INTRODUCTION

The very rapid advancements in assisted reproductive techniques (ART) during the last decades have been driven by a general progress in medical research but also by a great desire of the society to be able to fulfill the basic human need to reproduce. Since the birth of the first IVF-baby in 1978, new techniques such as intra-cytoplasmic sperm injection (ICSI), pregestational diagnosis (PGS) and ovarian cryopreservation have been introduced. The vast majority of infertile couples can now become parents with the aid of new sophisticated treatment modalities. The last hurdle to overcome in the effort to treat infertility is absolute uterine infertility.

The women with absolute uterine infertility are those that either are born with no uterus, women that have lost the uterus through hysterectomy, or women that have a deficient uterus in regards to implantation or pregnancy.

About one in every 4500 girls is born with the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (1). These girls have a total absence of the uterus and the vagina. The MRKH girls develop into female adults, with well functioning sexual life after surgical creation of a neovagina. The causes for hysterectomy in women of fertile age are emergency obstetric complications (uterine atony, uterine rupture), malignancy (cervical cancer, uterine malignancy) or benign uterine disease (symptomatic leiomyoma). Patients with intrauterine adhesions, iatrogenic after curettage or secondary to intrauterine infections, and those with leiomyoma that are large or otherwise distort the uterine cavity do also fall into the group of women with absolute uterine infertility. It is estimated that only in the UK, around 15000 women (3% of infertile women) are infertile due to uterine factor (2).

To treat uterine infertility, the ways to progress would be either to develop techniques for successful transplantation of the uterus from one woman (living or cadaveric donor) to another or to extend in vitro techniques that would allow for fetal development entirely outside the body (ectogenesis). Research on such artificial womb has been ongoing for the last 10 years (3) but it seems that it will be very difficult to develop this methodology further. Uterine transplantation may be a more feasible option to allow for women without a uterus to have their own genetic children, also in the light of that the clinical field of organ
transplantation has progressed from transplantation of vital organs to also include transplantation of non-vital organs such as the hand and the face (4).

There has been one reported case of an attempt to transplant a human uterus. In year 2000, a 26-year-old female that had previously lost her uterus at an emergency postpartum hysterectomy received a uterus from a 46-year living donor that was operated for benign ovarian disease (5). The patient was treated with standard immunosuppressant drugs and the uterus survived for 99 days, when it had to be removed due to signs of massive necrosis. The cause of necrosis was reported to be vascular thrombosis, possibly due to torsion of the vessels of the inadequately fixed uterus or to rejection. It is our opinion that this human trial was performed too prematurely, since very limited animal studies had been conducted by that research group prior to the human trial.

We predict that properly designed research studies in animal models for uterine transplantation will be beneficial in guidance concerning methodology that would be used in a new human trial. Such research studies could involve experiments in relation to surgery of the donor and recipient, immunosuppressant medications and their effects on the mother and fetus, as well as pregnancy and development of offspring. This research field of uterine transplantation has developed rapidly during the last few years and several animal models have been presented. These research studies and some ethical considerations that apply to the field of human uterine transplantation will be discussed in detail below. The present review article will first also briefly summarize the research that was performed 30-40 years ago when uterine-oviductal transplantation was primarily considered as a treatment for the largest group of female infertility, tubal occlusion. With the advent of IVF, this cause of infertility could be circumvented and the research area of uterine transplantation was almost closed.

Past research on uterine transplantation

To our knowledge the first mention about uterine transplantation in the scientific literature is from 1927 (6), reporting scantily described methodology and results in the dog. The experimental work on uterine transplantation was reinitiated in the 1960s and the 1970s, with the research primarily involving autotransplantations (replantations), where the uterus with its appendages was isolated from the animal, taken out for a short period of ischemia and then reintroduced into the same animal. Two principally different modes of securing blood flow to the transplanted uterus were tested. Vascular anastomosis, to achieve immediate reperfusion, and attachment of the uterus to an abdominal surface, to acquire a gradual revascularization through outgrowth of new blood vessels, were examined and compared. Vascular anastomosis, at the level of the internal iliac vessels, was first used in en bloc autotransplantations of the uterus, oviducts and ovaries in the dog (7). Pregnancies were reported in a minority of the transplanted animals. By means of a comparable surgical method, non-pregnant and pregnant uteri of dogs were allogeneic transplanted to both female and male recipients that were immunosuppressed by azathioprine (8). Most of the uteri were found to be necrotic at autopsy several weeks later but a small number were reported to be viable. The variable course of these allogeneic transplants may be explained by differences in histocompatibility disparity between the animals.

Revascularization by omental wrapping (omentopexy) and vascular anastomosis were first compared in the autotransplanted dog model (9, 10), demonstrating necrosis after omentopexy and survival of most uteri after vascular anastomosis. A single study on uterus transplantation in a primate species (rhesus monkey) showed that omentopexy was sufficient to reinitiate blood flow that was enough for resumed regular menstruations but pregnancies were not achieved (11). Viable uterine transplants were also reported in the rabbit (12) and in the guinea-pig (13) after reimplanting the uterus within the broad ligament or to the abdominal wall, respectively. Collectively, these studies from the 1960s and 1970s pointed towards that vascular anastomosis, with an immediate blood flow to the transplanted organ, is needed when transplanting a uterus of larger size.

Current research on uterine transplantation

The research area of uterine transplantation was reinitiated during the start of this century and
several new animal models have been put forward to address important questions. The questions, which will be discussed below, relate to surgical technique including sites of vascular anastomosis, positioning and structural support of the transplanted uterus, cold ischemia and reperfusion injury, influences on pregnancy, rejection mechanisms, and immunosuppression.

**Surgical technique and vascular anastomosis**

The cause for the demise of the graft in the human transplantation trial (5) was most likely related to the surgical techniques of vascular anastomosis and/or fixation of the transplanted uterus, since vascular thrombosis and prolapse of the uterus occurred after around three months. These facts point towards the necessity to improve the surgical technique in animal models prior to a new human case should be performed. The surgical method for harvesting and transplanting the uterus varies with the animal models which have been used. These variations in methodology are due to great inter-species differences in the size and anatomy of the uterus as well as that of the vasculature that feeds and drains the uterus.

All modern research in the uterine transplantation area has focused on vascularization through vascular anastomosis, even though it may be sufficient to rely on revascularization through neoangiogenesis in the smaller-sized animal models that have been used. Several sites for vascular anastomosis have been explored, depending on the size and the specific anatomy of the experimental animal used.

In our initial attempts to develop a suitable small-animal model for research on uterine transplantation we used syngeneic uterine transplantation between F1-hybrids of inbred C57BL/6 x CBA/ca mice (14). The advantage of the mouse as an experimental model in this type of research relates to the vast scientific knowledge about reproductive physiology and immunology of this species, the availability of recombinant mouse proteins and monoclonal antibodies as research tools, as well as the existence of technology for specific gene deletions in the mouse. In the methodology used by us, one uterine horn with the cervix, including the preserved vascular supply and drainage, was microsurgically isolated (14). Because of the small size of the vasculature of the mouse, the vessels had to be preserved all the way up to the aorta and the vena cava (diameters < 1mm) to include vessels of a size that would allow for vascular anastomosis. End-to-side anastomoses on the subrenal parts of the aorta and the vena cava of the recipient mouse were accomplished by suturing, under visualization through a microscope (magnification up to x40), with use of 11-0 sutures. These techniques for surgery and vascularization have later proved to be reasonable successful in this syngeneic mouse model with more than 90% of the transplanted uteri surviving, in the around 60% of the recipients that have survived the major surgery involved. It has to be pointed out that the donor mouse has to be euthanized during the procedure to obtain the vasculature that is necessary.

The rat has also been used as an experimental model for uterine transplantation research. We used a similar transplantation technique but with the anastomosis sites being the common iliac vessels of the organ and the aorta and vena cava of the recipient, in our newly developed rat model (our unpublished results). Another site for vascular attachment has also been used in the rat (15), where the uterus, oviducts and the ovaries were isolated on a vascular pedicle up to the level of aorta and vena cava with anastomosis end-to-side with the external iliac artery and vein.

To attain a large-animal model which would be more suitable for studies of surgical techniques we (16) and others (2) have developed a pig model for uterus transplantation. The large bicornuate pig uterus, with coiled uterine horns up to 1.0m in length, was harvested with transection through the mid-portion of the cervix. The inaccessibility for surgery deep down in the pelvis of the pig, necessitated the sites of vascular anastomosis to be at the mid level of the uterine artery and veins, well distal to their branching from the internal iliac vessels. The size of the uterine vessels of the pig at this level is about 3-4mm (2) and sutures of sizes 6-0 (2) or 7-0 to 9-0 (16) were used. In our hands the greatest difficulty in this surgery was the anastomosis of the uterine veins, due to their thin walls and the problem to visualize the lumen of the vessels during the creation of the end-to-end
anastomosis. This was in spite of that this vascular surgery was performed by the aid of magnifying (x5) lenses. The success rates in the reported autotransplantation experiments in the pig were low (2, 16) and we conclude that it is not a suitable large-animal model for future research on uterine transplantation.

Because of the difficulty experienced with the pig uterine transplantation model we are presently using the sheep as a large animal uterine transplantation model (17). The surgical access to the deep parts of the sheep pelvis is adequate and vascular pedicles can be attained up to the level just distal to the internal iliac artery. Up until now we have only performed auto-transplantations in the sheep model, with the uterus autotransplanted into an orthotopic position. Vascular connections were established by end-to-side anastomosis between the internal iliac artery and utero-ovarian vein of the specimen and the external iliac vessels using 6-0 sutures. The success rate with this auto-transplantation model has been above 85% (17).

The ultimate animal model for uterine transplantation research is a non-human primate model. We have recently initiated experiments in a baboon model, where the uterus and its appendages were surgically removed with a similar technique that is used when performing a radical hysterectomy. The uterus was autotransplanted into an orthotopic position but with vascular connections between the uterine arteries and ovarian veins to the external iliac artery (our unpublished results). The Saudi Arabian group, which carried out the human uterine transplantation attempt, reported briefly in their case report (5) experience with transplantation of the uterus in baboons with end-to-side uterine vessels-internal iliac vessels anastomoses.

The site and technique for an optimal vascular anastomosis that would have to be used in the human is not clear. In the human uterine transplantation case (5), grafts (around 4 cm long each) of the recipient’s saphenous veins were utilized to lengthen the two uterine arteries and four uterine veins that were used. This enabled the uterus transplant to be connected bilaterally to the external iliac arteries and veins by altogether 6 end-to-side anastomoses. It was stated in the case report (5) that thrombosis of the vessels was a major reason for the necrosis. Based on our experience in several animal species (see above), the most difficult part of the surgery is the creation of satisfactory anastomosis on the venous side, and it is likely that the saphenous grafts and the relatively long veins that are created that way are loci for thrombosis formation. An alternative approach for vascular anastomosis in the human, when using a living donor, would be to use a technique that we are currently using in the baboon model. We have simply bisected and sutured the ends of the two uterine arteries to create a larger vessel and a similar procedure has been used on the venous side. These two new vessels could then be attached end-to-side to the external iliac vessels by the same procedure as routinely used in renal transplantation. In the human uterine transplantation situation, harvesting of the uterus could also occur from a multi-organ, heart-beating, brain-dead donor or from a fresh cadaver. In these situations it will be easier to acquire a suitable vascular pedicle of the specimen. In a recently published report (18) it was shown that a vascular tree, including the internal iliac vessels, could be obtained from multi-organ donors and that the human uterus could be flushed through these vessels.

A critical question is of course whether the blood flow through these anastomoses would be sufficient to meet the demands of the markedly increased uterine blood flow at pregnancy. However, it is well known that a human uterus that have been constricted in regards to arterial blood flow by bilateral ligations of the anterior branches of the internal iliac arteries, to end massive postpartum hemorrhage, can carry a normal pregnancy (19). Most likely, there will also be an in-growth of new arteries to the uterine transplant with time. In our own experiments with the auto-transplanted sheep model we observed, during second-look surgery 2 months after transplantation, a substantial blood flow in the lower part of the uterus after ligation and severance of the uterine artery but with a remaining vaginal–cervical anastomosis (17). This implies that new arterial vessels grow from the vagina to the cervix to anastomose with the arterial system of the cervix.

**Uterus position and support**

In a clinic attempt to transplant the human uterus, the organ would naturally be positioned in
the pelvis with the cervix attached to the vagina. In the human transplantation case (5) the cervix of the uterus was attached to the vaginal vault of the recipient by interrupted 2-0 non-absorbable sutures and fixation of the uterus was also accomplished by “uterosacral shortening” after placement of two non-absorbable 2-0 sutures. These were the only points of fixation of the uterus, in addition to the six vascular anastomosis sites on the external iliac vessels. The authors point out (5) that suspension of the uterus also to the anterior abdominal wall (ventrouteropexy) may have been a method to avoid the displacement of the uterus, which in that case most likely caused torsion and tension of the vascular pedicles with the secondary formation of vascular thrombi.

In most animal models of uterine transplantation including the dog (7,8,9,10), rhesus monkey (11) and the rabbit (12) the uterus was placed in an orthotopic position but the sites of fixation, apart from the fixation to the vagina, were not mentioned. In our sheep model (17), the cervix of the autotransplant was attached to the vagina by uninterrupted, absorbable 2-0 sutures and the uterine body was bilaterally attached to the round and infundibulopelvic ligaments with 2-0 absorbable sutures. At laparatomy 2 months after transplantation, the uterus appeared functional in terms of contractility and blood flow. The uterus was found partly covered by adhesions within the lateral aspect of the pelvis, which was the position where it was originally placed at transplantation.

It should be pointed out that a heterotopic position of the uterus is also functional, at least in experimental animals such as the rat (15) and mouse (14). In our initial experiments in the mouse uterine transplantation model, the native uterus of the recipient was left in situ as an internal control and the transplanted uterus had to be placed in a lateral and cranial heterotopic position (14). In the first series of experiments (14), the cervix of the transplanted uterus was positioned inside the abdomen but due to poor implantation rate this technique was later modified to create a cervical-cutaneous stoma (20). In this mouse model natural birth occurred through the cutaneous stoma (20).

In a human situation, the cervix of the transplant should be attached to the vagina, being it a neovagina as in patients with the MRKH-syndrome or a natural vagina, to allow for drainage of menstrual fluid and cervical mucous as well as to enable embryo transfer through the vaginal route. It is advisable to also attach the fundus of the uterus bilaterally to the round ligaments and the lower uterine body to the sacrum, to prevent displacement of the organ and thereby to ensure undisturbed uterine blood flow.

Cold ischemia and reperfusion

Preservation of the graft from procurement until transplantation is a central aspect in any organ transplantation. The time limit for preservation under cold ischemic conditions is partly organ-specific. In human organ transplantation, the maximum cold ischemic time (CIT) is around 8 h for the heart and around 36 h for the kidney and the pancreas. It is likely that the uterus would tolerate a reasonable long CIT since it is mainly an organ made up of resistant muscle cells and also given that the endometrium has the capacity to regenerate from endometrial stem cells, a phenomenon occurring after each menstruation.

Any organ to be transplanted is normally flushed with a preservation solution (intracellular- or extra cellular-like in its composition) and stored in cold (+4°C) ischemic conditions before the organ is attached to the vascularity of the recipient. Injuries to the transplanted organs may arise during this ischemic period but most damage occurs during the reperfusion phase, when the graft, after hours of hypoxia and low metabolism, is exposed to oxygen. It is well known that reactive oxygen and nitrogen species form and that they can cause vascular and parenchymal injuries. The extents of cellular and vascular damage during cold ischemia and reperfusion seem to be predictive of the extent of rejection. Thus, in any transplantation situation the ischemic time should be kept minimal.

We tested the tolerability of the mouse uterus to long-term cold ischemic preservation and reperfusion (21). The mouse uterus could be preserved under cold ischemic conditions in the intracellular-like University of Wisconsin (UW) preservation solution for times up to 24 h and then successfully transplanted into the syngeneic recipient. Transplanted uteri regained their functionality in terms of implantation, pregnancy
and delivery of offspring. Thus, the murine uterus has considerably resistance to ischemia and reperfusion injury as well as restorative capacity.

Cold-ischemia, not including reperfusion events, was also studied on human uterine tissue (22). Small tissue pieces of human uteri were stored for 6 or 24 h at +4°C in either Ringer acetate (RIN), UW, or the extracellular-like Perfadex (PER) preservation solution. Degenerative cellular changes, on the electron microscopy level, were seen after 24 h in RIN, but not after 24 h of cold ischemia in UW or PER. Moreover, these preservation solutions conserved ATP-concentrations better than RIN. Since the contractile ability were superior after preservation in UW or PER for 6 h as compared to 24 h, we concluded that human myometrial tissue is resistant to cold ischemia for at least 6 h if a protective buffer is used for storage (22). In the recent report of human uterine retrieval from multi organ donors, UW solution was used and light microscopy did not reveal any tissue damage after 12 h of storage (18).

It may well be that cryopreservation of a whole uterus will become a possibility in the future, to be able to separate the time of procurement of the organ from the transplantation. Recently, a report indicating successful cryopreservation of the entire pig uterus was presented (23). In that report, contractility of the uterus was tested in vitro after cryopreservation and thawing.

**Pregnancy and offspring**

In a human transplantation situation it is of importance to assure that there exist reasonable chances for the couple to achieve a successful pregnancy. The fertilization would have to be through IVF since the oviducts would not be included in a transplant specimen. Thus, it would be advisable to perform IVF well before the transplantation to ascertain the potential for fertilization within the couple and also to store a reasonable amount of frozen embryos for transfer at a later stage after transplantation. The timing of ovum pick up at an occasion well before transplantation would also be an advantage so that the women would not be exposed to the risks of ovarian hyperstimulation syndrome (OHSS) and pelvic infection (after transvaginal ovum pick up) in a state during immunosuppression when these diseases may be aggravated. Moreover, an ovum pick up procedure may not be recommendable in a woman after having had a uterine transplant due to that a transplanted uterus would be in a slightly abnormal position and there would be the risk of causing injury to the atypically positioned uterine vascular tree.

Apart from the ability to establish a pregnancy after uterine transplantation, it is also important to determine that the entire pregnancy is not negatively affected after transplantation. The negative effects may relate to changed uterine blood flow, absence of lymphatic drainage, denervation and altered positioning of the uterus.

Few studies have looked at pregnancy after uterine transplantation. In the dog uterine auto-transplantation model pregnancy was achieved in around 15% of the animals (7, 8, 9, 10). We have examined the implantation rate and the pregnancy rate in the syngeneic mouse uterine transplantation model (14, 20). Since the implantation rate and potential for carrying pregnancies in this transplanted uterus was going to be tested through laparatomy and transmyometrial blastocyst transfer the cervix was initially placed inside the abdomen (14). Pregnancy in a strictly transplanted uterus of any species was reported for the first time (14). However, the implantation rate in this model was very low, possibly due to inadequate drainage of cervical and uterine fluid. Accordingly, the mouse uterine transplantation model was modified so that the cervix was brought through the abdominal wall and was connected as a cervical-cutaneous stoma. By the use of this modified method the implantation and pregnancy rates of the transplanted uteri were found to be similar as in controls (20). Offspring from a transplanted uterus was reported for the first time and it was demonstrated that the birth weight, growth trajectory as well as fertility were normal in offspring from these transplanted uteri.

It has to be pointed out that so far no pregnancy has been achieved in an allogeneic transplanted uterus, with its special issues relating to rejection and immunosuppression. We consider that the safety aspect of such pregnancies has to be established in animal models prior to any new attempt of uterine transplantation in the human.
Rejection

Rejection of a transplanted organ depends on recognition of the foreign HLA antigens of the transplanted tissue by the CD4+ T-cells of the host. The acute rejection phase generally occurs within weeks after transplantation, but can also occur at a later stage. The first morphological sign of acute rejection is an influx of immune cells, predominantly T-cells.

The process of rejection of a transplanted uterus was first studied in the dog model when allogeneic transplants were compared to autotransplantations (10, 24, 25). In these older studies autotransplantation generally resulted in viable grafts and in some cases pregnancies, but allogeneic transplanted uterine grafts were rejected with necrosis and fibrosis evident at examinations 1-3 months after transplantation. Similarly, allogeneic transplanted uteri of rhesus monkeys were rejected within 3 weeks (11). The time course and the events of the rejection process were poorly described in these studies.

Our research group has used the heterotopic uterine transplantation model in the mouse to study the changes during rejection of a uterus. We made use of a fully allogeneic mouse model with BalbC strain as uterus donor and C57BL/6 strain as recipient (26). Histological examination showed minimal inflammatory changes from day 2 after transplantation with an increase in the number of T-cells in the endometrium. Major inflammation and reduction of blood flow was seen from day 10-15 and at day 28 massive necrosis was seen. The early effects on the blood flow of an allogeneic transplanted uterus have also been described in the rat, where vascular patency was present at postoperative day 1 but at day 3 day blood flow was absent with signs of massive thrombosis (15).

In our study in the mouse (26), there were no signs of spontaneous acceptance of the uterine transplants, as sometimes seen in the mouse after allogeneic transplants of kidney and liver, but not of heart (27). Taken together, the time course for rejection of the uterus seems to resemble that of rejection of cardiac allografts in the mouse (27). Thus, organs with predominantly muscle tissue show similar rejection mechanisms and it may well be that information about suitable immuno-suppressive agents to control rejection in the heart can be used when finding suitable combinations of these pharmaceutical agents to suppress rejection of a uterine allograft.

Immunosuppression

Immunosuppressive medication would be required in a situation of a human uterine transplantation, if not a perfect tissue type match would be the case, as in transplantation between identical twins. There exists a long experience of outcome from pregnancies in human organ transplant patients that have been under immunosuppression, with more than 14000 pregnancies in kidney transplant patients and more than 1000 pregnancies in patients with liver, heart, lung or pancreas transplants. Collectively, the results from the three large registries of pregnancy data of transplanted patients (UK Pregnancy Registry, European Dialysis and Transplantation Association, National Transplantation Pregnancy Registry (NTPR) in the USA) has shown that there is no increased risk of congenital malformations in these patients. However, the risk of prematurity may be up to 50% and the risk for small for gestational age (SGA) may be up to 20% (28, 29, 30). The consequences for these children born prematurely includes a higher risk for neonatal–death, long-term childhood morbidity and also late onset diseases such as diabetes and hypertension. It should be noted, that the high risk for prematurity and SGA may not be a direct effect of the immunosuppressant agents since a large proportion of these patients has similar incidence of these complications at the deliveries that took place before the time of transplantation (31). An important issue is also possible long-term consequences on the immune system (30, 32) of the offspring after in utero exposure to immunosuppressants.

The modern maintenance immunosuppressive regimens in organ transplant patients often include combinations of daily corticosteroids, azathioprine and cyclosporine or tacrolimus. Usually this maintenance therapy is adjusted to a low baseline concentration during the first post-transplant year. In addition to this maintenance therapy, there is an induction therapy with addition of antilymphocyte
serum, used during the first weeks after transplantation. Moreover, antirejection therapies to treat episodes of acute rejection involves high dose of corticosteroids and/or antilymphocyte serum. During pregnancy it is advisable to monitor the concentrations of the immunosuppressants closely since pregnancy affects drug adsorption, distribution and elimination.

In most organ transplant programs it is recommended to avoid pregnancy during the first 1 to 2 years after transplantation since this is considered to be needed for establishment of allograft function and for reduction of the maintenance immunosuppression to moderate doses. Most of the immunosuppressants used today are grouped by the US Food and Drug Administration (FDA) into group C, which states that animal studies show an adverse effect or are unavailable and that there are no controlled studies in pregnant women.

The most widely used corticosteroids for immunosuppression in transplant patients are prednisone, prednisolone and methylprednisolone. They are categorized by FDA as category B (animal studies do not show an adverse effect and there are no controlled studies in pregnant women). The corticosteroids broadly inhibit both humoral and cell-mediated immune response probably by multiple site and mechanisms of action.

Azathioprine is a purine analogue, which by inhibiting clonal proliferation of T-cells, decreases delayed hypersensitivity and T-cell mediated cytotoxicity. Since teratogenecity of azathioprine has been noted in animal studies it is categorized by FDA as category D (evidence of human fetal risk, but benefits may be acceptable despite the risk). However, later data has suggested that azathioprine is not associated with any higher rate of congenital malformation than in the general population (29).

Cyclosporine has been the mainstay of immunosuppressive therapy since the early 1980s and is classified as a category C agent. It acts by blockage of calcineurin phosphatase activity, which leads to inhibition of interleukin-2 production and thereby impaired T-cell activation. There are some well described side effects of CyA such as hypertension, nephrotoxicity, hypertricosis and tremor. There is an increased incidence of neoplasms after long-term use of CyA. However, in a uterine transplantation situation use, of CyA would only be during a restricted time since the uterus would be removed by a caesarea hysterectomy at birth of the child, and the risk to develop neoplasms due to CyA would be minimal. There are no signs of teratogenecity of CyA in the human. Tacrolimus (also FDA category C) is also a calcineurin inhibitor. It has similar side effects as CyA but a higher incidence of post-transplant diabetes and neurotoxicity.

Only a handful studies have looked at immunosuppressive therapy to suppress rejection of uterine allogeneic transplants. In the dog uterine transplantation model, immunosuppression with azathioprine and prednisolone was used (33, 34) with reports of a small number of grafts remaining viable. However, there was no mention of the means of assessing viability. In another study, both nonpregnant and pregnant uteri were allogeneic transplanted under similar azathioprine immunosuppression (8). It was stated that the clinical phenomenon of rejection was less accentuated at transplantation of a pregnant as opposed to nonpregnant uterus (8). Thus, it may well be that the pregnant uterus with its special immunology, allowing a semi-allogeneic fetus to survive despite presence of maternal T-cells specific for paternally inherited MHC antigens, may be less likely to be rejected than a nonpregnant uterus. At the time of the studies on allogeneic uterine transplants in the dog (8, 33, 34) CyA and more modern immunosuppressants were not available and it may well be that rejection could have been controlled by these new pharmaceuticals.

Our group has recently evaluated CyA as a means of controlling rejection in a semi-allogeneic uterus transplantation model in the mouse (35). Rejection of the grafted uterus was inhibited but not fully suppressed by CyA even though high doses of this monotherapy was used. In ongoing experiments we use higher doses of CyA and also combinations of CyA with other agents.

In the human transplantation attempt (5) there is no data presented in regards to tissue compatibility between the donor and recipient. The immunosuppressants that were used were CyA, azathioprine and prednisolone. An episode of acute
rejection on day 9 was treated by addition of antithymocytic globulin and signs of rejection were resolved. The uterus had to be removed after 99 days because of vascular thrombosis and histopathological examination did not reveal any signs of rejection. Thus, it can be concluded that standard combination immunosuppression may be enough as maintenance immunosuppression after uterus transplantation.

In a situation with uterine transplantation, the transplanted uterus would be surgically removed after the woman has given birth once or several times, and immunosuppressants will only have to be used during a restricted time. Thus, the recipient would encounter less of the side effects of long-term immunosuppression. These side effects include a susceptibility to viral diseases and also a greater risk to develop some special types of neoplasms. In the future, with the fast development in the field of immunosuppressants, rejection does not have to be a major objection to a non-vital organ transplantation such as uterus transplantation. It is now appreciated that dendritic cells and regulatory T-cells are the major players in the induction of tolerance and novel ways to induce peripheral tolerance may be developed in the future (36). Moreover, uterus donors (mother, older sister, unrelated) with at least partly matched HLA-types to the recipients could be used in uterine transplantation.

Ethical considerations

Ethics in medicine is based on the moral, religious and philosophical principles as well as the values of the society. Since the issue of developing uterine transplantation into a clinical treatment for absolute infertility, also among patients born with a major congenital malformation and in women treated for cancer disease, touches several critical fields in medicine and society such as reproduction, transplantation, infertility, cancer and birth defects it is a subject which will be debated. It is essential that information about the ongoing uterine transplantation research and its ultimate goal of successful human uterine transplantation reaches the public arena at an early stage so that it is openly debated. The ethical standpoints concerning uterine transplantation as a clinical treatment will of course vary depending on the culture and religion of each specific society. In the Middle East, the place of origin of three major religions (Judaism, Christianity and Islam), religion is stronger than in many other parts of the world and the impact of religion on the ethics is bigger.

The only option to acquire genetic motherhood today for patients with absolute uterine infertility is through the use of gestational surrogacy. By gestational surrogacy, the women will obtain genetic and social motherhood (after adoption) but not gestational motherhood. Gestational surrogacy is prohibited because of legal, ethical and/or religious reasons in large parts of the world. It is practiced in countries such as the US, UK and in Israel. In the Islamic world surrogacy is not allowed (37) and uterine transplantation may instead become a possible treatment for these groups of women in the future. Surrogate motherhood raises fundamental questions about definition of parenthood, autonomy of the surrogate mother, potential risks for embryo (intake of alcohol, smoking, drugs) and surrogate carrier (pregnancy-induced thromboembolism, hypertension, diabetes, preeclampsia), as well as psychological implications for the surrogate mother and prospective child. The obvious advantages with gestational surrogacy in relation to uterine transplantation are that there is no exposure to immunosuppressant drugs to the fetus and the gestational carrier and that the risks connected with major surgery (live donor and recipient) are avoided. These risks have to be balanced by the possible benefits for the patient. An important issue is also health economics, where uterus transplantation would be a far more costly procedure for the society than the use of gestational surrogacy.

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