v. 2, n. 80, 2022

International Journal of Health Science

PERSPECTIVES OF UTERUS TRANSPLANTATION IN THE TREATMENT OF INFERTILITY: A LITERATURE REVIEW

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Abstract: Introduction: Absolute uterine factor infertility (AUFI) may have uterine transplantation (UT) as a therapeutic approach. The practical application faces challenges associated with the complexity of the procedure, ethical concepts and anatomical difficulties. Objective: To discuss the effectiveness and challenges of UT as a safe surgical treatment for uterine infertility in women of childbearing age. **Methodology:** Bibliographic review carried out based on searches in the PubMed and SciELO databases, of which 12 studies were considered to compose the collection after applying inclusion and exclusion criteria. **Review:** The choice of a living or deceased donor must undergo a thorough screening in terms of anamnesis, laboratory and anatomy. Postoperative complications, psychological factors and complications related to fetal development may occur. Regarding the success of the procedure, it was observed that UT from living donors obtained better results than those from deceased donors and most complications are due to vascular causes. **Final Considerations**: UT is an innovative therapeutic option, however, it is still considered an experimental procedure with positive results for future research.
Keywords: Uterus; Transplant; Surgery.

INTRODUCTION

Infertility in menacme by absolute uterine factor (AUFI) is due to the absence of uterus or uterine dysfunction. In this sense, uterine transplantation (UT) emerges as a revolutionary approach for the treatment of uterine infertility, considered irreversible until 2014, when it allowed the birth of the first child after UT in a woman of childbearing age with absence of the uterine organ (BRÄNNSTRÖM M.; DAHM-BAHLER P., 2019).

Mayer-Rokitansky-Küster-Hauser Syndrome

(SMRKH), previous hysterectomy or severe uterine adhesions, is the main indication for UT. UT corresponds to a treatment method that combines the principles of solid organ transplantation followed by assisted reproduction (BRÄNNSTRÖM M. et al., 2018). The purpose of such a procedure is to promote fertility and improve the quality of life of the patient, allowing them to reach genetic maternity and the gestational act, but without the intention of prolonging it, since the transplanted organ can be removed after reaching the objective (SILVA A.F.G. and CARVALHO L.F.P., 2016).

Despite being an alternative for the treatment of infertility, the use of UT is still considered experimental and is not the reality in several reference services due to its limitations and the high complexity of using the technique. Such complexity, in addition to the anatomical challenges that suggest a transplant of such magnitude, is also related to ethical concepts by involving issues such as a living or dead donor, conditions of the recipient and later of the fetus (SILVA A.F.G. and CARVALHO L.F.P., 2016). In this context, the aim of this study is to discuss the effectiveness and challenges of uterine transplantation as a safe surgical treatment for uterine infertility in women of childbearing age.

METHODOLOGY

The study is a bibliographic review developed between October and November 2022, according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. This strategy was used for the elaboration of the research through its guiding question: "Is uterine transplantation a safe surgical treatment for infertility due to uterine causes in women of childbearing age?". In this sense, according to the criteria mentioned above, the population of this research refers to female patients of childbearing age with different conditions of uterine infertility and for variables and outcome, the challenge and effectiveness of uterine transplantation as a surgical treatment for such frames. The searches were carried out through searches in the PubMed and Scientific Electronic Library Online (SciELO) databases. The descriptors were used in combination with the Boolean term "AND": Uterus, Transplantation, Surgery. Inclusion criteria were: articles in Portuguese and English; published in the period from 2016 to 2022 and that addressed the theme proposed for this research, studies of the type systematic reviews, meta-analysis and original articles, and made available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 41 articles were found. Of which, 38 articles belonged to the PubMed database and 3 articles to SciELO. After applying the inclusion and exclusion criteria, 11 articles were selected from the PubMed database and 1 article from SciELO, using a total of 12 studies to compose the collection.

RESULTS

UAFI of congenital or acquired origin is one of the main indications of UT in menacme (DAOLIO J. et al., 2020). This condition affects about 1.5 million women worldwide, and the congenital form originates from fetal uterine malformations at the level of the Mullerian conduits, especially SMRKH (DAOLIO J. et al., 2020; EJZENBERG D. et al., 2016). SMRKH is characterized by normal female karyotype with a solid rudimentary uterus or complete absence of the organ, in which carriers of the syndrome are unable to have a conception (BRÄNNSTRÖM M. et al., 2018).

Women with UAFI of acquired etiology are usually subject to hysterectomy due to uterine fibroids, intrauterine adhesions (Asherman's Syndrome), adenomyosis, and endometrial and cervical neoplasms. It is noteworthy that malignant cervical neoplasia is the third most frequent form of neoplasia in females (EJZENBERG D. et al., 2016). Radiotherapy treatments can also lead to changes in uterine functions, being an important cause of acquired FUAU (DAOLIO J. et al., 2020). When there is no need for a hysterectomy, uterine dysfunction does not allow the correct implantation of the embryo during pregnancy, and UT is a viable option also for women with a present uterus (BRÄNNSTRÖM M. et al., 2018).

Choosing a living donor requires a screening process that may be limited, but in order to maintain the safety of the recipient. Note the importance of reporting age, body mass index, comorbidities, mainly obstetric diseases, previous surgeries, lifestyle, also addressing data on alcohol and tobacco consumption. In addition to such factors, it is also extremely important to assess the psychological stability of the donor (BRÄNNSTRÖM et al., 2019).

According to Brannstroom M. et al. (2020), the donor must have uterine arteries with a diameter >1.5 mm on at least one side, in addition to the absence of atherosclerosis. As an exclusion factor there are some comorbidities such as diabetes, cardiovascular disease, lung disease, gynecological malignancy or previous major intra-abdominal surgery. along with serologies for cytomegalovirus, Epstein-Barr, human immunodeficiency virus, hepatitis and syphilis, are also part of such an investigative process (BRÄNNSTRÖM M. et al., 2020).

Note that, when dealing with deceased donors, the test results must be completed within 12 to 24 hours. To detect uterine malformation or even polyps and leiomyomas of relevant sizes, imaging tests such as computed tomography or magnetic resonance imaging are the main choice (BRÄNNSTRÖM et al., 2019). In addition to such evaluation methods, according to Brannstroom M. et al. (2020), magnetic resonance angiography with pelvic contrast and conventional digital subtraction angiography of the iliac and uterine arteries help in the success of uterine transplantation, since the vasculature of the donated organ is closely linked to the favorable outcome of the surgical procedure (BRÄNNSTRÖM et al, 2019).

The UT technique can be performed via robotic-assisted laparoscopy or traditional laparoscopy, both with their individual advantages. Robotic surgery has articulated instruments, including a three-dimensional camera that allows a wide view and access to the surgical field. Traditional laparoscopy, on the other hand, has a lower cost, in addition to providing good surgical results. In cases where conversion to laparotomy is required for bleeding resolutions, the conversion time is shorter when compared to robotic surgery (BRÄNNSTRÖM M. et al., 2020).

To perform the donor surgery, it begins with an infraumbilical incision in the midline, where the uterus and vascular pedicles are subsequently dissected. In order to guarantee a better fixation in the receiver's pelvis, parts of the round ligament, uterosacral ligament and peritoneum are removed. Next, the lateral walls of the pelvis are dissected, and the ureters are separated from the cervix and uterine vessels. The vagina also undergoes the dissection process, 10-15 mm distal to the vaginal fornix. After that, the blood supply is interrupted by clamping the vessels, and the uterus is removed and transported to the table, where it is washed with heparinized saline solution, placed in preservation solution, and preserved on ice until the opportunity to perform the transplant. (BRÄNNSTRÖM M; DAHM-BAHLER P., 2019). An average

time of 330 minutes was spent to perform the entire procedure (TESTA G. et al., 2017).

In recipient surgery, an infraumbilical incision is made in the midline as well, and the vaginal walls are detached from the bladder and rectum. For further fixation of the transplant, sutures are fixed in the round ligament, uterosacral ligament, uterine rudiment or paravaginal tissue. The bilateral external iliac vessels are dissected, and the uterus that was on ice is anatomically positioned in the recipient's pelvis. Then, end-to-side vascular anastomoses are performed between the graft vessels and the external iliac vessels. Prior to the release of arterial clamping, intravenous mannitol is administered as a bolus and systolic blood pressure is monitored to maintain a value above 100 mmHg. With the completion of the anastomoses, the blood flow in the uterine vessels is calculated using a Doppler probe positioned around the uterine arteries. A 40 mm longitudinal incision is made in the recipient's vaginal walls and an anastomosis is made between the cul-de-sac of Douglas and the vaginal portion of the graft. The uterus is fixed by pre-positioned sutures in the ligaments, and through an overlapping of the peritoneum of the graft to the recipient's bladder.

According to Bränström M., Kvarnström N., and Dahm-Kähler P. (2020), the most complex part of the surgery involves dissection of the distal ureter and uterine veins. In view of this, most of the surgical time is spent at this moment, in order to avoid ureteral injury, given that the ureter passes through the space between the vascular pedicle and the body of the uterus when entering the bladder. Added to this, veins with thin walls make anastomosis difficult, the presence of soft plaque around the uterine artery has the possibility of complicating the patch, and depending on its size there may be an incompatibility between the uterine cervix and the vaginal dome (TESTA G. et al., 2017).

UT has many particularities when compared to other types of vascularized composite allografts (TESTA G. et al., 2017). Because it is a recent and poorly described treatment method, the risks and possible complications are not well defined. Because it is considered an experimental and highly complex procedure, even with the positive results already presented from the application of the technique, there is still a need for studies to clarify some recurrent complications such as lacerations of arteries, veins, ureter and tissues (NOVOTNY R. et al., 2020).

The transplanted organ can be received from both a deceased donor and a living donor, transplants performed from living donors had a higher percentage of positive results and a lower percentage of negative results when compared to those from deceased donors (DAOLIO J. et al., 2020). The fact that deceased donors are related to a higher percentage of complications may be associated with their previous living conditions (EJZENBERG D. et al., 2016).

Postoperatively, patients are referred to an intensive care unit and during the first days, daily intravaginal Doppler ultrasounds and cervical biopsy of the graft are performed. Furthermore, the use of magnetic resonance imaging can be undertaken to assess the perfusion of the uterine veins due to the use of contrast, which allows identifying cerebral venous thrombosis and pelvic venous congestion (TESTA G. et al., 2017).

Among the postoperative complications described, vaginal cuff dehiscence, temporary gluteal cramps, urinary tract infection, minor depression and fecal impaction stand out. Furthermore, as an important psychological factor, the recipient of the organ must understand that the UT involves risks due to immunosuppression performed in the postoperative period, high-risk pregnancy

and the need for at least three subsequent surgical procedures. Among these three stages are the uterine transplant itself, the cesarean delivery and a hysterectomy of the graft after the delivery (TESTA G. et al., 2017). In addition to the aforementioned complications, graft rejection followed by necrosis of the transplanted uterus is also possible. In addition, the future baby may also experience complications. It appears that there is a greater chance of low birth weight and prematurity in pregnancies via UT, due to the immunosuppressive treatment to which the woman is subject during the gestation period (VALLE ROBLES M. et al., 2021).

Recent studies have shown that the cause of the main complications of transplantation is the result of reduced blood flow or problems (NOVOTNY R. et al., 2020). The first recorded human UT resulted in necrosis of the transplanted organ and hysterectomy three months after transplantation. According to Bränström M., Kvarnström N., and Dahm-Kähler P. (2020), this fact occurred due to insufficient perfusion of the graft. cases of UT had to perform hysterectomy postoperatively due to vascular complications (uterine infarction, thrombosis after graft inflow complications). In his study, Testa G, (2017), evaluating the UT process in the first 5 cases performed in the United States, by living donors, it was reported that the first 3 recipients had graft loss, due to vascular complications as the main reason for loss, grafting failure; and the other 2 recipients had grafts with normal menstrual cycles.

According to Novotny R. et al. (2020), arterial and venous thrombosis are identified as the main complications in uterine transplantation, in addition to others after the procedure, such as infections, highlighting the reduction or problems of blood flow involved.

According to Novotny R. et al. (2020), arterial and venous thrombosis are identified as the main complications in uterine transplantation, in addition to others after the procedure, such as infections, highlighting the reduction or problems of blood flow involved. Also, Testa G. et al. (2017) states that there are 5 well-defined steps that indicate success in the UT process, adequate vascular perfusion, assessed by the presence of vital tissue in the basal cervical biopsy; normal menstrual cycles, demonstrating good hormonal response; stable immunosuppression; success in the implantation of a fertilized ovum, generating, in fact, a pregnancy and, finally, the occurrence of a delivery of a healthy child. Although uterine transplantation is a very recent procedure, sharing information, surgical techniques, results and complications is essential for determining a procedure with a wide and safe indication (TESTA G. et al, 2017).

FINAL CONSIDERATIONS

The effectiveness and challenges of UT as a surgical treatment for infertility due to uterine causes show better results with living donors after extensive evaluation of compatibility and viability of the organ. Among the main challenges stem from the reduction or problems of blood flow. However, the application of UT is not the reality of many reference services worldwide and it is necessary to carry out new studies and research that allow the determination of a safe and effective procedure with the reduction of more severe complications, guaranteeing safety. not only for the mother but also for the fetus during the gestational process and afterwards.

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