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Current Therapies to Improve the Endometrial Receptivity of Patients with Repeated Implantation Failure in IVF-ET

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ABSTRACT

Endometrial receptivity disorder is the leading cause for failed embryonic implantation. Recently, the methods to ameliorate endometrial receptivity, to improve the success rate and increase the clinical pregnancy rate of in vitro fertilization-embryo transfer (IVF-ET) technology has become a research hotspot. In this article, we describe the treatment methods and elaborate the latest progress made in improving endometrial receptivity in the recent years.

Keywords: Repeated implantation failure (RIT); *In vitro* fertilization-embryo transfer (IVF-ET); Endometrial receptivity; Therapies

Introduction

Repeated implantation failure (RIF) implies at least 3 consecutive treatment cycles of failed *in vitro* fertilization-embryo transfer (IVF-ET), in which 1 or 2 quality embryos are implanted in each treatment cycle. RIF has gradually become the major problem that undermines the pregnancy rate of IVF [1]. A good endometrial tolerance is an important factor to ensure the implantation, growth and development of embryos; defective endometrial receptivity is one of the principal causes of RIF [2]. Previous studies have shown that endometrial thickness varies periodically within the menstrual cycle, and that maintaining a certain thickness of the endometrium during the planting window is conducive to increasing the success rate of embryo implantation [3]. The etiology and the underlying mechanism of low endometrial receptivity remain unclear. Clinically treatments are carried out to increase endometrial thickness, ameliorate endometrial blood flow, induce the secretion of regulative cytokines, and enhance the expression of pinopodes, which is the marker of endometrial receptivity in clinical practice.

Chemical Medicine and Hormone-Replacement Therapy

The human endometrium is a fluctuating and complex multicellular tissue that is affected by ovarian-derived steroid hormones. In the event of reduced ER level caused by low estrogen levels in the body and intrauterine adhesions, high doses of estrogen are used to promote endometrial regeneration [4]. Estrogen binds to the estrogen receptor and regulates cell-specific transcription of the target tissue, thereby exerting its cell proliferative effect. Under the effect of estrogen, the endometrium becomes thicker; with the synergistic effect of progesterone, the hyperplastic endometrium is transformed to enter the secretory phase [5]. Shen MS et al. [6] reported one case of patient receiving IVF-ET with repetitive failed implantation due to thin endometrium, and that the extended treatment of estrogen effectively guarantees the pregnancy and the subsequent delivery of twins. Currently, the medications used to improve endometrial microcirculation include aspirin, low molecular weight heparin (LMWH), microbial E and so on [7].

In recent years, the application of aspirin in assisting reproduction has received increasing attention. Studies indicate that [4], aspirin increases the blood flow of the uterine artery by inhibiting platelet aggregation. LMWH can prevent thrombosis formation in embryonic sites and placenta attachment sites in patients with thrombotic tendency during early pregnancy. Moreover, Aspirin can regulate the expression of certain cytokines

and growth factors in the endometrium, thereby promoting its decidualization and providing a good environment for embryo implantation [8]. As one of the most important antioxidants in the human body, Vitamin E also exhibits the effect of dilating blood vessels. Wilkens [9] observed that vitamin E increases the endometrial glands of patients and promote the development of blood vessels, to improve endometrial receptivity.

Surgical Treatment

Hysteroscopic surgery can detect and treat small lesions in the uterine cavity, therefore it has become an important means for the diagnosis and treatment of uterine cavity abnormalities [10]. The operation of Hysteroscopic surgery is simple. Under the visual condition, it can reveal whether there is an anatomical abnormality in the uterine cavity with good recognition and great accuracy. Studies have confirmed that [11] hysteroscopic endometrial minimally invasive surgery can clarify the morphological classification of endometrium, improve the distribution of blood flow and induce the development of endometrial vesicle, thereby enhancing endometrial receptivity. The clinical application value of hysteroscopic endometrial minimally invasive surgery has been corroborated regarding improving endometrial receptivity.

Stem Cells and Granulocyte Colony-Stimulating Factor (G-CSF)

Bone marrow mesenchymal stem cells (BMSCs) can differentiate into tissue cells belonging to three germ layers under specific induction conditions [12]. Zhao [13] injected BMSCs into the uterine cavity of SD rats with thin endometrium and found that the endometrium of rats was significantly thickened. Therefore, the researchers rationally speculated that BMSCs can differentiate directly into endometrial cells in the uterine cavity or stimulate the proliferation of endometrial cells through the secretion of cytokines and immune regulation. The effect stimulates proliferation of endometrial cells. It is suggested that stem cell perfusion not only improves the regeneration ability of the endometrium, but also raises endometrial receptivity. However, the perfusion of BMSCs is constrained in animal experiments only. More clinical trials are needed to confirm the effectiveness and safety of transplantation *in vivo*.

G-CSF is also used to treat RIF, owing to the main mechanism of stimulating the maturation of granulocyte and macrophage, promote the release of mature cells to the peripheral blood, and stimulate the multiple functions of macrophages and eosinophils [14]. Kunicki M et al. [15] conducted clinical study on 37 patients with thin endometrium (<7mm during ovulation) who received IVF-ET treatment, reporting that G-CSF intrauterine significantly increased the thickness of endometrium from 6.74±1.75 mm to 8.42 ±1.73 mm (mean ± SD). G-CSF is of great significance in endometrial regulation throughout the human menstrual cycles. However, due to its distressing side effects and high price, G-CSF has not yet been widely used in clinical practice. In addition, therapies of growth hormone (Gn), biofeedback (BF), and platelet-rich plasma (PRP) [16] are currently used to enhance endometrial receptivity.

Traditional Chinese Medicine (TCMs)

The history of using traditional Chinese medicine in treating gynecological diseases dates to long ago. The efficacy of numerous TCMs to improve endometrial receptivity has been confirmed. Wu Xiaoyu [17] observed that human placenta shows a certain effect on improving the endometrial receptivity of rats in an apparent dose-dependent manner. Ma Rong et al. [18] believe that Bushen Tiaochong recipe can improve the endometrial receptivity of patients with the obesity PCOS infertility.

Acupuncture

A plethora of evidence in recent years have highlighted the significant effect of acupuncture in assisting the treatment of infertility, especially regarding its low side effects in improving endometrial receptivity. Yan Honglian [19] suggested that performing acupuncture treatment 24 hours before transplantation and 30 minutes after transplantation alleviated the blood supply in the endometrium of patients who underwent IVF-ET. In addition, it is found that transcutaneous acupoint electrical stimulation (TAES) [20] can improve endometrial blood supply and regulate estrogen levels in the serum, thereby improving endometrial receptivity and enhancing clinical pregnancy rate.

Conclusion

At present, achievements have been made in the researches of improving endometrial receptivity and clinical pregnancy rate. These results bring good news to infertile patients, especially to those who have suffered from repeated failed implantations. Some patients have achieved favorable clinical efficacy. Nevertheless, given the lack of in-depth experimental researches and the limited number of clinical cases, the clinical application of some newly emerged methods is under constraint. In clinical applications, these methods should be handled with great discretion, with special attention paying to the possible side effects of medications and operational complications.

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