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Application of Intrauterine Perfusion in Patients with Recurrent Spontaneous

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Abstract: *Recurrent abortion (Recurrent Spontaneous Abortion, RSA) is a common disease in obstetrics and gynecology, which refers to three or more times of spontaneous abortion in the same woman, which can be characterized by vaginal bleeding and abdominal pain after menopause. Most of RSA are early abortion and a few are late abortion, which are related to genetic and endocrine factors. Due to the development of assisted reproductive technology, endometrial damage has been found to be an important factor leading to recurrent abortion. Intrauterine infusion of drugs or biological agents can directly contact the endometrial gland and act directly on the endometrium to improve and repair the endometrium. The treatment process has the characteristics of less trauma, no pain, simple operation and good patient compliance. This article will review the application of intrauterine infusion of different drugs in patients with recurrent abortion.*

Keywords: *Recurrent abortion; intrauterine perfusion; cyclosporine A; granulocyte colony stimulating factor; human chorionic gonadotropin; peripheral blood mononuclear cells*

1. Introduction

Recurrent Spontaneous Abortion (RSA) is a common disease in obstetrics and gynecology, which refers to three or more times of spontaneous abortion in the same woman, which can be characterized by vaginal bleeding and abdominal pain after menopause [1]. Most of RSA are early abortion and a few are late abortion, which are related to genetic and endocrine factors. Due to the development of assisted reproductive technology, endometrial damage has been found to be an important factor causing RSA. Intrauterine infusion of drugs or biological agents can directly contact the endometrial gland, directly act on the endometrium, improve and repair the endometrium [2]. There are many ways to improve endometrial thinning and endometrial receptivity (ER). In addition to drug therapy and endometrial curettage [3-5], intrauterine perfusion has also been applied in the past two years.

2. Intrauterine infusion of cyclosporine A

Cyclosporine A (CsA) is an immunosuppressive drug used to prevent allograft rejection and act on T lymphocytes [6,7], as shown in Figure 1. The biological properties of cytotrophoblasts in early pregnancy are similar to those of tumor cells [8]. Human early pregnancy studies have confirmed that appropriate dose (0-1 μ M) of CsA can not only induce maternal immune tolerance to embryonic antigen, but also promote the proliferation of chorionic trophoblasts, inhibit trophoblast apoptosis, enhance their ability of movement, migration and invasion, and thus play a dual role in regulating pregnancy [9,10]. The results show that CsA can reduce the damage of trophoblasts and improve the proliferation and invasiveness of trophoblasts by activating intracellular MAPK/ERK signal transduction pathway under oxidative stress. In the study of early mouse embryo culture in vitro, it was found that C. (CsA) is an immunosuppressive drug used to prevent allograft rejection and act on T lymphocytes [6,7]. The biological properties of cytotrophoblasts in early pregnancy are similar to those of tumor cells [8]. Human early pregnancy studies have confirmed that appropriate dose (0-1 μ M) of CsA can not only induce maternal immune tolerance to embryonic antigen, but also promote the proliferation of chorionic trophoblasts, inhibit trophoblast apoptosis, enhance their ability of movement, migration and invasion, and thus play a dual role in regulating pregnancy [9,10]. The results show that CsA can reduce the damage of trophoblasts and improve the proliferation and invasiveness of trophoblasts by activating intracellular MAPK/ERK

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signal transduction pathway under oxidative stress. In the study of early mouse embryo culture in vitro, it was found that CsA promoted the blastocyst formation and hatching of mouse embryos in a dose-dependent manner in a certain concentration range (0-10 μ M), and the best concentration was 1 μ M. in the mouse pregnancy failure model, it was observed that intraperitoneal injection of CsA could significantly reduce the embryo absorption rate of mice with pregnancy failure model [11]. In addition, the study on the molecular mechanism of CsA improving mouse embryo implantation showed that CsA at a certain concentration did not affect the pre-hatching development of embryos, including proliferation, apoptosis, blastocyst formation, the differentiation of inner cell mass cells and trophoblast cells and the expression of COX2 on trophoblast cells, but the expression of Oct4 was up-regulated in inner cell mass cells closely related to embryo implantation. CsA may enhance the ability of embryonic adhesion and migration by up-regulating the expression of synthase α v β 3. By up-regulating the expression of MMP-9, the ability of embryos to cleave extracellular matrix is improved, thus the invasive ability of embryonic trophoblasts is improved [12]. Therefore, CsA may have an impact on the development of peri-implantation embryos, such as promoting the value of trophoblasts, enhancing the implantation ability of embryos, increasing the implantation rate of embryos, and improving the outcome of IVF-ET pregnancy. The most important lymphocytes in the pregnant uterus are uterine NK cells, namely uNK cells. Its phenotype is that CD56brightCD16-, uNK cells play an important role in the normal growth, differentiation and implantation of embryos. UNK proliferate after ovulation and account for more than 30% of immune cells in the late secretory stage. In the early stages of pregnancy, CD56+ cells are still up-regulated, accounting for 70% of immune cells at the maternal-fetal interface. UNK cells may play a key role in the invasion and migration of trophoblasts and placenta. The concentration of uNK cells in endometrium of women with RSA changed significantly. CD57 is generally regarded as a biomarker of the final differentiation of cytotoxic T cells. A large number of CD57+NK cells can be detected in the decidua of patients with RSA. Studies have shown that oral CsA can inhibit NK cells and increase the live birth rate in patients with refractory immune RSA [13,14]. Intrauterine infusion of CsA is a new study. In the study of Zhao et al. [15], it was used to treat refractory recurrent spontaneous abortion patients with endometrial alloimmune disorder. Participants were randomly divided into two groups: the CsA group received 250mgCsA intrauterine infusion on the 3rd and 7th day after menstruation for 2 menstrual cycles, and the placebo group received placebo. The results showed that intrauterine infusion of CsA could significantly affect the refractory alloimmune RSA, significantly increase the success rate and reduce the abortion rate. However, there are few studies on the efficacy of intrauterine infusion of CsA in the treatment of RSA patients, and there is still a lack of more strong evidence to prove its efficacy.

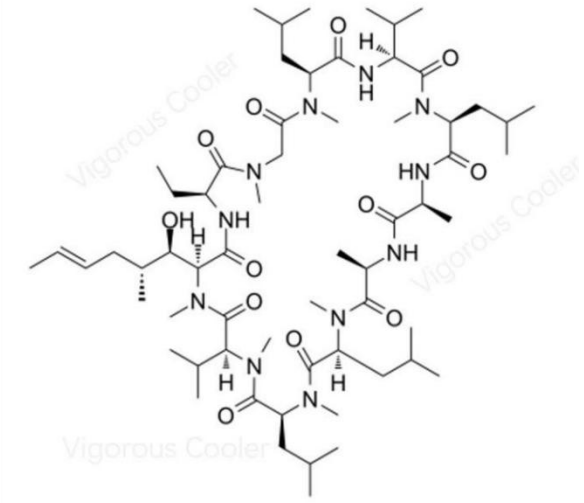

Figure 1: Cyclosporine A (CsA)

3. Intrauterine infusion of granulocyte stimulating colony factor

Granulocyte colony stimulating factor (G-CSF) is one of the cytokines that play an important role in embryo implantation and normal pregnancy, as shown in Figure 2. In 1983, G-CSF was first discovered and purified in mice. Three years later, in 1986, humans cloned the glycoprotein. In 2011, some researchers tried to use intrauterine infusion of G-CSF in the field of fertility for the first time. They conducted an experiment in 4 patients with thin endometrium. All the subjects received IVF-ET-assisted

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pregnancy. Before using assisted reproductive technology, G-CSF was perfused into the uterine cavity to prepare the endometrium. It was found that 4 patients successfully obtained fresh embryo transfer and pregnancy. This experiment opened up the exploration of the application of G-CSF in the field of reproduction. Especially in the application of assisted reproductive technology. Studies have shown that the mechanisms of G-CSF on endometrium include anti-inflammation, repairing endometrium and promoting angiogenesis: G-CSF converts local endometrial monocytes into macrophages, phagocytosis local inflammatory factors, reduces inflammatory response, repairs damaged endometrial tissue and promotes enrichment; G-CSF promotes matrix diversification and repairs damaged cells and endometrium through paracrine or autocrine. G-CSF stimulates the secretion of vascular endothelial growth factor, promotes cell proliferation and migration, and then regenerates intimal microvascular network, promotes basilar artery formation, improves intimal blood circulation, recovers blood supply, and gives intimal rich nutrients. G-CSF inhibits NK cells, positively regulates endometrial receptivity, promotes endometrial growth, and improves pregnancy outcome [16]. Scholars consider that G-CSF can give full play to the role of bone marrow mesenchymal stem cells by regulating immunity, increasing the expression of markers related to embryo implantation, mobilizing hematopoietic stem cells and other mechanisms to effectively promote endometrial repair and regulate endometrial receptivity [17]. In the reproductive system, G-CSF is produced by granulosa cells, which is beneficial to follicular development, ovulation and ovarian response [18,19]. In addition, G-CSF plays an important role in maintaining pregnancy by regulating the immune response of macrophages, lymphocytes and Th2 cells. Studies have shown that rhg-CSF intrauterine infusion therapy for patients with recurrent abortion can increase the levels of estrogen and progesterone in patients, significantly improve the receptivity of endometrium, and significantly reduce the rate of abortion and increase the probability of successful pregnancy [20,21]. However, in the study of ZafardoustS [22], a total of 50 patients were randomly assigned to two groups, including intrauterine injection of G-CSF (n = 23300 μ g) and control group (n = 27, without G-CSF). Of the 23 subjects who received intrauterine injection, 6 (26.1%) tested positive, while in the control group, 8 (29.6%) tested positive for β hCG. There was no significant difference between the two groups (P :0.781), indicating that patients with RSA could not improve the pregnancy rate by intrauterine infusion of G-CSF. Therefore, the study on whether intrauterine infusion of G-CSF can improve the pregnancy outcome of patients with RSA is affected by different doses and duration of drugs, different inclusion and exclusion criteria, and there is still no clear evidence that G-CSF can effectively treat RSA.

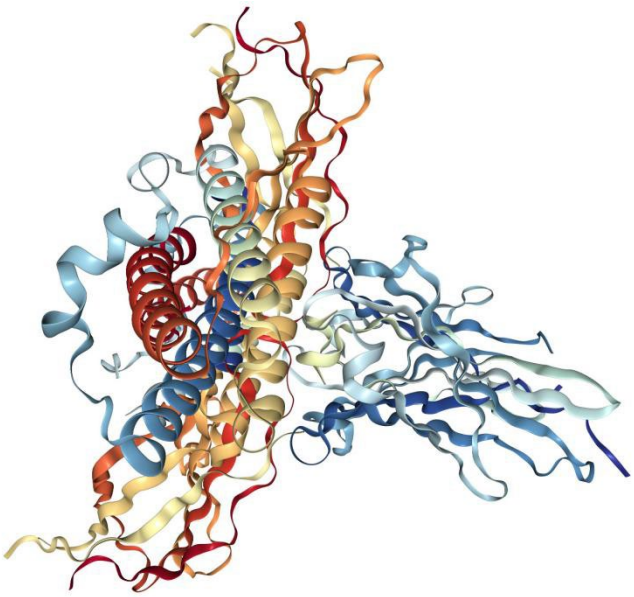

Figure 2: Granulocyte colony stimulating factor (G-CSF)

4. Intrauterine infusion of human chorionic gonadotropin

Human chorionic gonadotropin (HCG) is a commonly used drug for intrauterine infusion (Figure 3). HCG, a glycoprotein hormone secreted by trophoblasts, is the earliest embryonic signal in humans. HCG is produced before the embryo is implanted into the uterus. It is a heterodimer placental glycoprotein hormone and plays an important role as an autocrine factor in regulating embryo implantation, trophoblast invasion and cell growth [23]. It plays an important role in maintaining pregnancy. HCG can

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up-regulate the interleukin-1 receptor in endometrial stromal cells, which plays a key role in angiogenesis and placental development. In addition, it can also change the immune microenvironment of the maternal-fetal interface and mediate immune tolerance. In addition, it was found that hCG, hCG receptors secreted by endometrium during secretory phase were mainly expressed in mid-luteal phase, suggesting that hCG secreted by endometrium as a paracrine factor is beneficial to predecidual progression of endometrium [24,25]. In addition, hCG can also induce endometrial decidua and promote endometrial identity, thereby regulating endometrial receptivity and maternal immune system [26-29]. Previous studies have shown that intrauterine infusion of hCG can increase the percentage of Treg cells in peripheral blood of RSA patients during the implantation window, change the number of natural killer cells, inhibit macrophage migration, regulate the balance of Th1/Th2 and complement system C3/C4, thus regulate maternal immune response, promote embryo implantation and maintain pregnancy. Furthermore, it can enhance the immune tolerance between mother and fetus and enhance the endometrial receptivity, but its mechanism is not clear at present [30]. In the study of Wang Shan [31], through the detection of serum E2 and P in the implantation window of patients with intrauterine infusion of HCG, as well as the sudden pregnancy rate of pinocytosis and clinical pregnancy rate, it was confirmed that intrauterine infusion of HCG could significantly increase the expression rate and clinical pregnancy rate and reduce the risk of abortion in patients with recurrent abortion. A Meta analysis conducted by Gao M et al. [32] in 2019 shows that the timing of HCG infusion varies from 3min~72h before embryo transfer, which may induce the secretion of different factors, thus affecting the process of embryo implantation. HCG infusion of 15min before transfer can obtain the highest clinical pregnancy rate. This study also found that PI and RI in the study group were lower than those in the control group. PI and RI were used to measure the endometrial spiral artery, which could reflect the endometrial blood flow. The decrease of PI and RI indicated that the endometrial blood flow was well improved [33]. It is suggested that intrauterine infusion of rHCG into 15min before FET can significantly improve the endometrial blood flow in patients with RIF and thus improve the outcome of pregnancy.

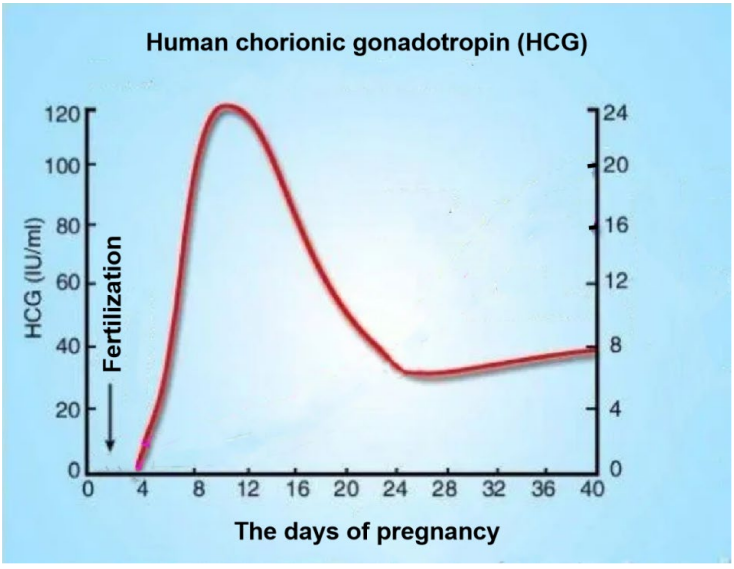

Figure 3: The relationship between HCG and Gestational days

5. Intrauterine infusion of autologous peripheral blood mononuclear cells

PBMCs was obtained by density gradient (Ficoll-Hypaque) centrifugation of peripheral blood cells. The final product of this process (95%) consists of lymphocytes (such as T cells, B cells and NK cells) and monocytes as well as a small number of red blood cells and granulocytes [34], as shown in Figure 4. Macrophages, dendritic cells and regulatory T cells involved in adaptive immunity provide a unique endocrine immune microenvironment for embryo implantation and promote embryo implantation [35]. FujiwaraH [36] believes that intrauterine infusion of PBMCs can lead to endometrial differentiation, thus preparing for embryo implantation. Secondly, the protease secreted by PBMCs can effectively change the molecular structure and function expressed in endometrial lumen epithelial cells. Yu et al. [37] observed in animal experiments that administration of autologous PBMCs activated by hCG can increase the levels of endometrial leukemia inhibitory factor and vascular endothelial growth factor (VEGF), thus increasing the rate of embryo implantation. At the same time, the scholar also observed that hCG can

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stimulate human peripheral blood monocytes to secrete cytokines and stimulate trophoblast invasion. In recent years, the treatment of intrauterine infusion of autologous lymphocytes is mainly focused on patients with repeated implantation failure. Zhao Ting et al. [38] applied this treatment to patients with unexplained recurrent spontaneous abortion (URSA) for the first time. The results showed that intrauterine infusion of PBMCs could reduce the local inflammatory response of endometrium in patients with URSA, inhibit the toxic effect of mixed lymphocyte reaction on embryos, and regulate Th1/Th2 immune response. Make the maternal endometrial microenvironment to be beneficial to pregnancy.

Human PBMCs	Frequency (%)
Monocytes	10-30%
Lymphocytes	70-90%
Total T cells (CD3+)	45-70%
CD4+ T cells	25-60% of total CD3
CD8+ T cells	5-30% of total CD3
Total B cells	5-15%
NK cells	5-10%
Dendritic cells	1-2%
Stem cells	0.1-0.2%

Figure 4: PBMC

6. Conclusion

Intrauterine infusion of drugs or autologous blood components is easy to operate, and local administration can achieve higher local concentration, lower systemic adverse reactions and lower cost. Patients were treated with intrauterine infusion of autologous platelet-rich plasma, granulocyte stimulating colony factor, chorionic gonadotropin, growth hormone, mononuclear cells and cyclosporine A. most studies have confirmed that intrauterine infusion therapy can increase embryo implantation rate, clinical pregnancy rate and live birth rate, and improve the pregnancy outcome of patients with repeated implantation failure, assisted reproduction and repeated abortion. However, the metabolism of the drug in the uterine cavity is still unclear, and the mechanism of the drug infusion in the uterine cavity epithelium and whether it will cause immune response in the uterine cavity and affect embryo implantation is still unknown. At present, due to the small sample size included in various intrauterine perfusion studies, a large number of randomized controlled studies are still needed to provide reliable evidence of evidence-based medicine to confirm its clinical effectiveness.

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