Uterus transplantation: How far away from human trials?

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Abstract

Uterus transplantation is being developed as a possible future method to treat uterus factor infertility. This commentary gives an overview of the animal research that has been conducted in preparation for human uterus transplantation. In addition, requirements for further specific research activities within the field are identified. It is our prediction that uterus transplantation will be introduced as an experimental procedure in the human within a few years.

Key words: Uterus, transplantation, infertility

Absolute uterus factor infertility is the cause of infertility in 3–5% of all infertile women (1,2). The groups of women who are irreversibly uterus factor infertile are those that lack a uterus or have a uterus that is non-functional in terms of ability to carry a pregnancy. The uterus may be absent due to congenital Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser or MRKH-syndrome) or after a hysterectomy because of cervical cancer, myoma or life-threatening peripartum bleeding. Non-function of the uterus may be due to uterine anomalies, such as bicornuate/unicornuate uterus, large/distorting myoma, intrauterine adhesions or radiation damage (1,2). Gestational surrogacy, to acquire genetic motherhood for uterus factor infertile women, may be an alternative for some (3). However, this procedure is not approved by most societies in the world, including the Nordic countries, because of legal, ethical and/or religious reasons (3). Transplantation of the uterus has been proposed as a fertility treatment for women with absolute uterus infertility who cannot or do not wish to use surrogacy or adoption as a means to form a family and who have a strong desire to carry a pregnancy.

Uterus transplantation would be considered as a quality-of-life-enhancing transplantation and thus be comparable to the newly introduced procedures of transplantsations of the hand (4), face (5) and larynx (6). However, the number of patients who may require uterus transplantation would most likely be far larger (7) than those who would request hand or face transplants.

Introduction of uterus transplantation as an experimental procedure in the human will most likely come within a few years, since several groups around the world, including our group at Sahlgrenska University Hospital in Göteborg, are making preparations along those lines (8). It must be pointed out that there has already been one human uterus transplantation attempt, but this was a failure. Eight years ago, a 26-year-old female, who had previously lost her uterus during an emergency peripartum hysterectomy, received a uterus from a living donor in Saudi Arabia (9). The uterus had to be removed after three months due to massive necrosis of the organ. The cause of the degeneration of the transplant was reported to be vascular thrombosis rather than rejection. The failure of this case, the fact that human uterus transplantation would not be a life-saving-procedure, and that risks have to be taken by several individuals (the uterus donor, the uterus recipient and the prospective child), are facts that support the need for profound research studies in experimental animal models before a new attempt
on a human is made. We initiated our research on uterine transplantation 10 years ago, after the possibility of such a procedure was suggested to us by a young woman who underwent a radical hysterectomy due to cervical cancer.

Several animal models, including the mouse, rat, dog, pig, sheep and non-human primates have been used by us and others to investigate and optimize numerous procedures that apply to a uterus transplantation situation. Aspects that have been looked into in these animal models are surgical techniques for retrieval of the uterus and its vasculature in a uterus donor, sites and techniques for vascular anastomosis, tolerance of the uterus to cold-ischemia and reperfusion, implantation and pregnancy outcome in syngenic (identical tissue type) or auto-transplanted uterus, patterns of rejection in allogenic transplanted uterus, and suitable immunosuppression to suppress uterus rejection after allotransplantation.

The uterus retrieval procedure entails a total hysterectomy with preservation of long vascular pedicles of the uterine arteries and veins. This procedure has been successfully mastered in rodents (10–13), large animals such as the sheep (14,15) and the pig (7,16), as well as in the baboon (our unpublished observations). The procedure is less demanding and longer vascular pedicles can be obtained, when it is not planned that the uterus donor animal will survive the surgery (10,11), a situation comparable to that in a heart-beating but brain-dead multi-organ donor (17).

Sites for vascular anastomosis may be the aorta and caval vein in the event of a multi-organ/cadaveric donor as demonstrated in animal models (10) or the external iliac vessels which have been used in the sheep model (14) and in the baboon (our unpublished observations). When removal of a non-functional uterus is performed as part of a human transplantation procedure, the site for vascular anastomosis could be the uterine artery as also tested in sheep (15) and pig (7,16) uterus transplantation models.

Solid organs and composite tissues show great variation in their tolerance to ischemia in clinical transplantation, with time limits of about 36 hours for the kidney and eight hours for the heart. Damage to the tissue/organs occurs during the cold ischemic time in ice-chilled preservation solution, during the warm ischemic time when the organ is being attached to the recipient, and particularly during reperfusion of the organ by blood in the donor when the transplant is exposed to high oxygen levels. The duration of ischemia of the uterus at transplantation can most likely be up to at least 24 hours, based on studies in vivo in the mouse (12) and in vitro in the human (18).

The potential for implantation of an embryo and pregnancy in a transplanted uterus has so far only been tested in animal models with no rejection. In a uterus transplantation model in the mouse involving syngenic transplantation, pregnancy rate and offspring were similar to controls (11). Pregnancies with live births have also been achieved in the sheep auto-transplantation model (Dahm-Kähler, personal communication).

Rejection of a transplanted uterus will occur in all transplantation situations, except between identical twins, as recently achieved in human ovarian transplantation (19), or if a perfect tissue type and blood group matching exists between donor and recipient. The rejection process of an allogenic transplanted uterus has only been fully studied in the mouse model (13), with results indicating a similar rejection process and time course as for a cardiac allograft. Initial studies have also been performed to suppress rejection by cyclosporine after allogenic uterus transplantation in the mouse (20) and sheep (15), as well as after use of tacrolimus in the sheep (Dahm-Kähler, personal communication). It should be pointed out that there is a vast experience of more than 10,000 pregnancies in organ transplantation patients that have been under immunosuppression during the entire pregnancy. Registry data does not point towards any increased rate of congenital malformations, but an increase in the rate of preterm birth, pre-eclampsia and intrauterine growth retardation has been indicated (21). However, a population-based study of all patients who have delivered children after organ transplantation in Sweden up to and including 2002 (22), showed that the rate of these obstetric complications were similarly increased in pregnancies of these patients before transplantation, strongly indicating that it is not the immunosuppressive drugs per se, but the underlying systemic diseases that are the causes.

Notwithstanding the important research on uterus transplantation that has been done during the last decade, further animal studies should be performed and show success before a new attempt on a human. In our opinion, a high rate of surgical success has to be demonstrated in a non-human primate species, which has a uterine and pelvic vascular anatomy similar to the human. The surgery in the human will most likely be markedly easier than in a non-human primate because of the bigger size of pelvic structures. Moreover, normal pregnancies in allotransplanted uteri have not yet been demonstrated and this should be a requirement. Taking into account the vast experience of pregnancies during immuno-
suppression in the human (21, 22), these studies of implantation, pregnancy and offspring development in an allogenic transplanted uterus may not necessarily have to involve a primate species, but can be in a rodent model. A model such as the rat uterine transplantation model, presented in this issue of the journal, may be very useful since the model shows an acceptable learning curve. The rat also has the advantage of a short gestation, multiple offspring and this species is widely used as an experimental animal in transplantation research. Thus, important general background data concerning immunosuppression and rejection exist for the rat model.

There are also possibilities to perform some preparatory studies in the human. We are presently performing studies of uterine vein anatomy at surgery involving radical hysterectomies. These studies aim to define whether it is possible to obtain long enough vascular pedicles on a uterine specimen so that direct vascular anastomosis onto iliac vessels of the recipient can be achieved, instead of using saphenous grafts as in the failed human uterus transplantation attempt (9). Moreover, further in vitro studies on human uterine specimens, involving tissue or the whole organ, can be performed for studies aiming to optimize organ preservation.

It is important that clinicians, particularly in the fields of obstetrics and gynecology, as well as the public, are aware of the research activities in the field of uterus transplantation, so that the procedure can be discussed and modified before it reaches the clinical stage. All surgical innovations should reach the operating room only after extensive laboratory work aimed at optimizing the procedure and minimizing all the possible risks involved has been carried out. The research on uterine transplantation has come to include all relevant animal models from rodents to non-human primates, but all the key experiments have not yet been done, as stated above. We still predict that uterus transplantation will be introduced as an experimental procedure in the human within two years. Preparations to screen potential patients are already under way (8) at one center in the US, and at that center the plan is to retrieve the uterus from a multi-organ donor (17). Our group is working along the concept of a living donor, which could be a close relative such as the mother. Conception should be through IVF with cryo-preservation of several high quality embryos at a time point well before transplantation, to ensure that fertilization can take place within the couple. Embryo transfer attempts could be performed after a period of 6–12 months post-surgery to allow for healing and for stabilization of the graft, when lower doses of immunosuppressants are needed.

Uterus transplantation should be introduced as an experimental procedure, where the patient, her partner and the donor are informed about the experimental nature of the procedure and the risks involved. The preparation for the procedure, the surgery and the post-transplantation period will need active participation of expertise within several specialized medical fields, such as gynecologic oncology (for uterus retrieval), transplantation surgery, reproductive medicine, high-risk obstetrics, anesthesiology and psychology. An attempt to transplant a human uterus should preferably be performed by a group with vast experience of uterus transplantation in animal models and within a large hospital that has a long tradition in organ transplantation. It is important that the next human uterus transplantation attempts are considered experimental procedures and that maximal groundwork is done to optimize the procedure to become successful in terms of continued health for the uterus donors, the uterus recipients and the children born after transplantation.

References
