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Research progress of cyclosporine A in treatment of recurrent abortion

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Abstract: *Recurrent spontaneous abortion (RSA) is one of the common complications of pregnancy in obstetrics and gynecology, and it seriously threatens the physical and mental health of women in the reproductive period. The etiology of RSA is complex, and based on the basic national conditions and clinical practice in China, it is found that the incidence rate of RSA among women of childbearing age increases year by year. At present, the etiology of some patients with RSA is unknown, and some studies have reported that its pathogenic factors are closely related to immune abnormalities. At present, immunization-related therapeutic scheme of RSA has attracted more and more attention from scholars. Many studies have found that the immunosuppressive agent A (cyclosporine A, CsA) has an affirmative effect on the prevention and treatment of RSA by benign regulation of maternal-fetal immune tolerance and positive regulation of trophoblast biological function. However, the application of CsA in the reproduction field is still in the exploratory stage, and there are no standardized treatment standards, large samples and high quality clinical trials. In view of this, we reviewed the mechanism of action of CsA in the treatment of RSA and the research progress of combination therapy in recent years, in order to provide new theoretical support for the subsequent clinical treatment of RSA.*

Keywords: *cyclosporine A; recurrent abortions; Maternal and fetal immune tolerance; nurse cell*

1. Introduction

The maintenance of pregnancy requires a complex multisystem synergy process that relies on good embryo implantation and placental vascular recasting. The process cannot be separated from the synergistic effects of the immune system, hormones, cytokines, and adhesion molecules. The adhesion, migration and invasion of trophoblasts can lay the foundation for placental vascular recasting, and the embryo's immune rejection and tolerance as well as the balance of the mother-fetal interface can ensure the smooth implantation of the embryo. At present, the recurrent spontaneous abortion rate of women of childbearing age increases year by year. Immune factors have attracted more and more attention in the diagnosis and treatment of RSA, and its scientific and normative treatment is an urgent problem to be solved. cyclosporine A (CsA), an immunosuppressive agent, has been widely used for the prevention and treatment of CsA due to its efficacy in promoting maternal and fetal immune tolerance and regulating the physiological function of trophoblasts. Previous studies theoretically support that CsA can improve the embryo development and implantation microenvironment and enhance the embryo implantation potential. This indicated that it had a good development prospect as a clinical fetal protector for the treatment of RSA, and provided a new treatment idea for clinically refractory recurrent abortion. This article reviews the research progress of CsA in the treatment of recurrent spontaneous abortion in recent years.

2. The Definition of RSA and Etiological analysis

Recurrent abortion,a high-prevalence disease, refers to the embryo loss before 28 weeks of gestation that occurs two or more times in a row with an identical partner [1], including continuous biochemical pregnancies, emphasizing its continuity and recurrence. The etiology of RSA is complex and may be either a single factor contributing to the loss of the embryo or confounded multiple factors. As shown in Figure 1 and Figure 2, the reasons inculde immunological abnormalities, prethrombotic

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state, chro-mosoe or gene abnorma-lities (including embryo chromosome or gene abnormalities and chromosome or gene abnormalities of both husband and wife), anatomical abrma-lities of female reproductive tract, endocrine abnormalities, males' reproductive tract infection and other factors such as bad living habits and exposure to harsh environme-nts [2]. After careful and scientific exclusion of all definite causes, about 50% of RSA patients fail to be interpreted by the known causes of morbidity, which is called unex-plained recurrent spontaneous abortion (URSA) [3-5]. It has been reported URSA mainly associated with immune imbalance [6]. A series of treatment measures for RSA caused by immune factors and unexplained reasons are currently the hot spots in the research of reproduction field.

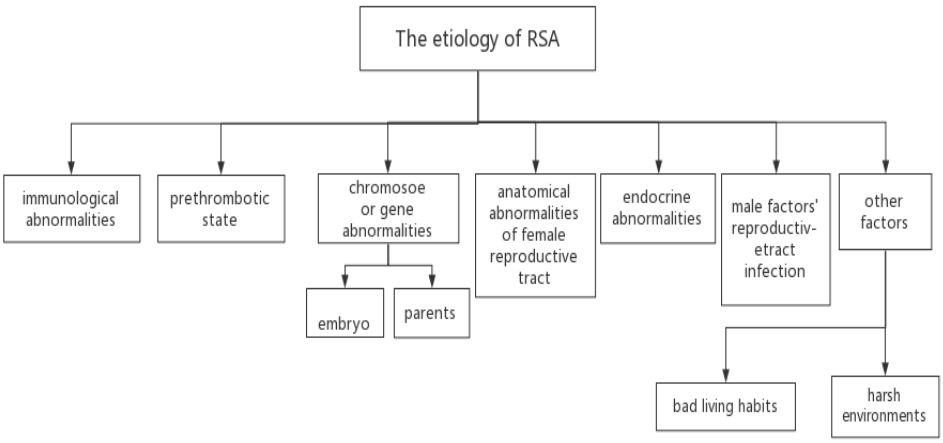

Figure 1: The etiology of RSA

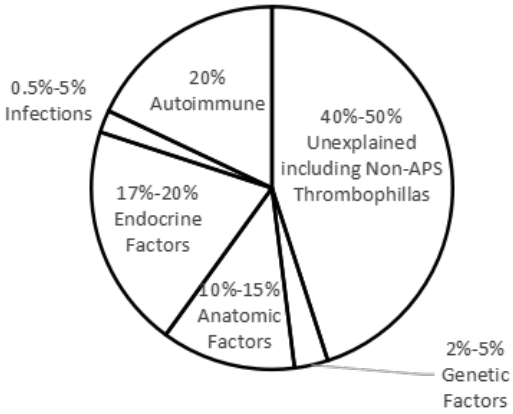

Figure 2: The rates of RSA factors

3. Overview of Cyclosporine A

Cyclosporin A, also known as cyclosporin A (CsA), is a macrolide immunosupp-ressive agent consisting of 11 amino acids [7]. In the 1980s, CsA firstly used in clinical and has since been widely used for organ and bone marrow transplantation as well as for the treatment of autoimmune diseases.

CsA acts on the Ca2+/calcineurin/NFAT signaling pathway and affects the expre-ssion of T-cell receptor avidin (CYP) by inhibiting the secretion of human calmodulin (CaM)-calcineurin, and further inhibits the activation of calmodulin on neural calcine-urin, blocks the pathway of cell activation nuclear factor (NFAT), and inhibits cell activation to exert immunosuppressive effect [8]. CsA can directly regulate the immune cells, as well as endothelial cells, myocardial cells, epit-helial cells and tumor cells. Also specifically block humoral and cellular immunity involved in rejection without affecting the general defense function [7]. CsA has the function of promoting the migration, invasion and proliferation of cells. CsA has been reported have good clinical efficacy in the treatment of myocardial ischemia-reperfusion injury, brain injury, nephrotic syndrome, rheumatoid arthritis, corneal inflammation, hepatitis, cholecystitis, gastritis, etc. [9-14]. It also blocks the activation of JNK and p38

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signaling pathways triggered by antigen recognition, making a highly specific inhibitor of T cell activation [15].

4. Csa Treatment of Recurrent Spontaneous Abortion Immune Mechanism Research

The essence of pregnancy is allotransplantation, and the fetus carrying paternal human leukocyte antigen (HLA) stimulates the maternal immune system. From the perspective of immunology, an embryo can be considered as a special "tumor". besid-es the factors of the embryo itself, a variety of immune cells and cytokines in mother body will produce immune rejection. However, in normal pregnancy, the fetus as a se-miallogeneic graft can avoid maternal immune attack and survive and develop until successful delivery. The essence of pregnancy is the maternal immune tolerance to the fetus, in order to protect the embryo from maternal rejection.

Recently CsA has been widely used in recurrent spontaneous abortion. Professor Huang's research [16] revealed that the early pregnancy study indicated that CsA, while inducing the maternal immune tolerance to the embryo antigen, could promote the proliferation and invasion of villi TB within 50-60 days of pregnancy and reduce its apoptosis. In the mouse abortion model, CsA acts by binding to cyclophilin through the MAPK3/MAPK1/AP1 signaling pathway and the Ca2+/calcinations/NFAT signal-ing pathway, thereby reducing embryo resorption rate. The research by Wang [17] and others reported, CsA can induce maternal and fetal immune tolerance, exert a benefic-ial regulatory effect on the biological behavior of trophoblasts, help to improve the pregnancy outcome, and is expected to become a new type of fetal protection drug.

The regulation of fetal antigen response by maternal CD4+T cells is an important component of maternal and fetal immune tolerance during pregnancy. Immature CD4+T cells are able to differentiate into different subsets including Type 1 T helper cells (Th1/Th2/Th17), and CD4+ CD25+ T regulatory (Treg) cells when encountering antigen on the surface of antigen-presenting cells or when driven by a set of cytokines. In additio, CsA can prevent and inhibit maternal rejection of the embryo or fetus from the following aspects, and induce maternal-fetal immune tolerance.

4.1. Regulatory Effect of Csa on Helper T Cells

Th1 and Th2 (Figure 3) are important cell populations for regulating matern-alfetal immune response. Th1 cells secrete IL-2 and IFN-γ, and enhance the immunot-oxicity of NK cells, thereby inhibiting embryo implantation, trophoblast growth and embryo development, leading to abortion, fetal Growth restriction (FGR) and hyperte-nsive disorder complicating pregnancy. Th1 can induce intravascular coagulation, microthrombosis, decidual vessel rupture, and subcallofacial hemorrhage, leading to maternal rejection of the embryo [18]. Th2 cells secrete IL-4 and IL-10 to effectively protect the embryo and protect the embryo from the immune system by inhibiting Th1-type immune response [19]. During normal pregnancy, the change in the ratio of Th1/Th2, the related factor secreted by Th cell subtypes, is converted to a model dominated by Th2 cytokines, so that the Th1/Th2 immune balance at the maternal-fetal interface is always maintained in a Th2 immune bias state that is conducive to maintaining pregnancy. In addition, the shift from Th1/Th2 to Th1-type cellular immune regulation imbalance has been confirmed in multi-directional studies to be related to the occurrence of RSA [20].

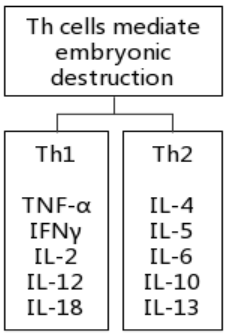

Figure 3: The cells mediate embryonic destruction

Lin Dong et al. explored the impact of CsA on the pregnancy prognosis of a mouse model of spontaneous abortion and its action mechanism, and found that CsA during the implantation phase could effectively attenuate the synergistic stimulation signals, recover the formation of Th2-type

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immune deviation needed to maintain pregnancy, induce maternal-fetal immune tolerance, and reduce the embryo absorption rate [21]. The follow-up study found that CsA could reduce the expression levels of Th1 cytokines IFN-γ and TNF-α in peripheral blood of patients with unexplained recurrent spontaneous abortion [22]. Yong Chen et al. divided 60 patients with URSA into two groups. Patients in the conventional group were given intramusc-ular progesterone (20mg, qd) and human chorionic gonadotropin (1000U, qd). At 10 weeks of gestation, intramuscular drug therapy was discontinued and progesterone capsules (100mg, bid) were administered orally until 12 weeks of gestation. The obse-rvation group was treated with CsA in combination with the conventional group. On the 30th day before pregnancy, CsA(30mg/d) was administered according to the conc-entration of anticardiolipin antibody (ACA) and anti-β2 glycoprotein I antibody in the patient. On 10th and 20th days of medication, the patient was examined for blood CsA concentration, which was maintained at 100ng/ml. After conception, the drug concentration was maintained, and the antibody was examined every month. For patients whose antibody became negative, the administration of various drugs was gradually stopped. For patients with recurrent antibody positivity, the above drugs were continued to be administered. The levels of IL-2, IL-10 and anticardiolipin antibody (ACA) before and after treatment were observed (Table 1), and the pregnancy outcomes of two groups were recorded. The results showed that after treatment, the levels of IL-2 and ACA in the observation group were lower than those of the conventional group, and the level of IL-10 was higher than that of the conventional group. The successful delivery rate in the observation group was higher than that in the conventional group, and the incidence of ectopic pregnancy and recurrent spontaneous abortion were lower than those in the conventional group. The differences between the two groups were statistically significant ($P<0.05$). It is proposed that the combination of conventional treatment with CsA can achieve the fetal protection of URSA by regulating the balance of cytokines, which is worthy of promotion and application [23].

Table 1: The ratio of IL-2, IL-10, and ACA levels before and after treatment between the two groups

Groups	IL-2/u·L-1		IL-10/u·L-1		ACA/RU·ml-1	
	before	After	Before	After	Before	After
The observation group	(33.01±1.54)×103	(18.23±1.78)×103	8.40±1.38	12.75±0.83	6.58±3.15	3.84±0.92
The conventional group	(32.12±1.46)×103	(9.13±2.14)×103	8.38±1.35	18.47±3.85	6.61±3.19	1.02±0.57
P	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

4.2. Effects of Csa on Regulatory T cell Balance

Helper T-cells 17 (Th17) and regulatory T-cells (Treg cells) are two different subtypes that CD4+ cells differentiate into after antigen stimulation. Treg cells can inhibit multiple immune responses, while Th17 hinders immune tolerance. Studies have found that the Th17/Treg ratio in RSA patients is significantly higher than that in normal pregnant women. The overexpression of Th17 in RSA patients proves that the abnormal expression of Th17/Treg cells is related to the occurrence of RM [24]. In the research by Guan et al. [25], CsA significantly and positively regulated the normal expression of cytotoxic T lymphocyte associated antibody 4 (CTLA-4) in the window of embryo transplantation, and reduced the CD80 /CD86 /CD28 level at the maternal-fetal interface, thus improving the pregnancy outcome. A recent study found that CsA could reduce the production of IL-17A, the main Th17 effector, and upregul-ate TGF-β1, IL-10, Tregs-related factors in peripheral blood of RSA pregnant women, as well as cytotoxic T lymphocyte associated protein 4 (CTLA-4) and T cell immunoglobulin mucin-3 (Tim-3), promoting Tregs advantage [26].

There were a certain number of CD4+CD25+TR cells in the peripheral blood of normal women, and the lack of these cells will lead to autoimmune diseases and abor-tion [27]. The research results of Professor Li's team showed that when CsA was applied around the bed, the embryo absorption rate of pregnant rats in the sponta-neous abortion model was significantly reduced, and at the same time, the CD4+ CD25+ TRcell subsets were significantly expanded, thus improving the pregnancy prognosis of pregnant rats in the spontaneous abortion model [28].

5. Effect of Csa on Villous Trophoblast

Normal placental formation is an important basis for maintaining a normal pregnancy. Trophoblasts, derived from the embryo, are not only the main cells that make up the placenta, but also the only

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embryonic cells that come into contact with the maternal decidua and its immunologically active cells. Extra-villous cytotrophoblasts are derived from the differentiation and development of trophoblasts located in the inner layer of the villi. They enter the uterine endometrium through adhesion, migration and invasion, and can also invade the uterine spiral arteries and replace vascular endothelial cells, thereby playing a role in fixing the placenta, fetus and recasting the uterine vasculature, providing adequate nutrition and appropriate partial pressure of oxygen for embryonic development. Therefore, the normal migration and invasion of trophoblasts are crucial for the implantation of fertilized eggs, the formation of placenta, and the establishment of maternal-fetal circulation. Inadequate migration and invasion of nutrients, which can lead to preeclampsia, intrauterine growth restriction, spontaneous abortion and other diseases; conversely, excessive invasion of trophoblasts will induce gestational trophoblastic disease. M Hojo et al. [29] published in Nature found that CsA had a significant proliferation effect on tumor cells. Yan et al. [30] studied that CsA in a suitable concentration range could stimulate the proliferation of human cytotrophoblasts to increase the number of cells in the meiosis stage (G2-M) and their transformation into DNA synthesis stage (S stage), decrease the number of apoptotic cells, and increase and lengthen cell pseudopodia. These results suggested that CsA might play a dual regulatory role in the maternal-fetal immune regulation, inhibiting the maternal immunologic rejection of embryo antigens in pregnancy failure, promoting the growth, movement and invasiveness of cytotrophoblasts, thus potentially becoming an effective drug for the treatment of pregnancy diseases such as repeated spontaneous abortion. (Figure 4)

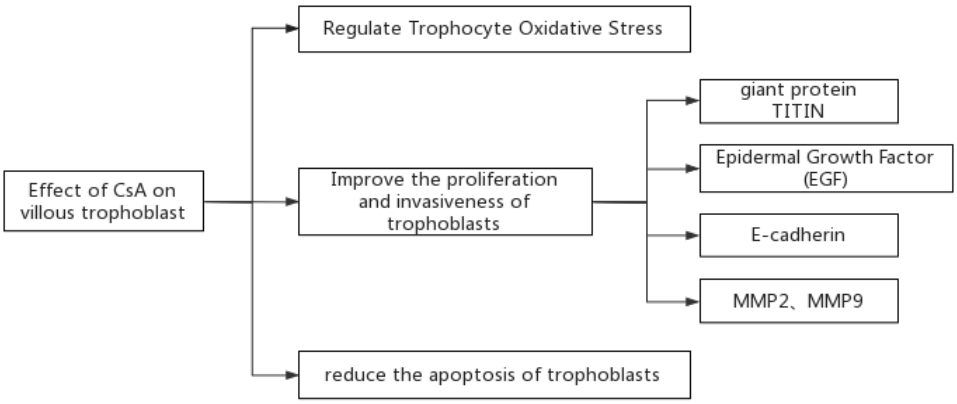

Figure 4: Effect of CsA on villous trophoblast

5.1. Csa Regulating Trophocyte Oxidative Stress

Oxidative stress is a key factor in the development of adverse pregnancie. ROS are produced in large quantities under oxidative stress. Excessive ROS free radicals damage the trophoblasts, leading to apoptosis, reducing cell invasion, and causing the superficial implantation of the placenta. This results in intrauterine growth restriction of the fetus and associated placental pathology such as preeclampsia, stillbirth and placental abruption. The intervention of CsA could significantly improve the biologic-al behavior of cells under oxidative stress. Reduce that oxidative damage degree of cells and enhance the antioxidant damage capability, Inhibit mitochondrial-related apoptotic signaling pathways and activation and reduce trophoblast apoptosis [31].

5.2. Csa Improves the Proliferation and Invasiveness of Trophoblasts

CsA can induce the expression of giant protein Tintin. Tintin, also known as cascade protein, is the structural basis for cell movement, cell morphology and transmembrane information transmission, and also an important regulatory factor involved in vascular reconstruction. It is speculated that Tintin participates in CsA-promoted migration and movement of trophoblasts and participates in maternal vascular reconstruction, thus opening the placental blood supply [32].

CsA enhanced the activation of epidermal growth factor (EGF)-induced EGF receptor in trophoblasts and promoted the invasion of trophoblasts [33]. Another study found that CsA could increase the activation level of trophoblast focal adhesion kinase (FAK) and form an activation complex with activated Src kinase in the cytoplasm, thus promoting the activation of the downstream signaling pathway ERK, which was involved in the regulation of trophoblast invasion and migration

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[34].

Cadherin, an important member of the adhesion molecule cadherin family, widely distributes on the surface of various epithelial cells and inhibits tumor invasion and metastasis by mediating intercellular calcium-dependent adhesion. E-cadherin was also expressed on the surface of trophoblast membrane, and E-cadherin expression in trophoblasts at the site of placenta accreta was significantly decreased. Wheelock et al. [35] found that extravillous trophoblasts obtained a highly aggressive phenotype by down-regulating the expression of E-cadherin in a hypoxic environment. Studies have shown CsA down-regulates the transcription and expression of Ecadheri-n, and thus participates in the regulation of trophoblast migration and invasion [16].

5.3. Csa Reduces the Apoptosis of Trophoblasts

Yan et al. [30] showed that CsA had a concentration-dependent regulation on the proliferation of trophoblasts. Low concentrations exhibited a promoting effect, while high concentrations exhibited an inhibiting effect. Hung et al. [36] found that CsA-pretreated placental tissue showed a decrease in the number of apoptotic cells accompanied by a decrease in ROS production when compared with the non-added group. The existence of a large number of trophoblasts in the placenta suggested that CsA might inhibit the mitochondrial pathway of apoptosis by affecting the production of ROS, Bax and Bcl-2, and thus reduce the apoptosis of gestational trophoblasts.

6. Clinical Study on Treatment of RSA with Csa

Recent years, Low Molecular Weight Heparin (LMWH) has been widely used in the fields of obstetrics and gynecology and reproduction. It has definite effect and has made certain progress in the reproduction field such as repeated planting failure and repeated biochemical pregnancy treatment. LMWH is recognized as an effective drug for the treatment of RSA caused by prethrombotic state (PTS), anti-coagulation lipid syndrome (APS), autoimmune disease, and others. Xiong [37] divided URSA patients into CsA group (23 cases, orally administered CsA), LMWH group (23 cases, receiving subcutaneous injection of LMWH) and CsA combined with LMWH group (24 cases). The final results showed that CsA combined with LMWH could significa-ntly increase the blood HCG value of patients with unexplained recurrent abortion, which was conducive to maintaining pregnancy and improving the clinical pregnancy rate. At the same time, no significant adverse drug reaction was found in the clinical observation, so it was worthy of clinical reference and promotion.

Yang [38] divided the URSA patients into the treatment group (43 cases, orally taking Bushen Antai Formula combined with CaA) and the control group (38 cases, orally taking CsA). The results showed that the serum HCG and E2 levels of the two groups were significantly higher after treatment. The serum HCG level of the patients in the treatment group was higher than the control group after treatment, suggesting that CsA alone could effectively improve the hCG and E2 levels of URSA patients. In addition, the curative effect in the traditional Chinese medicine group was more significant. No abnormality was found in the follow-up Therefore, CsA may be a new option for patients with URSA, and in view of the possible adverse reactions, patients can be considered to be better treated with the combination of traditional Chinese medicine.

7. Conclusion

More in-depth mechanisms of CsA in treatment of recurrent abortion need to be further studied. CsA plays a dual regulatory role in the maternal-fetal immune regulation. It can not only inhibit the maternal immunologic rejection of embryo antigens in pregnancy failure, regulate immune factors, and inhibit the generation of reactive oxygen species, but also promote the growth, movement and invasion of cytotrophoblasts, and reduce the apoptosis of trophoblasts. Thus, CsA may become an effective drug for the treatment of pregnancy diseases such as repeated spontaneous abortion. All these support CsA in theory to improve the embryo development and implantation microenvironment and enhance the embryo implantation potential. These results indicated that it had a good development prospect as a clinical fetal protector for the treatment of RSA, and provided a new treatment idea for clinically refractory recurrent abortion. However, due to the complexity of the pharmacological effects of CsA and the fact that the specific mechanism is not yet fully clarified, there still exist such problems as systematic standardized clinical diagnosis and treatment standards, lack of large-sample RCTs, legal risks of drug use and risks of offspring, and large-sample and high-quality randomized double-blind

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controlled trials and basic research are still needed to further guide clinical practice. It is believed that with the understanding of the action mechanism of CsA, it will have a broader application prospect in the reproductive field.

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