety in pregnancy and in the long-term well-being of children born after this procedure.

Authors’ roles
I.B. drafted and edited the manuscript. S.G.-M. and R.P. reviewed and edited the manuscript and contributed substantially to the content.

Funding
No external funding was either sought or obtained for this editorial.

Conflict of interest
The authors have none to declare.

References