Uterus transplantation was a milestone
in the development of reproductive medicine

UTERUS TRANSPLANTATION AS A NEW METHOD IN UTERINE – FACTOR INFERTILITY (UFI)

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ABSTRACT

Approximately 0.2 % of women suffer from absolute uterine infertility. There used to be no existing treatment for this condition. However, up till now, a total of sixteen cases of human uterus transplantation have been reported worldwide. It seems that the procedure is to become the method of choice in the treatment of women with UFI.

We introduce a review which summarizes current experience in this field, with long-term patient analysis included. It also covers such important issues as potential risks for both involved parties and immunosuppressive therapy during pregnancy

BACKGROUND

Uterine factor infertility is caused mostly by Asherman's syndrome, myomas, history of hysterectomies or by congenital Müllerian malformations (the Mayer–Rokitansky–Küstner–Hauser syndrome–MRKH)). Until the first uterus transplantation was performed, there had been no successful treatment for absolute uterine factor infertility.

Transplantation of a uterus is a complex procedure which involves at least four parties: a recipient, a donor, a partner of the recipient, the future child, as well as medical staff. Since 2000 sixteen cases of human uterus transplantation have been reported [3-5], followed by five live births from the transplanted wombs [1, 2]. To obtain a successful pregnancy in a patient suffering from uterine-factor infertility, one should pay much attention to all the nuances and details of the procedure. They include election of a suitable donor, implications of live and deceased uterus donation, surgical risk for both parties, immunosuppressive therapy with its influence on possible pregnancy

DONORS

An intended donor should meet all the donor criteria applied in a general organ transplantation setting and be a female, also preferably premenopausal, of proven fertility and not hysterectomized previously. It is also recommended to analyse the donor's psychological profile to identify patients with inappropriate expectations of the procedure.

LIVE UTERUS DONATION

Out of the sixteen reported cases of human uterus transplantations, live donation occurred in ten [3, 4]. Exclusion of unsuitable donor candidates and organs of inferior quality is crucial to the outcome. The exclusion criteria include the presence of a systemic illness, donor infertility or subfertility, cervical or endometrial dysplasia, human papillomavirus infection, myomas, adenomyosis, polyps, vascular anatomy abnormalities, and intrauterine adhesions [9].

THE SURGICAL RISK

A live uterus donor is exposed to the risk of surgical complications during retrieval. This involves an intraoperative laceration of the ureteral wall or a postoperative ureterovaginal fistula. Duration of surgery (mean of 12 hours) poses an increased anaesthesia risk [3]. The most time-consuming part of the procedure is the dissection of uterine vessels, mainly the veins [3]. It has been suggested that a larger vein diameter, like the ones of the ovarian veins, would be preferable to use for anastomosis [10]. However, this would require removal of the ovary itself, resulting in potential hormonal dysfunction in a premenopausal woman. The upper part of the uterine vessels (the vessels connecting the uterine vessels to the ovarian vessels) may provide an adequate substitute for anastomosis.

DECEASED UTERUS DONATION

In the reported cases of human uterus transplantations, there was only one deceased donor uterus donation [6]. In this instance, there is no donor risk associated with the surgery. The surgical procedure itself is easier, shorter and vessels of larger diameter can be used for the anastomoses [5]. However, the ischemic time is longer than in live donation which poses the risk of reduced graft function and increases the incidence of acute and chronic postoperative rejections [11, 12].

IMMUNOSUPPRESSION IN PREGNANCY AFTER UTERINE TRANSPLANTATION (UTX)

Data on the influence of immunosuppressive medications on a fetus during post-UTx pregnancies are limited because only one study was carried out in humans, namely the observation analysis of 5 mothers-to-be who underwent womb transplantation at Sanglerska University Hospital.

First post-transplant pregnancy took place in 1958. A kidney transplant recipient from her twin sister gave birth to a healthy male newborn by caesarean section [13]. Since then over 14,000 births in transplant recipients have been reported worldwide [14].

There is an increasing number of women on immunosuppression to avoid rejection of organ transplants or to control underlying autoimmune diseases [15]. Immunosuppressive drugs cross the placental barrier, but fetal distribution is determined by complex pharmacokinetic and pharmacodynamic factors [16]. Despite the fact, that data on the influence of immunosuppressive drugs on the fetus have been collected, the exact impact is difficult to determine and may not be obvious at birth [17].

Pregnancies in organ transplant recipients have an increased risk of complications such as pre-eclampsia (22%), preterm birth, low birth weight, intrauterine growth retardation, infant death [18]. It is more likely related to the underlying disease rather than to the transplantation and immunosuppressive drugs themselves [19].

The US Food and Drug Administration (FDA) divided immunosuppressive medications into different categories for their safety in pregnancy: A (no risk), B (animal studies showing risk, but no evidence of risk in humans), C (risks cannot be ruled out), D (positive evidence of risk) and X (contraindicated) [Table 1] [20].

There are 3 types of immunosuppressive regimens:

- induction - used during the first weeks after transplantation,
- maintenance - long-term immunosuppression in order to prevent rejection,
- antirejection - high dosage, short-term treatments.

CORTICOSTEROIDS

Corticosteroids (cathegory B) have anti-inflammatory and immunosuppressive effects and are part of basically all immunosuppressive therapy regimens – both in maintenance and rejection [20]. Of the given dose, 90% is metabolized in the placenta before reaching fetal circulation [21]. Corticosteroid usage is associated with

an increased risk of premature rupture of membranes and higher incidence of adrenal insufficiency in newborns [22]. It has been reported that prednisolone administered in doses exceeding 20 mg per day can be associated with birth defects [23]. Moreover, animal studies, especially in mice, revealed that they reproducibly cause cleft palate [24].

CYCLOSPORIN

Cyclosporin (category C) is a calcineurin inhibitor often used along with azathioprine and prednisone. It has become the basis of immunosuppression. Passage of cyclosporin into the fetal circulation reaches about 37-64% of the maternal drug concentration [25]. Researchers report that high doses of cyclosporin accumulate in the placenta and in the umbilical cord [26]. In animal studies, fetal toxicities and abnormalities were observed at dosages higher than those used clinically, which justifies a need to control its maternal blood concentrations. Although clinical data reveal that the magnitude of teratogenic risk of malformations is minimal, a small to moderate risk of fetal growth impairment exists [27].

TACROLIMUS

Tacrolimus (category C) is a more potent calcineurin inhibitor than cyclosporin. Tacrolimus crosses the placenta and in significant amounts accesses fetal circulation. Umbilical blood concentrations constitute approximately 50% of maternal concentrations [28]. There is a need to measure its maternal blood concentration too, because resorption of fetuses was observed while using higher doses in experiments on mice [29]. As revealed in the study in 100 pregnant women exposed to tacrolimus, 68 of them gave birth to living children. Of the deliveries, 59 were premature and the most prevalent complication in newborns were hyperkalemia, hypoxia and temporary renal dysfunction. Four of them were diagnosed with congenital malformations but no pattern could be drawn from that [30].

AZATHIOPRINE

Azathioprine (category D) is an inhibitor of purine metabolism. After its absorption, the liver converts it rapidly into a number of metabolites. Studies have shown that azathioprine accumulates in high doses in a placenta (64%–93% of concentration reached in maternal blood), but accumulation in fetal blood constitutes only 1%–5% of maternal blood concentration [31]. The teratogenicity of azathioprine has been observed in animal studies where embryonic resorption and/or fetal anomalies occurred, however, clinical data reveal that the risk of malformation in human is small [32]. Thymic atrophy, leukopenia, anaemia, thrombocytopenia, chromosome aberrations and reduced immunoglobulin levels along with infections and sepsis were problems reported in newborns. Preterm delivery and intrauterine growth restriction were recorded, but without any prevalent structural malformation pattern [22].

MYCOPHENOLATE MOFETIL (MMF) AND MYCOPHENOLATE ACID (MPA)

Mycophenolate mofetil (category D) is an ester of the active metabolite mycophenolic acid (MPA). Mycophenolate mofetil is a prodrug. Its metabolite blocks de novo purine synthesis which lymphocytes are dependent on. It is typically used in combination with a calcineurin inhibitor and/or corticosteroids. Animal studies on pregnant rabbits and rats demonstrated developmental toxicity, malformations, intrauterine death or intrauterine growth retardation at clinically recommended doses based on body surface area [33]. Human studies showed that MMF and MPA exposure during pregnancy is related to an increased risk of miscarriage during the first trimester and congenital defects such as cleft lip and palate, malformations of external ear and abnormality of distal limbs, oesophagus, heart and kidneys [34, 35]. Due to this, female patients at reproductive age should use contraceptive methods during, and for at least 6 weeks after cessation of MMF treatment (36). Before a planned pregnancy, the usage of MMF and MPA should be discontinued and replaced with azathioprine [34].

ANTITHYMOCYTE GLOBULIN

Antithymocyte globulin (category C) is a polyclonal antihuman thymocyte serum produced from horses or rabbits, which depletes T cells. Fevers and chills are its main side effects. It has been studied neither in animals nor pregnant women.

HUMAN UTERUS TRANSPLANTATIONS

Up till now, a total of sixteen cases of human uterus transplantation have been reported worldwide, including five cases of live births from transplanted wombs. However, long before any attempts were made in humans, models of the surgical procedures had been developed in several animal species, namely in mouse, rat, sheep, domestic pig, baboon, and macaque. As stated in numerous reports and reviews by the researchers, successful pregnancies had been reported in the majority of them [37].

The first human uterus transplantation was performed on the 6th of April 2000 by a Saudi Arabia surgical team [4]. According to the report published by the researchers, the medical circumstances and the procedure were as follows [4]. The recipient was a 26-year-old woman who had suffered a miscarriage and peripartum hysterectomy. The uterus originated from the 46-year-old donor diagnosed with multiloculated ovarian cyst who underwent a hysterectomy modified to preserve tissue and integrity of the vessels. The surgical procedures consisted of the connection of the graft to the recipient's vaginal vault in orthotopic position and shortening of the uterosacral ligament to achieve more firm fixation. In order to extend the short, retrieved uterus vessels saphenous veins of the recipient were anastomosed and connected to the external iliac artery and vein respectively. Intraoperatively i.v. methylprednisolone was given. Following the procedure, the recipient was administered oral immunosuppressants (cyclosporine A -

divided into two doses, azathioprine, and prednisolone) as well as cyclic hormonal therapy with estrogen and progesterone to which the graft responded with endometrial proliferation up to 18 mm. On the 9th POD, a reversible acute rejection episode occurred, but it resolved soon after administration of antithymocyte globulin. Shortly after cessation of the hormonal therapy, the patient experienced two withdrawal bleedings. However, on the 99th POD, the recipient reported a sudden sensation of heaviness accompanied by a foul-smelling vaginal discharge. In the gynecological examination, the cervix was dusky-coloured and prolapsing into the vagina. Doppler ultrasound confirmed cessation of blood supply to the graft. During laparotomy, the uterus was found to be necrotic and so the organ was removed. Histopathologic examination revealed acute thrombosis in the vessels of the uterine body with resulting infarction. It was most likely caused by inadequate uterine structure support that led to tension and thrombosis of the supplying vessels [4].

The second attempt to perform the procedure was made in 2011 in Turkey [5]. The medical circumstances and the procedure itself are described basing on the report published by the researchers [5]. A 21-year-old woman with MRKH syndrome, who had undergone a jejunum-derived vaginal reconstruction, was transplanted with a uterus from a deceased 22-year-old nullipara donor. The uterine graft was recovered within 12 hours after the donor's brain death confirmation. The whole procedure including the allograft retrieval (2 hours), transfer between hospitals (30 minutes) and finally its implantation in the recipient lasted 8 hours. The implantation involved an end-to-side manner anastomosis of the internal iliac artery and vein of the donor to the corresponding external iliac vessels of the recipient. Thymoglobulin was administered intraoperatively, continued and withdrawn on the 10th day after the transplantation. An initial intraoperative dose of prednisolone was administered and then it was significantly reduced at 1 week after the surgery. Tacrolimus dosage was initiated on the 7th POD. During the first 10 days following the procedure, the patient received infection prophylaxis, namely fluconazole, piperacillin/tazobactam, cotrimoxazole, nystatin, and valacyclovir. Maintenance immunosuppression therapy consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Additionally, cotrimoxazole was continued for the first 6 months along with subcutaneous heparin for antithrombotic prophylaxis. On the 20th POD, the patient had her first menstruation. For the following two cycles bleeding was irregular and the endometrial thickness reached 21 mm. She subsequently received cyclic hormonal therapy, to be continued for 5 months, in order to decrease the risk of endometrial hyperplasia. Monthly withdrawal bleedings occurred. In 4th and 6th month post transplantation, the patient underwent two successfully treated urinary tract infections. The patient has been sexually active since the third month after the procedure [5]. A year and a half later the patient underwent two single embryo transfers resulting in two pregnancies. The first was biochemical, but in the second one, an intrauterine gestational sac was visualized during an ultrasound examination. Unfortunately, in the 8th

gestational week, it was miscarried. The graft is still viable [38].

In 2012 and 2013 the first clinical series of uterus transplantations was conducted at Sahlgrenska University Hospital in Gothenburg, Sweden [3]. The recipients were eight women with MRKH syndrome and one woman after radical hysterectomy due to cervical cancer. Their ages ranged from 27 to 35-years-old. Four from the group of patients with MRKH syndrome had had vaginal reconstruction with a skin graft, one had undergone therapeutical dilatation, while the rest had self-dilated vaginas. The donors were in five of the cases mothers of the recipients and in the other four - a sister, a family friend, a mother's sister and a mother-in-law. The youngest donor was 50-years-old while the oldest was 62. The average number of pregnancies in the donor group was 3.3. [Table 2]

The implantation procedure consisted of creating vascular anastomoses between the graft vessels and the external iliacs of the recipient. In six recipients, the uterine branch of the ovarian artery was anastomosed to the ipsilateral uterine vein or directly to the external iliac vein. Then, the recipient's previously opened vaginal vault was connected to the vaginal rim of the graft. The uterus was fixed by attaching its ligaments to their pelvic counterparts and by overlaying its excessive bladder peritoneum over the recipient's bladder fundus. The donor surgery lasted on average 11h 37 min, while the implantation 4h 46min. Preoperatively the recipients were given mycophenolate mofetil, intraoperatively methylprednisolone and antithymocyte antibodies or antithymocyte globulin with identical doses repeated after 12 hours. Maintenance immunosuppressive therapy consisted of tacrolimus and MMF twice a day along with oral prednisolone once a day starting from the day of surgery and continuing throughout the first 4 PODs. Antiviral prophylaxis was a daily oral dose of valganciclovir which was given when either both the donor and the recipient were positive (3-months therapy) or only the donor was positive (6-months therapy). The thrombosis prophylaxis in the patients consisted of acetylsalicylic acid administered during the 6-month follow-up period together with dalteparin (until the 42nd POD). On the 16th POD, donor 2 was diagnosed with ureterovaginal fistula. A ureteral catheter was inserted and the ureter reimplanted after 116 days. In the recipients' group - recipients 1 and 2 presented pleural fluid on the first day after the procedure (it was reabsorbed until the 2nd or 3rd POD). In one recipient a retroperitoneal hematoma occurred and a blood transfusion was required. Recipient 2 developed cervical/uterine infection (Enterococcus faecalis). After 4 days of i.v. antibiotics the symptoms resolved and she was discharged home on the 38th POD with oral antibiotics. However, between 78th and 83rd POD, a febrile episode took place and so i.v. therapy was reintroduced. On 98th POD due to aggravated symptoms and an intrauterine abscess (3x4cm), she was readmitted to the hospital. Unfortunately, despite two attempts at surgical drainage, the patient developed septicemia and hysterectomy was performed on 105th POD. Postoperative examination of the graft revealed extensive areas of necrosis and neutrophil-dominated

inflammation with no signs of rejection. On the 3rd POD recipient 9 presented cessation of Doppler signal in the uterine artery. As laparotomy showed congested uterus and uterine arteries with palpable pulses, the graft was removed. Its examination revealed focal necrosis, moderate ischemic myometrial damage and occluding thrombi in both major vessels. No signs of rejection were found. Spontaneous and regular (27-32 days) menstruation in all the recipients started within two first months after the transplantation with a mean endometrial thickness of 14 mm. Recipients 1, 5 and 7 suffered from single mild rejection episodes during the first postoperative month while recipient 8 developed two such episodes in the first and third month after the procedure [3]. As stated in the 1-year analysis of the patients a total of nine rejection episodes occurred during the first postoperative year and they were restricted to 5 recipients only. All the episodes were successfully resolved by temporary therapy with 7 to 10-days treatment with glucocorticoids. Moreover, all of them were subclinical without any symptoms presented by the recipient and were detected by cervical biopsy. The plan for the seven women with viable uteri was to proceed to embryo transplantation after 12–18 months from UTx on the condition that the postoperative months would be uneventful with no severe rejection episodes for at least 4 preceding months. The uteri were to be removed after one or two successful pregnancies [7].

The first human live birth from a transplanted womb was reported in September 2014. Recipient 5 had a single embryo-transplantation twelve months after the surgery. During the pregnancy until the delivery, the patient was being given triple immunosuppression scheme (tacrolimus, azathioprine, and corticosteroids). A single mild rejection episode occurred in the second trimester, but it was controlled with i.v. corticosteroids. All the fetal parameters were normal throughout the pregnancy. The patient was admitted to hospital in the 31st+5 gestational week due to preeclampsia with a blood pressure of 180/120 mm Hg, mild headache, proteinuria (urine albumin 18 mg/L), and platelet count lowered to 96×10 9 /L. The patient was administered with labetalol and nifedipine orally as well as i.v. betamethasone to protect the fetus from respiratory distress syndrome. CTG registry showed an increasing number of uterine contractions and occasional variable decelerations from the 10th hour after admission. Sixteen hours later, owing to repeated episodes of an abnormal cardiotocography pattern a cesarean section was performed. The patient delivered a healthy male newborn. The newborn's weight was 1775 g (normal for the gestational age), length - 40 cm and head circumference – 28.5 cm. The Apgar scores were assessed for 9, 9, and 10 and the pH of the blood sample from the umbilical artery was 7.21. After the delivery placenta examination didn't show any abnormalities (the basal plate had no changes affecting deep placentation). After the surgery, the mother was in a good condition and her blood pressure normalised immediately after the delivery. She was discharged home after 3 days. The newborn left the neonatal unit in a good health 16 days after birth. His last published weight measurement of 2040 g on the 21st day of life suggested the baby's normal development [1].

The second world live birth from a transplanted womb took place in 2015. Recipient 7 got pregnant owing to a single embryo transfer performed 12 months after the uterus transplantation. During the pregnancy, the patient continued with triple immunosuppression therapy (tacrolimus, azathioprine, and prednisolone). In the 18th gestational week, the recipient's hemoglobin level declined to 79 g/L. Anaemia was successfully treated with i.v. ferric carboxymaltose and darbepoetin alfa so that the subsequent hemoglobin levels reached 95 g/L. Fetal growth and development parameters were normal and the patient's condition was satisfactory until the 33rd gestational week when she developed intense pruritis with elevated serum levels of bilirubin that indicated intrahepatic cholestasis. On the 34th+4 gestational week, an elective cesarean section was performed. The patient delivered a male newborn weighing 2335g (normal for the gestational age) whose Apgar scores were 9, 10, 10. His length was 44cm and head circumference - 33cm. The newborn presented symptoms of mild respiratory distress which was treated with CPAP and surfactant during 2 following days. Maternal hemoglobin after the surgery decreased to 78g/L and so patient was administered 2 units of erythrocyte concentrate. The bilirubin levels normalised within 5 days after the delivery. Both mother and child were discharged home on the 8th day after the surgery. The child was breastfed for 3 months starting from the 2nd week after birth. He developed normally and his weights were 4.0, 6.2, 7.4 and 9.3 kg at ages of 2, 4, 6 and 12 months, respectively [39].

In the subsequent three pregnancies of the Swedish trial, the recipients suffered from occasional controllable episodes of mild rejection, but all the children were born healthy [40].

On the 24th of February 2014, as reported in the press [41] and confirmed by the clinic itself, the pioneering uterus transplantation in the United States was performed at Cleveland Clinic [42]. The recipient was a 26-year-old woman suffering from MRKH syndrome who received a womb from a deceased donor. Unfortunately, on the 8th of March 2014, the recipient had to have the graft removed due to Candida albicans infection which compromised the blood supply to the uterus [43, 44]. Numerous press sources [45, 46], as well as the clinic itself, state that the first American uterus transplantations from live donors were performed between 14th and 22nd of September 2016 at Baylor University Medical Center, when four women received womb transplants. Their ages ranged from 20 to 35 years old and all of them suffered from MRKH syndrome. The donors were women between 35 and 60 years old of proven fertility, not related to the recipients. It took about five hours to retrieve the grafts and another five to implant them to the recipients. The team included two Swedish surgeons experienced in uterus transplantation. Unfortunately, shortly after the procedure, three recipients had to undergo a hysterectomy due to blood flow abnormalities in the graft vessels. The fourth recipient has a viable uterus.

As we can read on the official website of Womb Transplant UK Foundation - uterus transplantations are being planned for the near future in the United Kingdom.

CONCLUSIONS

Uterus transplantation was a milestone in the development of reproductive medicine. For women suffering from uterine factor infertility, it is a possibility to carry and deliver their own offspring. Numerous experiments in animal species such as mouse, rat, dog, pig, sheep and nonhuman primates resulted in the collection of important data on UTx and the following pregnancy. Additionally, as proven and described by many researchers, immunosuppressive therapy is no longer contraindicated during pregnancy. Nonetheless, childbearing should be attempted after at least 1 year post transplantation as the exact influence of the analysed immunosuppressive drugs is still being investigated. In spite of many successful transplantations, pregnancies and undeniable progress being made in this field, we are still faced with technical obstacles and rising ethical concerns. Indeed, vascular anastomoses, possible rejections, and infections still pose many difficulties to the surgeons. There is also a debate on the ethical side of the procedure which not only reminds us of its complexity but also sets the course for its future development.

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ABBREVIATIONS

CTG	– cardiotocography
CPAP	– Continous Positive Airway Pressure
FDA	– The US Food and Drug Administration
MMF	– Mycophenolate mofetil
MPA	– Mycophenolate Acid
MRKH	– the Mayer–Rokitansky–Küstner–Hauser syndrome
POD	– postoperative day
UFI	– uterine – factor infertility
UTx	– uterus transplantation

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LIST OF THE TABLES

TAB. 1. IMMUNOSUPPRESANT RISK CATEGORIES ACCORDING TO US FOOD AND DRUG ADMINISTRATION (BASED ON [20])

Category	Drug	Animal/human studies
B	Corticosteroids	Risk in animal studies, but no evidence of risk in humans.
C	Cyclosporine A Tacrolimus Sirolimus Everolimus	Fetal risk demonstrated in animal studies but no adequate and well-controlled studies in humans. Drug can be used if potential benefits outweigh risks.
D	Mycophenolate Mofetil Azathioprine	Fetal risk demonstrated in human studies. In exeptional circumances, drugs can be used if potential benefits outweigh risks.