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Observation on the Therapeutic Effect of Lymphocyte Immunotherapy for Repeated Biochemical Pregnancy Loss

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Abstract: *Objective:* To investigate the clinical effect of lymphocyte immunotherapy for women with repeated biochemical pregnancy loss. *Methods:* A retrospective study was conducted from January 2015 to January 2016, involving 100 patients with repeated biochemical pregnancy loss as observation subjects. After enrollment, patients were divided into two groups (50 patients in each group) according to different treatment regimens. The observation group received conventional tocolysis combined with lymphocyte immunotherapy, while the control group only received conventional tocolysis treatment. The pregnancy outcome, improvement of serum factor levels, and treatment safety were evaluated to compare the clinical effects of different treatment regimens. *Results:* The pregnancy success rate was 82.00% in the observation group and 48.00% in the control group (χ^2 = 12.7033, $P < 0.05$). After treatment, the interferon-y (IFN-y) level in the observation group was higher than that in the control group, while the interleukin-8 (IL-8) and regulated upon activation, normal T-cell expressed and secreted (RANTES) levels were lower than those in the control group ($P < 0.05$). There was no significant difference in treatment safety between the two groups ($P > 0.05$). *Conclusion:* The introduction of lymphocyte immunotherapy in patients with repeated biochemical pregnancy loss can improve the success rate of pregnancy and has a significant therapeutic effect, which is worthy of application.

Keywords: Lymphocyte; Immunotherapy; Repeated biochemical pregnancy loss; Efficacy

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1. Introduction

Repeated pregnancy loss, also known as "recurrent pregnancy loss," is a type of pregnancy loss that occurs with a certain incidence in obstetrics and gynecology. The pathological mechanism of this disease is complex and associated with multiple factors, including infection, endocrine abnormalities, and genetics. Modern pathological research has clarified that nearly half of recurrent pregnancy losses are essentially linked to immune factors [1]. In the past, clinical interventions for pregnancy loss mainly focused on tocolysis, achieving

the desired tocolytic effect through drug control, regulating the body's embryonic response, reducing local sensitivity, and providing favorable conditions for normal fertilization [2]. However, for patients with recurrent pregnancy loss, due to the specificity of their pathological factors, symptomatic treatment targeting immune factors is needed based on basic tocolysis to improve clinical efficacy [3]. To further explore treatment options and help patients control their condition, the study analyzed the effects of conventional tocolysis and lymphocyte immunotherapy, focusing on the separate and combined application of these two strategies. 100 subjects were included in the controlled study, and the results are reported below.

2. Materials and methods

2.1. General information

In this retrospective study, a total of 100 patients with recurrent biochemical pregnancy losses were selected as observation subjects. All patients were admitted between January 2015 and January 2016. Based on differences in treatment measures, they were divided into two groups, with 50 cases in each group, and different treatment measures were implemented: conventional fetal protection + lymphocyte immunotherapy (observation group) and conventional fetal protection therapy (control group). In the observation group, the age ranged from 22 to 42 years old, with an average age of (30.24 ± 2.36) years old; the number of miscarriages (2 times/3 times/4 times and above) was 26/8/16. In the control group, the age ranged from 22 to 45 years old, with an average age of (30.33 ± 2.28) years old; the number of miscarriages (2 times/3 times/4 times and above) was 20/12/18. The above data were collated and analyzed using SPSS 22.0 system, with $P > 0.05$ indicating clear comparability. The research process was sorted out, archived, and submitted to the ethics committee for approval before conducting the study. Patients and their families were informed of the project, and consent documents were obtained.

Inclusion criteria: (1) Complete medical history and treatment records; (2) History of spontaneous miscarriage with a frequency of ≥ 2 times; (3) No reproductive tract deformities; (4) Husband's cooperation in physical examination with normal sperm quality; (5) Normal/regular menstruation at the time of enrollment; (6) Normal chromosome screening results; and (7) The patient is aware of the research project and has a certain degree of participation compliance.

Exclusion criteria: (1) Presence of endocrine or autoimmune system disorders/abnormalities; (2) Combined with reproductive system diseases, such as reproductive tract infections, abnormalities, chromosome abnormalities, etc.; (3) Other fetal protection measures have been taken before entering the project; (4) Allergic or contraindicated reactions to medications involved in this project; and (5) Accompanied by psychiatric symptoms, cognitive impairments, and other manifestations.

2.2. Methods

For the control group, only conventional fetal protection measures were intervened. Progesterone (Tongyong Pharmaceutical; National Medicine Approval Number: H31021401; Specification: 1 mL: 20 mg) was administered at a dose of 20 mg via intramuscular injection once a day until 12 weeks of gestation.

On this basis, patients in the observation group were treated with lymphocyte immunotherapy. With the cooperation of their husbands, 20 mL of venous blood (from the upper arm elbow) was collected and anti-coagulant was added. Under a sterile environment, the lymphocyte suspension was washed with 0.9% normal

saline for 3 times. The lymphocytes were then diluted to maintain a concentration of (2–3) × 107/mL and injected into the patients' anterior thigh medially in a radial pattern. Each injection was followed by another injection 2 weeks later, for a total of 4 consecutive times until 12 weeks of gestation.

2.3. Observation indicators

(1) Pregnancy outcome: The follow-up time was set for 12 months, and the pregnancy outcomes of patients after the end of treatment were recorded. Successful pregnancy [4]: The duration is not less than 20 weeks, and the fetal heart is confirmed to be alive by prenatal examination (ultrasonography).

(2) Serum factor levels: According to the research design requirements, two detection time points were defined to measure patients' serum factor levels, which is before treatment (last prenatal examination) and after treatment (first follow-up examination). Measurement items included IFN-y, IL-8, and BANTES.

(3) Treatment safety: During the study period, the responsible nurse followed up on the treatment process and recorded the types and number of adverse events, mainly including nausea, vomiting, bleeding, breast pain, etc.

2.4. Statistical Analysis

Data analysis was performed using SPSS 26.00 statistical software. Enumeration data (including pregnancy outcome items, treatment safety items, etc.) were expressed as the number of cases (n) and percentage (%), and a chi-square test was conducted. Measurement data conforming to a normal distribution (including serum factor level items, etc.) were represented by mean ± standard deviation (SD), and an LSD-t test was used for comparison between groups. A student's t-test was used for comparison within groups. Statistical differences were considered significant when $P < 0.05$.

3. Results

3.1. Pregnancy outcomes

After treatment, the pregnancy outcome items were evaluated. The statistical value of successful pregnancy rates in the observation group was higher than that in the control group, while the statistical value of miscarriage rates in the observation group was lower than that in the control group ($P < 0.05$) (**Table 1**).

Table 1. Comparison of pregnancy outcomes (cases, %)

Group	Successful pregnancy	Miscarriage
Observation group (n = 50)	41 (82.00)	9 (18.00)
Control group (n = 50)	24 (48.00)	26 (52.00)
χ^2	12.7033	12.7033
P	0.0003	0.0003

3.2. Serum factor levels

After treatment, a comparison of serum factor items showed that the measured values of IFN-y in the observation group were lower than those in the control group, while the measured values of IL-8 and BANTES

were higher than those in the control group ($P < 0.05$) (**Table 2**).

Table 2. Evaluation of serum factor levels

Group	IFN-y (ng/L)		IL-8 (pg/L)		BANTES (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group ($n = 50$)	358.45 ± 58.56	248.42 ± 32.18*	310.24 ± 51.58	589.54 ± 82.27*	220.23 ± 64.15	435.17 ± 54.91*
Control group ($n = 50$)	354.37 ± 57.74	298.24 ± 35.86*	307.37 ± 50.55	497.66 ± 74.72*	223.35 ± 63.91	362.04 ± 52.16*
t	0.3508	7.3114	0.2810	5.8458	0.2436	6.8278
P	0.7262	< 0.01	0.7799	< 0.01	0.8080	< 0.01

Note: Compared with before treatment in this group, *$P < 0.05$.

3.3. Treatment safety

In terms of treatment safety items, there was no statistically significant difference in the total incidence of adverse events between the observation group and the control group ($P > 0.05$) (**Table 3**).

Table 3. Evaluation of treatment safety (cases, %)

Group	Nausea	Vomiting	Bleeding	Breast Tenderness	Total Incidence(%)
Observation group ($n = 50$)	3 (6.00)	3 (6.00)	1 (2.00)	2 (4.00)	18.00
Control group ($n = 50$)	2 (4.00)	2 (4.00)	1 (2.00)	1 (2.00)	12.00
χ^2	-	-	-	-	0.7059
P	-	-	-	-	0.4008

4. Discussion

The causes of recurrent biochemical pregnancy losses are complex, primarily related to the weakened antigen recognition and decreased antigen reactivity of patients after recurrent miscarriages. Typically, due to insufficient secretion efficiency of blocking antibodies in the mother, the fetal surface antigen stimulation is weakened, and the antibody regulation ability is lacking, ultimately leading to unsuccessful pregnancies. Therefore, immunological factors have become a new direction for the treatment of recurrent biochemical pregnancies [5].

Currently, conventional measures for the treatment of recurrent biochemical pregnancies include hormone supplementation, such as progesterone. This study adopted this drug for treatment. As an endogenous hormone, progesterone can promote the recovery of ovarian function after physiological supplementation, affect the fertilized egg, enabling it to implant normally, and influence the body's immune response, weakening the mother's immune reaction [6]. However, in a monotherapy environment, the efficacy is not satisfactory, and patients with insufficient blocking antibodies cannot achieve the desired treatment effect. Therefore, it is clinically recommended to combine other immunotherapy techniques to improve efficacy [7].

Lymphocyte immunotherapy is a new treatment technique in obstetrics and gynecology. Its basic

mechanism is to extract lymphocytes from the father, prepare them, and then inject them into the mother. Through a series of physiological effects, it promotes the generation of antibodies, thereby influencing the body's immune mechanism and protecting normal embryo formation and development, resisting the negative effects of the immune mechanism [8]. Among pregnant women, due to the special physiological internal environment during this period, the normal function of lymphocytes is limited. Targeted immunotherapy can achieve immune intervention, protect normal embryos, resist the influence of immune cells, promote normal pregnancy, and improve success rates [9].

For patients with recurrent pregnancy losses, due to changes in the physiological environment, substances such as interferons will continue to be disordered and exhibit hyperreactivity, thereby affecting the body's normal immune mechanism. The toxic effects of some killer cells will continue to increase, thereby affecting embryonic cells and causing trophoblast casualties. Under normal circumstances, the body's serum inflammatory factors are at a low level, and they are in a balanced state with the body's immune function. When this state is destroyed, it will activate the body's immune function, enhance the activity of mother cells, strengthen their immune tolerance, produce physiological reactions that are contrary to antigen stimulation, and affect the pregnancy state [10]. Therefore, lymphocyte immunotherapy is selected to strengthen the physiological immune function through immune influence, maintain the corresponding lymphatic function, and keep it in an immune balance state to achieve better efficacy [11].

In addition, in terms of treatment safety, because lymphocyte immunotherapy does not increase additional medications for patients and does not affect other physiological functions during immune regulation, it has high safety and does not increase patients' toxic and side effects. Patient acceptance is relatively high [12].

In the study by Yang *et al.* [13], active immunotherapy was introduced for patients with recurrent miscarriages. The efficacy data showed that the pregnancy success rate of patients under active immunotherapy was 83.30%, while the pregnancy success rate without active immunotherapy was 44.00%. The difference was statistically significant. This illustrates the positive effect of immunotherapy on patients with recurrent miscarriages, which is consistent with the research conclusions of this article.

5. Conclusion

In summary, for patients with recurrent biochemical pregnancies, the introduction of lymphocyte immunotherapy technology under basic fetal protection can effectively improve the success rate of pregnancy, regulate the level of serum-related factors in the body, and the treatment has good safety and high patient acceptance. The value is significant and worthy of clinical practice and application.

Disclosure statement

The authors declare no conflict of interest.

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