EXPERIMENTAL ANIMAL MODEL FOR TREATMENT OF ABSOLUTE UTERINE FACTOR INFERTILITY

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Reproductive organ transplantation was considered as a potential method for treatment of the ovarian factor, tubal factor, and uterine factor infertility before the advent of advanced assisted reproductive technologies. Uterus transplantation can be considered as the method for treatment of absolute uterine factor infertility similar to transplantation of non-vital organs. However, the clinical use of uterus transplantation in humans causes a lot of problems. The study was aimed to develop a program for assessment of various surgical tissue revascularization techniques for restoration of reproductive function in experimental animals with uterine factor infertility. Chinchilla rabbits (n = 20) were selected for experiments because of the fact that all mammals have similar structure of the organs. The innovative technique involving the use of ovarian arteries instead of uterine arteries (as in the standard protocol) was used in laboratory animals to develop the surgical protocol for transplantation of reproductive tissues. The animal study results show that hemodynamic characteristics of blood supply to the transplanted uterus remain unchanged. This makes it possible to use the surgical method in the experiments on the uterus transplant from a deceased donor. The proposed uterus transplantation protocol ensures high transplant survival rate and normal blood supply to the transplant, along with the reduced risk of injury to the donor and reduced complexity of the surgical procedure.

Keywords: uterus transplantation, treatment of uterine factor infertility, organ transplantation, organ donation, comparative analysis

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Compliance with the ethical standards: the study was conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986) and the Rules for Handling Experimental Animals (order № 755 of 12.08.1977 of the Ministry of Health of the USSR).

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МОДЕЛЬ ЛЕЧЕНИЯ АБСОЛЮТНОГО МАТОЧНОГО БЕСПЛОДИЯ НА ЭКСПЕРИМЕНТАЛЬНЫХ ЖИВОТНЫХ

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До появления современных вспомогательных репродуктивных технологий трансплантацию репродуктивных органов рассматривали как потенциальное лечение яичникового, трубного и маточного бесплодия. Трансплантацию матки можно рассматривать как метод лечения абсолютного маточного бесплодия, подобный пересадке нежизненно важных органов. Однако клиническое применение трансплантации матки у человека вызывает много проблем. Целью исследования было разработать программу по оценке различных хирургических методов реваскуляризации тканей для восстановления репродуктивной функции при маточной форме бесплодия на экспериментальных животных. Выбор кроликов породы шиншилла (n = 20) для экспериментальной работы обусловлен идентичностью строения органокомплекса всех млекопитающих. Для разработки хирургического протокола пересадки тканей репродуктивной системы на лабораторных животных применили инновационную методику по использованию яичниковых артерий вместо маточных, как в стандартном протоколе. Согласно результатам, полученным на лабораторных животных, гемодинамические характеристики кровоснабжения пересаженной матки не меняются, что позволяет имплементировать данную хирургическую методику для использования в эксперименте на трупном материале для пересадки матки. Предлагаемый протокол проведения операции по трансплантации матки обеспечивает высокий уровень приживаемости трансплантанта и его нормальное кровоснабжение с минимизацией рисков травматизации донора и снижением сложности операции.

Ключевые слова: пересадка матки, лечение маточного бесплодия, трансплантация органов, органное донорство, сравнительный анализ

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Absolute uterine factor infertility (AUFI) have historically been regarded as an incurable form of infertility, however, the first case of a child born after allogeneic uterus transplantation (UT) was reported in 2014 [1]. The success of this surgical procedure was the substantial progress in treatment of AUFI. AUFI may be caused by past surgical interventions preventing embryo implantation or positive pregnancy outcome [2]. About 20 women per 100,000 female population of reproductive age have AUFI [3, 4]. Uterus transplantation is associated with a number of ethical challenges, which, in turn, can produce medical, psychological, and legal risks for both genetic and biological mothers of the unborn child [4].

Absolute uterine factor infertility (AUFI) can have various causes: uterine agenesis, anomalies of uterine development, congenital uterine anomalies or the history of organ retrieval surgery preventing embryo implantation or positive pregnancy outcome [2, 4].

The absent uterus is the most obvious cause of AUFI. The uterus is most often absent due to the history of hysterectomy used for treatment of such disorders as uterine fibroid, cervical or endometrial cancer, severe adenomyosis [1, 3].

The Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome associated with abnormal formation of Müllerian ducts is the cause of congenital aplasia of the uterus [4]. There is a number of AUFI causes found in women with the preserved uterus, such as congenital uterine anomalies with partial developmental defects and fusion defects of the Müllerian ducts [5].

AUFI may result from complications of intrauterine manipulation or severe endometritis [6]. UT can be the only method for restoring fertility in this group of patients. The estimated prevalence of AUFI is 20,000 cases in women of reproductive age per 100 million population [4].

The cold or warm ischemia is one of the most important issues to be dealt with when treating infertility using UT. Cells of the transplant are damaged since the moment of artery clamping in the donor's body to the moment of reperfusion after revascularization in the recipient's body. The mouse study has shown that spontaneous pregnancy is still possible after 24 h of cold ischemia; the loss of function occurs after 48 ч h of cold ischemia [7]. The sheep uterus that was as large as the human uterus remained viable after 24 h of cold ischemia, viability was assessed within 8 days after the organ auto-transplantation [8]. Sensitivity to warm ischemia was studied in rats [9], Macaca fascicularis macaques [10], and sheep [11]. The organ remained viable after 5, 4, and 3 h of ischemia, respectively. The innate regenerative potential that includes, among other things, organ-specific stem cells, ensures the ability of the uterus to compensate possible ischemia injury during transplantation [7–9, 12].

Immunosupression is one more important issue. The rat studies show excellent results of using tacrolimus [13] for prevention of rejection compared to cyclosporins [14]. Tacrolimus also proved effective in the rabbit study [15], and, according to the findings, it effectively prevented rejection in pigs for 12 months [16]. Cyclosporine monotherapy was effective in the studies involving sheep [17]. These data combined show that monotherapy with cyclosporins or tacrolimus is effective in rodents and large domestic animals.

Organ transplantation is a complex surgical problem, the main aspect of which is restoration of graft perfusion through establishing arterial inflow and venous outflow [2, 15]. When performing organ transplantation, blood flow restoration results from performing anastomosis of the main artery responsible for blood supply to the donated organ and the large main blood vessel of the recipient; venous outflow is restored in the same way [18]. In this regard many authors report the development of complications associated with abnormal venous outflow after transplantation. These data have provided the basis for identification of several major ways of blood flow restoration in the transplant, however, the optimal method has not been defined [7, 11].

When preparing for the first living donor UT in human, the surgical technique for retrieval of uterine arteries and veins in patients who underwent surgery due to uterine cancer and cervical cancer and lymphadenectomy was tested [19]. Later the results of this study provided the basis for the development of surgical protocol for the living donor UT in humans [20].

The study was based on the hypothesis that it was possible not to use uterine veins in the transplantation method since ovarian veins were enough. The other papers report the use of both groups of veins during transplantation [21].

All the researchers point out that the use of uterine arteries is associated with a number of complexities.

It is difficult to retrieve uterine veins when retrieving organ from a living donor (it is difficult to separate these from the ureter which is located in close proximity in terms of anatomy).

Uterine veins are intricately woven highly branched thin blood vessels that present a challenge when performing surgery, as a result, the surgical procedure is very time-consuming.

In case of multiorgan donation from a deceased donor the uterus is not a priority (it is retrieved last, if necessary), therefore it is difficult to retrieve the kidney: the kidney must be retrieved with the ureter of maximum length, that is why the uterus would be unusable (adjacent uterine blood vessels would be destroyed).

To date, there is no approved protocol for surgical treatment of AUFI by uterus transplantation in the Russian Federation. The study was aimed to review the results of the studies of uterus transplantation in model animals (rabbits) reported in the world literature.

METHODS

The study was conducted in 2021 by the research team of the Federal Siberian Research Clinical Center of the Federal Medical Biological Agency of the Russian Federation. Laboratory animals were used: 20 female rabbits of the Chinchilla breed with the body weight of 1800–2000 g and the confirmed normal reproductive function (parous rabbits).

The animals underwent a two-week quarantine in the vivarium according to the animal housing requirements before the experiment, they were given specialized wafers supplemented with vegetables, cereals, hay, and dairy products. The following light/dark cycle was used: 12 : 12 h, light since 08:00 am. There was one rabbit per cage. The animals' health status was assessed daily, and the data were recorded in the measurement diary.

Blood flow parameters, vascular resistance index, and blood pressure were measured by Doppler ultrasound (Hitachi Aloka ProSound Alpha 6; Japan). All the experiments were recorded, photographic evidence was provided. Statistical data processing involved the use of the standard algorithm of statistical procedures, and the methods of statistical analysis were applied in accordance with the studied trait type and the number of comparison groups. The Shapiro–Wilk test was used to assess the distribution of quantitative indicators. In case of non-normal distribution the descriptive statistics was presented as median and percentiles. The Kruskal–Wallis test was used for multiple comparisons to assess the significance of differences, while the Mann–Whitney U test was used for pairwise comparison.

Table 1. Anatomic and hemodynamic parameters of the rabbit female reproductive blood vessels

Parameter		Value
Weight		3700 g
Body length		37 cm
Right uterine artery length		52 mm
Left uterine artery length		54 mm
Right ovarian artery length		43 mm
Left ovarian artery length		45 mm
Doppler parameters		
Right uterine artery	V_{min}	3,1
	V_{max}	29,7
	PI	3,92
	RI	0,89
Left uterine artery	V_{min}	3,3
	V_{max}	27,8
	PI	3,89
	RI	0,88
Right ovarian artery	V_{min}	1,42
	V_{max}	22,78
	PI	4,02
	RI	0,77
Left ovarian artery	V_{min}	1,53
	V_{max}	23,62
	PI	3,97
	RI	0,69

In case of normal distribution the descriptive statistics was presented as mean and standard error of the mean. Significance of differences between the normally distributed indicators in the studied groups was assessed using the Student's *t*-test.

Program of experimental studies

The experiment involved 20 model laboratory animals (rabbits), divided into four study groups:

– group 1 (n = 5) — the animals underwent ligation of the uterine veins;

– group 2 (n = 5) — the animals underwent ligation of the ovarian veins;

– group 3, controls (n = 5) — intact animals;

– group 4, controls (n = 5) — the animals underwent ligation of the uterine and ovarian veins.

The animal experiments were carried out in three phases. Various vessels that supplied blood to the uterus were ligated, a total of two blood vessel groups: the ovarian artery and ovarian veins, the uterine artery and uterine veins. When the uterine veins were ligated and the ovarian venous outflow was preserved only, the animals were monitored for two weeks in order to make sure that they had no dystrophy of the organ.

Experiment 1. Anatomical evaluation of the vascular territories (inflow and outflow vessels) of female reproductive organs

Dissection of blood vessels of the uterus, ovaries, and vagina was performed with subsequent labeling of the vessels to determine the vessel length and the sites of anastomosis with the main arteries and veins, reveal collateral circulation, and identify shunts. After the blood vessel retrieval, the vessel length and diameter were measured; Doppler ultrasound was used to assess blood flow parameters, vascular resistance index, and blood pressure.

Experiment 2. Assessment of the compensatory capabilities of various venous vascular territories responsible for drainage of reproductive organs

At this stage ligation of various main blood vessels providing blood inflow and outflow from reproductive organs was performed with subsequent immediate and delayed assessement of their impact on blood flow and functional state of the reproductive organs.

The animal was followed-up for 14 days during the experiment. After 14 days, midline incision was performed again in order to revise pelvic organs and the site of previous surgery. Blood flow parameters were measured by Doppler ultrasound in the pelvic blood vessels and the uterus once again.

Experiment 3. Uterus transplantantation involving the use of ovarian veins as the only venous outflow tract

The uterus was separated from the parametrial tissue, the urinary bladder and the colon were separated from the uterus, and the ligaments of those were transected. At the next stage vagina was transected. Then ligation and transection of the uterine veins was performed that was followed by clipping of the iliac arteries and transection of those at the sites where the uterine arteries arised. After that the donor animals were withdrawn from the experiment by intravenous administration of the lethal dose of magnesium sulfate. Cannulation of the uterine arteries and ovarian veins of the transplant and the transplant perfusion using the Custodiol solution (at least 200 mL, in accordance

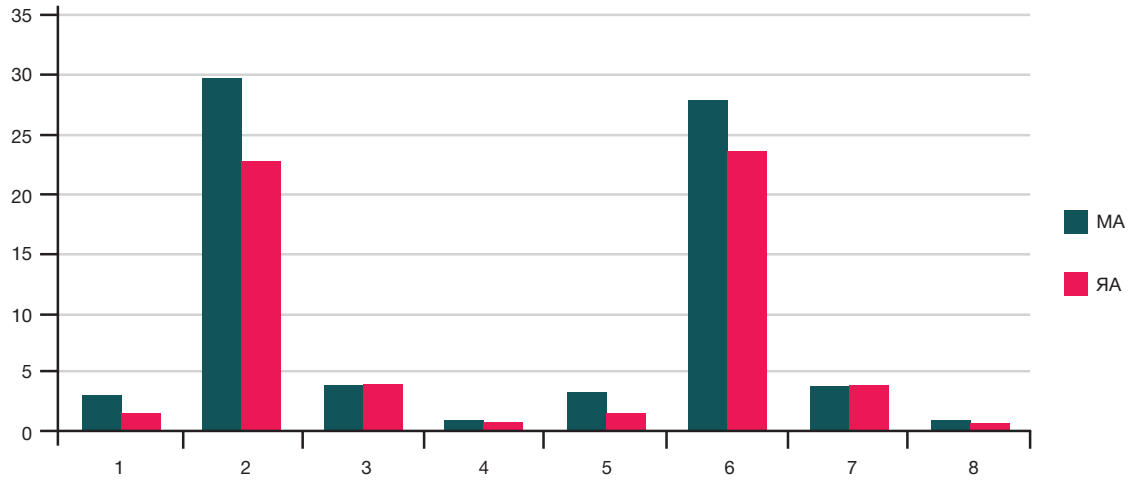

Fig. Doppler parameters of animal 1

with the transplant size) combined with heparin solution (1 : 5000) were performed. After adequate washing (i.e. until there were no blood components in the washing fluid) the transplant vascular pedicles were prepared for transplantation.

After 14 days, midline incision was performed again in order to revise pelvic organs, the site of previous surgery, the transplant condition, and anastomoses. Blood flow parameters were measured by Doppler ultrasound in the pelvic blood vessels and the transplanted uterus once again.

RESULTS

The data obtained by assessing the anatomic parameters and hemodynamic indicators of blood flow in the reproductive organs of female rabbits by Doppler ultrasound are provided in Table 1.

Comparative analysis of the parameters of anatomic and substitutional curculation was performed for each of 20 animals. Consider these with an example of animal 1 (Figure).

The data provided in Figure show that the differences in V_{min} values between the uterine and ovarian arteries can be explained by the differences between the anatomic vessel diameters. Both the length and the diameter of these blood vessels vary considerably (the uterine artery has a much larger diameter) and, since the V_{min} value represents blood flow during diastole, it is obvious that blood flow is greated in the vessel with the larger diameter, and the differences between blood vessels may be considerable. That is why it should be expected that the V_{min} value of the uterine artery would be significantly higher than that of the ovarian artery. The measurements performed in 20 animals confirm that it is 2–2.5 times higher.

Comparative analysis of blood flow parameters was performed in all experimental animals.

The V_{max} value represents blood flow during systole, it is slightly higher in the uterine value than in the ovarian artery. This can also be explained by anatomic features. The aorta is divided into two common iliac arteries, which, in turn, are divided into two external and internal iliac arteries. The uterine artery arises from the internal iliac artery, while the ovarian artery arises directly from the aorta.

In contrast to V_{min}, the differences between the V_{max} values of the uterine and ovarian arteries should be insignificant (15–30%). This was confirmed by measuring the Doppler parameters in all 20 animals. In animal 6, minimum blood flow velocity in the left UA was more than two times higher than in the OA (227%). In animal 7, minimum blood flow velocity in the left UA was twice as high as in the left OA, the same differences were observed in the right arteries. The differences between V_{max} values were insignificant: 26% for the left ovarian arteries, 22% for the right arteries.

Statistical processing of the results using the Student's *t*-test is provided in Table 2.

A total of 20 surgeries were performed in model animals (rabbits). Parameters of blood inflow/outflow were defined in each animals for the following pairs: right and left uterine arteries, right and left ovarian arteries (Table 2). No pairs showed significant differences between the total blood flow values.

DISCUSSION

The criteria of successful transplantation and uterus removal must be defined prior to transplantation. The uterus transplant failure is determined by the following charateristics: no return of menstruation within certain period after transplantation, no pregnancy regardless of multiple embryo transfer procedures, uterine atrophy. The time period for these outcomes has not been defined, however, it must be determined prior to transplantation, since the long-term use of immunosuppressive drugs poses a risk to the recipient. The measures to counter functional failure are as follows: assessment of the transplanted uterus by echography with subsequent prescription of immunosuppressors. No immunosuppression was used during our study.

The uterus transplantation clinical use in humans requires a thorough discussion of issues related to reproductive ethics. Medical, ethical, social, and religious background is different in the countries that have performed such surgical procedures, such as Saudi Arabia, Turkey, and Sweden, that is why transplantation of the uterus should be thoroughly discussed taking into account all the provisions. It is important to consider the question, whether uterus transplantation is socially significant, i.e. whether the method of uterus transplantation satisfies the need of patients with uterine factor infertility for childbirth. The uterus transplantation method contributes to improving the methods for treatment of such patients and probably improves their health and quality of life. Based on the urgent issues in the countries where surrogacy is not allowed, the surgical procedure is not unnecessary or excessive. However, a handful of gynecologists and a much smaller number of patients and people in society are aware of the issues of uterus transplantation, that is why it is important for the surgical procedure to be widely perceived by the public. The large-scale public opinion polls aimed at studying the

Table 2. Student's t-test for the comparison group

Comparison groups	*p*
Right uterine artery V_{min}	< 0,001
Right ovarian artery V_{min}	
Right uterine artery V_{max}	< 0,001
Right ovarian artery V_{max}	
Right uterine artery PI	0,032
Right ovarian artery PI	
Right uterine artery RI	0,003
Right ovarian artery RI	
Left uterine artery V_{min}	< 0,001
Left ovarian artery V_{min}	
Left uterine artery V_{max}	< 0,001
Left ovarian artery V_{max}	
Left uterine artery PI	0,491
Left ovarian artery PI	
Left uterine artery RI	0,01
Left ovarian artery RI	

Note: *p* — significance level of the differences

social needs and attitude towards surgical procedure are the next step.

CONCLUSIONS

The main idea of the study is that it is possible to artificially change the nature of blood flow in the implanted organ during the uterus transplantation: the proposed method is aimed at avoiding the time-consuming and potentially dangerous surgical procedure involving restoration of blood outflow through the uterine artery in the recipient. Such an approach makes it possible to develop a new protocol for treatment and surgery that would significantly reduce the risk of postoperative complications.

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