https://doi.org/10.23873/2074-0506-2023-15-1-79-88

Issues of preparation for implementing uterine transplantation in clinical practice

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Abstract

The absolute uterine factor infertility is a non-treatable cause of female infertility. Surrogacy has become the only option that allows this group of patients to achieve genetic, although biological motherhood. According to statistics there are more than 30 thousand women of fertile age in Russia who cannot get pregnant due to the absolute uterine factor infertility. The recently emerged possibility of uterine transplantation has become the only treatment for this kind of female infertility.

Prior to the very first clinical study of human uterine transplantation which was carried out in 2013 in Sweden, scientists had conducted systematic studies in animals (rodents, pigs, cattle and primates). The first clinical trial with the uterine transplantation performed resulted in a

live birth in September 2014. Currently, cases of successful uterine transplantation in humans have been reported in Sweden, Brazil, USA and Italy. Experience and practice in animal research played a key role in the success of the first clinical study on uterine transplantation. The application of this method is fundamental in the introduction of the scientifically grounded technology of uterine transplantation in Russia.

Aim. *Analysis of the problems of the clinical application of the uterine transplantation based on a literature review.*

Keywords: uterine infertility, reproductive medicine, assisted reproductive technologies

Conflict of Interests. The authors declare no conflict of interest.

Financng. The study was conducted within the framework of the State Assignment and financed from the Budget of the Federal Medical and Biological Agency

For citation: Polstyanoy AM, Gubarev KK, Polstyanaya OYu, Rendashkin IV. Issues of preparation for implementing uterine transplantation in clinical practice. *Transplantologiya. The Russian Journal of Transplantation.* 2023;15(1):79–88. (In Russ.). https://doi.org/10.23873/2074-0506-2023-15-1-79-88

AUFI absolute uterine factor infertility

UT, uterine transplantation

Introduction

The absolute uterine factor infertility (AUFI) has historically been considered an incurable form of infertility. This statement was refuted in 2014, when there was reported a case of a child born after allogeneic uterine transplantation (UT) [1]. The cause of AUFI is the pathology or complete absence of the uterus, either due to congenital developmental anomalies (such as aplasia or underdevelopment of the organ) or due to surgical interventions, which prevent implantation of the embryo or pregnancy resolution on time [2].

Based on statistical data, about 20 thousand female patients suffer from AUFI per every 100 million women of childbearing age [3]. For this category of patients, until recently, the only way to get genetically related children was the surrogacy program. This method allows one to get genetically related and, upon completion of the adoption process, legitimate child. Surrogate maternity is practiced in Russia, however, this does not negate the fact that most women strive to bear a child on their own and not lose that psycho-emotional connection between mother and child that only pregnancy can give. In addition, surrogacy is associated with a number of ethical difficulties, which, in turn, may carry medical, psychological and legal risks for both the genetic and biological mother of the unborn child [4].

The Swedish group of uterine transplant scientists started their research on UT in 1999 with experiments in a mouse model, after which the experimental research was successfully continued using four more animal species, including primates, and then preclinical studies in humans were started [5]. When implementing the clinical protocol, IDEAL principles were used to develop innovative surgical interventions [6].

Experiments in animals

In preparation for uterine transplantation, experimental trials were performed in all classical animal models using a step-by-step approach to develop an acceptable surgical algorithm for operations in humans, taking into account all possible risks. We would like to emphasize that the development of surgical techniques on animal models, including primates, is necessary to obtain and sufficiently develop special skills that are required when conducting clinical studies in humans.

Surgical technique

The surgical technique of UT depends on the anatomy of an animal model, the size of the vascular bed being especially important. The first trials on animal models were conducted in small rodents. In particular, a model with a postmortem donor was tested on hamsters. This was grounded by the fact that due to the small size of the vessels for transplantation, it became necessary to remove fragments of the great vessels together with the graft in order to obtain adequate vascular conduits for anastomoses.

In the mouse model, the graft was transplanted into a heterotopic position - the upper part of the abdominal cavity with the cavo-caval and aorto-aortic end-to-side anastomoses. Successful uterine transplantation in a mouse model was achieved in 87% of cases [7]. In this experiment, the cervix was positioned into the abdominal cavity, after which an additional intervention was performed to create a cervicocutaneous stoma to drain the uterine and cervical muci. A blastocyst was transferred into the transplanted uterine horn, at which result the normal process of implantation and the birth of offspring with normal weight was observed [8].

The surgical technique in the rat model differed significantly due to the larger size of the anatomical structures. In this model, the uterus with the excised horn was transplanted orthotopically with end-to-side anastomoses between the uterine vessels and the common iliac vessels. In this study, despite the more convenient conditions for surgical intervention, the authors managed to achieve a survival rate of up to 70% of the operated animals [9]. Studies were also conducted on rabbits [10] and pigs [11], during which the technique of transplantation from a postmortem donor was worked out with forming anastomoses with the vena cava and the aorta.

In rabbit studies, a long-term survival rate after uterine transplantation was only 11%, compared to postsurgical one of 56%. These results were explained by a large number of postoperative complications, such as anastomotic leaks, thromboembolic complications, and pneumonia [10].

In a pig study, 5 of 10 operated animals lived up to one year after transplantation. The rest of the operated individuals died from complications during surgery (3 animals) and from postoperative complications such as pneumonia and graft ischemia (2 animals) [11].

To date, the operation of uterus transplantation in a sheep model is represented by two surgical techniques.

In the first study by a Swedish group of scientists experimenting on a sheep, authors performed 14 womb transplants. The method to restore the blood flow included the technique of using a unilateral vascular pedicle, which structure included the anterior branch of the internal iliac artery, the entire uterine-ovarian vein, and a fragment of the aorta with the ovarian artery coming from it. As a result of the experiment, the operation was recognized as successful in half of 14 operated animals. In other cases, the animals were excluded from further observation for various reasons: due to peritonitis (1 case), paresis of one of animal's hind legs (3 cases), early intestinal obstruction (2 cases), vascular anastomosis failure (1 case). Of the remaining 7 animals, 4 were selected for fertilization. Three operated sheep gave birth to healthy offspring [12].

In a study by a Colombian team headed by Dr. E.R. Ramirez, during uterine transplantation, end-to-end anastomoses were applied between the uterine vessels. Scientists managed to achieve long-term graft survival in 6 of 10 operated animals [13]. The main limiting factor in this approach was the need to perform a very careful and gentle

hysterectomy on the recipient in order to preserve the potential to form anastomoses.

Three separate research groups, independently of each other, came to the conclusion about the efficacy of forming an aorto-caval macrovascular pedicle on the graft during operations with a postmortem donor in a sheep [14–16]. It is worth noting that the sheep model is excellent for surgical training before coming to UT surgery in humans, due to the similar sizes of vessels and reproductive organs, as well as an easier vessel dissection.

Two primate studies were used to develop the UT surgical technique. In a living donor baboon study, uterine allotransplantation was performed in 18 donor-recipient pairs. Side-to-side anastomoses between the internal iliac and ovarian veins were placed on a section table, after which end-to-side anastomoses with external iliac vessels were made in the recipient's body [17]. As a result of surgical interventions, all operated animals (both donors and recipients) survived [18, 19]. A study was also conducted in baboons using a dead donor, where the macrovascular flap technique of the aorta and vena cava was used [20].

Crab-eating macaques were used to develop the UT surgical technique. In that study, the autologous UT model was initially used, in which the uterus was removed with the isolation of the uterine vessels: arteries and veins [21]. In the recipient, end-to-side vascular anastomoses into the external iliac artery and vein were made using 11/0 suture. The time of removal and transplantation in this model was longer due to the need to use a surgical microscope and a special microsurgical technique for anastomoses. These features are uncharacteristic for human operations where the vascular anastomosis can be performed with a 6/0-7/0 suture using conventional surgical loupes instead of a microscope. In subsequent studies, the ovarian vein was used as the venous outflow tract, while the

time of surgical intervention was reduced due to easier vessel dissection and the experience gained by the investigators earlier. A study on allogeneic transplantation from a dead donor was also performed using cynomolgus monkeys [22]. In a comparative surgical experiment, the vascular pedicles of the graft included either the common iliac arteries or the aorta and vena cava [23]. As a result, there were no significant differences in the time spent on surgical intervention with regard to the technique used.

It can be concluded that the study in the primate model is an important step in preparing for surgical intervention in humans as this model provides the possibility to study the anatomical and surgical features of the UT operation. However, it should be added that the smaller size of the body of primates makes this object quite difficult for surgical interventions as an object for training.

Cold and warm ischemia

Damage to the graft cells occurs from the moment of clamping the donor's vessels to the moment of reperfusion after revascularization in the recipient's body. The warm ischemia time during the imposition of vascular anastomoses in recipient's body is more important than the cold ischemia time when working at the section table. The survival time of organs during cold ischemia has been studied in various model animals. A study in mice showed that the possibility of spontaneous pregnancy retained after 24 hours of cold ischemia, the loss of this function occurred after 48 hours [24]. The sheep uterus, which is comparable in size to the human one, also showed viability after 24 hours of cold ischemia, meanwhile the viability was assessed at 8 days after organ autotransplantation [25].

Susceptibility to warm ischemia was also studied in rats [26], cynomolgus monkeys [27], and sheep [12]; viability was shown after 5, 4 and 3 hours, respectively. These studies suggest that the uterus is as resistant to warm ischemia as other transplanted solid organs; it is resistant to cold ischemia for 12–24 hours and to warm ischemia for at least 3–5 hours. During human organ transplant operations, warm ischemia time is reduced to the minimum acceptable.

One of the advantages of the uterus over other parenchymal organs is that if the uterus survives for a month after transplantation, its functionality can be judged by the restored menstrual function and, later, by the implantation of the ovum and the onset of pregnancy. The innate regenerative potential, including but not limited to organ-specific stem cells, allows the uterus to compensate for possible damage from ischemia during transplantation.

Immunosuppression

The experience of allogeneic UT investigations shows conflicting results regarding immunosuppressive therapy protocols. Studies in rats show excellent results in preventing rejection with tacrolimus [28] compared to those with cyclosporins [29]. Tacrolimus has also been shown to be effective in a rabbit study [10], and the results show that it is effective in preventing rejection within 12 months in pigs [11]. Monotherapy with cyclosporines is effective in studies on sheep [13]. These data taken together suggest that cyclosporin or tacrolimus monotherapy is effective in rodents and large domestic animals.

In primates, immunosuppressive therapy should be complex; tacrolimus monotherapy does not prevent graft rejection after UT in baboons [19]. In both baboons [19, 20] and macaques [23], the induction protocol included triple therapy, which included tacrolimus, steroids, and

mycophenolate mofetil. With this therapy combination, the immunosuppression efficacy and long-term protection against graft rejection have been noted. This protocol is similar to that for human kidney and heart transplantation.

Rejection

It is important to monitor a possible graft rejection. Of particular importance is the detection of cytological changes in tissues at an early stage of the rejection reaction before any severe damage to the organ or fetus during pregnancy has developed. Early studies in mice describe the characteristic changes that have been observed in the graft upon rejection. There are macroscopic changes, histopathological changes, changes in the nature of blood flow in the graft, as well as in the migration of immune cells into the graft [30, 31]. The primary rejection scoring system was based on histopathological examination of cervical biopsy [20]. Diffuse infiltration with lymphocytic cells was assessed as a slight rejection reaction. In a moderate rejection reaction, inflammatory infiltration by lymphocytes and a large number of apoptoses were histologically reported. In a severe rejection reaction, a neutrophilic inflammatory infiltration was described in combination with the erosions formed on the epithelium. This scoring system is currently used in humans.

Pregnancy planning

Under these conditions, the marker of graft functionality is the restoration of the uterine menstrual cycle, but this is only an indicator of the surgical efficacy of the operation rather than the ultimate goal of infertility treatment. The first successful experience in obtaining offspring after UT was an experiment on syngeneic mice [8].

The study compared two groups of mice of 12 individuals each; in the study group, the possibility of pregnancy after uterine transplantation was assessed, 12 intact mice were used as controls. As a result, 66% of cases in the study group and 75% of cases in the control group became pregnant. The offspring in this study were of normal birth weight and subsequently grew and developed normally. Thus, the concept of orthotopic uterine transplantation for the treatment of infertility has been confirmed to be effective in a mouse model [32].

The concept of autologous uterine transplantation has proven to be effective in a sheep model after natural conception [12]. Pregnant individuals in this study were delivered by caesarean section, and the offspring were born with normal weight. A single case of offspring in non-human primates was after autologous UT in macaques [33].

Since the above cases are limited to describing syngeneic/autologous UT, they are mainly proof-of-concept surgical techniques: changes in arterial nutrition, venous drainage, and ligamentous attachment.

Animal studies of allogeneic uterine transplantation have also been conducted in order to assess fertility, and the effect on offspring. Pregnancy after allogeneic transplantation was first reported in rats [34]. However, a subsequent study confirmed only the presence of an intrauterine pregnancy. Similar data have also been obtained in studies in rabbits with a tacrolimus-based immunosuppression protocol [35]. In this study, the presence of a fetus in the uterine cavity was confirmed by ultrasound on the 16th day after the embryo transfer.

Live births after allogeneic UT have only been reported in a sheep and rat model. A single case of preterm live birth after allogeneic UT and immunosuppression with cyclosporine was published based on the results of studies conducted in a sheep model in 2011 [36]. Several live births

have been reported in rats after allogeneic UT and tacrolimus therapy [37].

Preclinical studies in humans

Only a small number of studies can be regarded as preclinical studies on UT in humans. One of the studies on the myometrium tolerance to cold ischemia in vitro evaluated myometrium tissue obtained as a result of hysterectomy. Myometrium tissue was placed for a day either in a preservation solution or in Ringer's solution, after which the tissue was assessed histomorphologically; in addition, the preservation of its contractility was evaluated. Tissues incubated in preservation solutions (Custodiol or University of Wisconsin solution) showed intact ultrastructural morphology compared to non-incubated samples, after which the samples also showed spontaneous and prostaglandin-induced contractile activity. This study demonstrates for the first time the similarity of the uterus and kidneys in terms of resistance to cold ischemia. However, these experiments did not allow modeling possible reperfusion-associated tissue damage [38].

Two studies are known to have investigated the possibility of hysterectomy in deceased donors. An earlier study in 2007 showed a surprisingly low percentage (10%) of consents to cadaveric hysterectomy for investigational purposes [39]. However, one should note that this study was conducted 5 years before the first publication of successful uterine transplantation [1], when positive experience with UT had not yet been accumulated. In that study, the investigators encountered significant difficulties in forming the graft vascular pedicles. In most cases described, the uterine vessels did not depart bilaterally from the internal iliac vessels. In 2014, a study with a similar design was conducted in France [40]. The consent rate for hysterectomy had already reached 80%.

They also used the method of washing the uterus through catheters in the femoral arteries, which did not affect the removal of other organs. As a result, the investigators managed to achieve good results: in 85% of cases, the uterus was removed along with the bilateral vascular bed of the internal iliac vessels; the removal process took less than one hour.

The intimate attachment of the uterine veins to the ureters makes hysterectomy operations on a living donor much more technically difficult compared to operations on a post-mortem donor. In preparation for the first living donor UT in humans, a surgical method for isolating the uterine arteries and veins was tested in patients operated on for cancer of the uterus and cervix with lymphadenectomy [41]. Patients previously obtained consent to some expansion of the scope of surgical intervention. In this research project, they managed to surgically form potential vascular pedicles of the uterine arteries and veins, which length was about 6 cm. It should be noted that the distance between the external iliac veins averages about 10 cm, which allowed the authors to conclude that anastomoses between the vascular pedicles of the graft and the external iliac vessels are possible. The results of that study subsequently served as the basis to develop a surgical protocol for UT from a living donor in humans.

Conclusion

The Swedish uterine transplant group was the first to achieve both a successful human uterine transplantation, and also a successful pregnancy. To date, 8 births have been reported after 10 uterine transplants in Sweden, with a graft loss rate of only 20% (2 grafts of 10 transplants). In America and Brazil, there are also cases of successful pregnancies after uterine transplantation. This technology is a unique way

to treat a previously incurable form of uterine factor infertility and requires further study of its efficacy.

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10%, data collection and handling, data analysis, statistical processing

The article was received on October 17, 2022;
approved after reviewing October 31, 2022;
accepted for publication December 28, 2022