



The Role of Immunological Factors in Recurrent Miscarriage and Advances in Immunotherapy

Lingyan Zhang, Kai'e Zhe*

Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi, China

DOI: 10.32629/ajn.v5i2.2449

Abstract: Recurrent miscarriage is a complex reproductive health problem when a woman suffers spontaneous miscarriage during two or more consecutive pregnancies. Recurrent miscarriage is a distressing condition in which immune factors play an important role. The immune system has an impact on the processes of embryo implantation, growth and development, and immune abnormalities may lead to rejection of the foetus or difficulties in implantation, thus triggering recurrent miscarriage. Therefore, the role of immune factors in recurrent miscarriages and advances in immunotherapy will open up more possibilities and hopefully bring new reproductive hopes and possibilities to couples who suffer from recurrent miscarriages.

Keywords: immunological factors; recurrent miscarriage; immunotherapy

1. Introduction

Recurrent miscarriage (RSA) is a common complication of pregnancy, which refers to two or more consecutive spontaneous miscarriages occurring at less than 28 weeks of gestation when the foetus weighs less than 1,000 grams. In China, the incidence of RSA among women of childbearing age is about 5 per cent, causing physical and psychological pain to women. The causes of RSA are varied, with immune factors accounting for 50-60 per cent of the total number of RSA. Immunological RSA can be divided into autoimmune and homoimmune types. Autoimmune RSA is mainly caused by autoantibodies such as antiphospholipid antibodies, which can lead to problems such as thrombosis and placental insufficiency. Homozygous RSA is caused by the mother's immune rejection of the foetus. Treatment of RSA requires a personalised treatment plan that takes into account various factors, including immunotherapy, cause screening and treatment. Through comprehensive diagnosis and treatment, the incidence of RSA can be effectively reduced and women's reproductive health protected.

2. Analysis of the role of immunological factors in recurrent abortion

Among the many reasons explored for recurrent miscarriage, immune factors cannot be ignored. Immune factors directly or indirectly affect the survival and development of the embryo.

Immune factors are mainly divided into two categories: autoimmune factors and homoimmune factors. Autoimmune factors usually refer to an attack on the embryonic tissue by immune cells or antibodies in the woman's body, resulting in damage or death of the embryo. This attack may be due to the immune cells incorrectly recognising the embryonic tissue as foreign and launching an immune attack. For example, antiphospholipid antibody syndrome is a common autoimmune disorder that causes the immune system to attack the endometrium and embryo, increasing the risk of recurrent miscarriage [1].

Homoeopathic immune factors, on the other hand, involve the maternal immune response to the foetus. Under normal circumstances, the maternal immune response to the foetus is tightly regulated to ensure normal foetal development within the mother. However, under certain circumstances, the maternal immune response to the foetus may be abnormal, resulting in maternal aggression against the foetus. For example, in the case of Rh blood group incompatibility, the mother may develop an immune response to the red blood cells of the foetus, leading to haemolytic anaemia and recurrent miscarriages.

For a deeper understanding of the role of immune factors in recurrent miscarriage, we can refer to some empirical studies. A study published in the *New England Journal of Medicine* found that the risk of recurrent miscarriage was more than three times higher in women with autoimmune diseases [2]. Another study found that recurrent miscarriage due to homozygous immune factors was particularly common in pregnant women with Rh blood group incompatibility.

In addition to empirical studies, we can further illustrate the role of immune factors in recurrent miscarriage with some vivid examples. For example, some women develop a type of autoantibody called "antinuclear antibody" after pregnancy, which attacks the embryonic tissues and leads to recurrent miscarriage. Some women with Rh blood group incompatibility

have repeated miscarriages in their fourth or fifth pregnancies even though their first pregnancies went well, which is likely to be related to abnormalities in the mother's immune response to the foetus.

In summary, immune factors play an important role in recurrent miscarriage. Understanding and identifying these immune factors is important for the prevention and treatment of recurrent miscarriage. Future studies can further explore the specific mechanisms of recurrent miscarriage caused by immune factors, providing more basis for clinical diagnosis and treatment. Meanwhile, for couples who have already suffered from recurrent miscarriage, doctors should also fully consider the possibility of immune factors and conduct appropriate examinations and treatments in order to improve their fertility success rate.

3. Advances in immunotherapy for immunological factors in recurrent abortion

3.1 Lymphocyte active immunotherapy in RSA

Lymphocyte active immunotherapy is a method of preventing miscarriage by injecting lymphocytes from the patient's husband or a third-party donor in order to stimulate the mother to develop immune tolerance. This treatment is based on immunological principles and aims to modulate the immune status of the mother and reduce immune attacks on the foetus.

In the treatment of RSA, lymphocyte active immunotherapy works through several mechanisms of action. Firstly, the injected lymphocytes stimulate an immune response in the mother, thereby creating immune tolerance to the foetus. Secondly, lymphocyte active immunotherapy regulates maternal immune function and reduces immune attacks on the foetus, thereby protecting the foetus from the maternal immune system. Finally, the therapy also improves the environment for embryo implantation and development by regulating the mother's endocrine system, providing better conditions for the growth of the foetus.

Lymphocyte active immunotherapy has been used with some success in the treatment of RSA. A study found that the pregnancy success rate of RSA patients was significantly improved after being treated with lymphocyte active immunotherapy [3]. At the same time, this therapy can also effectively reduce the risk of recurrent miscarriage in RSA patients and improve the stability of pregnancy.

Of course, there are some limitations and risks associated with lymphocyte active immunotherapy. For example, the therapy does not completely guarantee the success of pregnancy in RSA patients, and the injection of lymphocytes may trigger some adverse reactions, such as fever and allergic reactions. Therefore, when applying this therapy, the patient's specific situation and the doctor's advice need to be considered comprehensively.

At the present stage of therapeutic conditions, lymphocyte active immunotherapy provides a new treatment option for RSA patients. By modifying the immune status of the mother, reducing the immune attack on the foetus and improving the environment for embryo attachment and development, the therapy offers hope to RSA patients. However, the safety and efficacy of lymphocyte active immunotherapy needs to be further developed to bring more hope for the treatment of RSA.

During the treatment process, we also need to pay attention to the psychological needs of RSA patients. Miscarriage not only brings harm to the patient's body, but may also have a serious impact on his or her psychology. Therefore, in the course of treatment, doctors and family members should give full care and support to patients to help them get through the difficult times and regain confidence.

3.2 Immunoglobulin intravenous infusion therapy in RSA

Immunoglobulin intravenous infusion (IVIG) therapy has been shown to have unique efficacy in the management of recurrent miscarriage (RSA). The main mechanism of action of IVIG therapy is to inhibit the antiphospholipid antibodies, which tend to be highly expressed in patients with RSA. By inhibiting these antibodies, IVIG is effective in maintaining pregnancies in patients with RSA. These patients often carry normal embryos with missing karyotypes and have high circulating levels of NK cells, which are natural killer cells with potentially negative effects on embryo development. IVIG is able to down-regulate the activity of NK cells, thus providing a more friendly environment for the embryo to grow.

The use of IVIG in the treatment of RSA has been widely researched and validated. Christiansen et al. found, through an IVIG versus placebo blank controlled trial, that immunoglobulin infusion therapy with small doses and fewer injections achieved significant efficacy in patients with RSA. Specifically, 25 g of IVIG was administered weekly from 5 to 9 weeks of gestation, every 2 weeks after 9 weeks of gestation until 14 weeks of gestation in patients with recurrent spontaneous abortions in early pregnancy only, and every 2 weeks after 9 weeks of gestation until 24 weeks of gestation in those patients who had experienced spontaneous abortions in mid-pregnancy. With this regimen, pregnancy success was 78 per cent in patients with a history of two miscarriages, 89 per cent in patients with recurrent spontaneous abortions, including mid-pregnancy intrauterine foetal death, and only 50 per cent in patients with a history of only one miscarriage.

The effectiveness of IVIG in the treatment of RSA was also confirmed in another blank controlled trial conducted by Carp et al. They gave IVIG 400mg/kg per day by infusion during the follicular phase to patients with RSA who were planning to become pregnant, with a total dose not exceeding 30-45g per day, and continued consolidation of the treatment until termination of pregnancy after the diagnosis of pregnancy was made. Monitoring of embryonic heart tube pulsation at 6 weeks of gestation has been found to be critical in predicting the efficacy of IVIG therapy. 80% of patients with early pregnancy spontaneous abortions present with atrophied embryos, and further IVIG therapy is not necessary in these non-heart tube pulsating embryos. However, if the embryo has a heart tube beat, the rate of early pregnancy spontaneous abortion can be reduced to 10%. The results of the trial showed that the IVIG pregnancy success rate was 49 per cent, compared with 31 per cent in the control group, further confirming that IVIG can improve the prognosis of RSA patients to some extent.

Although the application of IVIG in the treatment of RSA has achieved certain results, more studies and clinical trials are needed to further verify its efficacy and safety. Meanwhile, individualised treatment plans and comprehensive medical assessment are also crucial for RSA patients.

3.3 Heparin, aspirin and other anticoagulant therapy in RSA

Anticoagulants such as heparin and aspirin are mainly used in patients with antiphospholipid antibody-positive RSA to prevent thrombosis in the placental circulation by inhibiting TXA₂ synthesis and reducing platelet aggregation. Silveira et al. treated patients with RSA with low-dose aspirin plus prednisone, which was successfully maintained until full term. Prednisone was tapered to 10 mg/d, but may have adverse effects. Replacement of prednisone with heparin has been suggested. Carolyn et al. demonstrated a 77% pregnancy success rate in patients with RSA treated with prednisone in combination with aspirin. Aspirin and prednisone are recommended for patients with RSA diagnosed with antiphospholipid antibody syndrome and autoimmune diseases. In RSA patients with antiphospholipid antibody syndrome, treatment with aspirin plus heparin was significantly more effective (80% pregnancy success) than heparin or aspirin alone (44% pregnancy success.) Coulam et al. reported that the use of low-dose aspirin and prophylactic doses of plain sodium heparin reduced osteoporosis caused by long-term heparin application. Contraindications to treatment with aspirin and heparin are heparin or aspirin allergy, osteoporosis and heparin-induced thrombocytopenia. Studies have shown better ACA conversion with low molecular heparin than with low dose aspirin [4]. IVIG combined with heparin and aspirin has a treatment success rate of 70% to 100% in antiphospholipid antibody positive patients with RSA. Heparin 5000IU subcutaneously twice a day, aspirin 50mg or 75mg orally once a day, and IVIG 400-500mg/(kg-d) for 1-3d at intervals of 3-4 weeks were started immediately after pregnancy.

3.4 1 α ,25-dihydroxyvitamin D₃ (VD₃) in RSA

In recent years, more and more studies have begun to focus on the potential of vitamin D in the treatment of RSA. In particular, 1,25-dihydroxyvitamin D₃ (VD₃), as a novel immunosuppressant or adjunct to conventional immunotherapy, has gradually shown its unique advantages in the treatment of RSA [5].

Bubanovic et al. investigators studied VD₃ therapy in RSA patients, and they gave patients VD₃ at a therapeutic dose of 5 to 10 μ g /kg. The results showed that VD₃ had a positive effect in the prevention and treatment of RSA. This positive effect may be related to the ability of VD₃ to down-regulate the activity of interleukin-2, interferon- γ and tumour necrosis factor- α gene transcription. These cytokines play a key role in the pathogenesis of RSA, and by inhibiting their activity, VD₃ may help maintain pregnancy stability.

In addition to this, VD₃ may also maintain pregnancy through direct action on the endometrium. The health of the endometrium, which is the site of embryo implantation and development, is critical to the success of pregnancy, and VD₃ has been shown to promote the proliferation and differentiation of endometrial cells, thereby contributing to the implantation and development of the embryo. In addition, VD₃ can regulate the local immune environment of the endometrium and reduce the attack of immune cells on the embryo, thus maintaining the stability of pregnancy.

4. Conclusion

In conclusion, a growing body of research suggests that immune factors play an important role in the pathogenesis of RSA. For example, abnormal activation of the maternal immune system may lead to problems such as failure of embryo implantation and poor meconium response, which in turn may lead to miscarriage. In addition, genetic factors are also an important etiological factor in RSA. Factors such as chromosomal abnormalities and gene polymorphisms may lead to abnormal embryo development, thus increasing the risk of miscarriage.

In order to further improve the treatment of RSA, we need to continue to study the etiology of RSA in depth. Through in-depth research, we can more accurately diagnose the etiology of RSA and provide more targeted solutions for clinical

treatment. At the same time, with the development of reproductive immunology and molecular biology, we are expected to discover new treatments that will bring better results for RSA patients.

References

- [1] Zhao A-M, Lin Q-D. Etiology and diagnosis and treatment of homozygous autoimmune recurrent miscarriage[J]. Chinese Journal of Practical Gynaecology and Obstetrics, 2022, 23(12):91-93.
- [2] Wang Wenjuan. Significance of autoimmune antibody testing in infertile patients[J]. Chinese Experimental Diagnostics, 2022, 14(6):144-145.
- [3] Liang Baozhu. Clinical study on active immunotherapy of lymphocytes for recurrent miscarriage[J]. China Maternal and Child Health Care, 2022, 22(1525):162-163.
- [4] Wu Jing, Huang Huamei, et al. Active immunotherapy for unexplained recurrent miscarriage[J]. Journal of Gannan Medical College, 2022, 27 (33):192-193.
- [5] Bao Hongchu. Progress in the treatment of unexplained recurrent spontaneous abortion[J]. Journal of Straits Preventive Medicine, 2022, 10(111):32-33.