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Observation on the Efficacy of Lymphocyte Immunotherapy for Recurrent Biochemical Pregnancy Loss

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Abstract: *Objective:* To implement a lymphocyte immunotherapy program for women experiencing recurrent biochemical pregnancy loss and explore its clinical effects. *Methods:* The study employed a retrospective design. From January 2015 to January 2016, a total of 100 patients with recurrent biochemical pregnancy loss were enrolled as observation objects. Subsequently, the patients were divided into two groups based on different treatment plans, each comprising 50 cases. The observation group received conventional tocolysis in addition to lymphocyte immunotherapy, while the control group received only conventional tocolysis treatment. Evaluation criteria included pregnancy outcomes, improvements in serum factor levels, and treatment safety, enabling a comparison of the clinical effects of different treatment options. *Results:* In the observation group, the pregnancy success rate was 82.00%, whereas in the control group, it was 48.00% (χ^2 = 12.7033, $P < 0.05$). Following treatment, levels of interferon-γ (IFN-γ) were higher in the observation group than in the control group, while levels of interleukin-8 (IL-8) and regulatory protein (BANTES) were lower in the observation group compared to the control group ($P < 0.05$). The difference in treatment safety between the two groups was negligible ($P > 0.05$). *Conclusion:* The incorporation of lymphocyte immunotherapy for patients with recurrent biochemical pregnancy loss can enhance successful pregnancy rates, demonstrating significant efficacy and warranting further application.

Keywords: Lymphocytes; Immunotherapy; Recurrent biochemical pregnancy loss; Efficacy

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1. Introduction

Recurrent miscarriage, also known as "recurrent pregnancy loss," is a condition characterized by repeated pregnancy losses and is of significant concern in obstetrics and gynecology. The pathological mechanisms underlying this condition are multifaceted and involve various factors such as infection, endocrine abnormalities, and heredity factors. Modern pathological research has elucidated that nearly half of recurrent miscarriages are fundamentally associated with immune factors [1]. Previously, clinical interventions for miscarriage patients primarily centered on tocolytic therapy, with progesterone and other tocolytic drugs

commonly employed to address embryo rejection, enhance the success rate of fertilized egg implantation, reduce uterine smooth muscle activity, and diminish uterine sensitivity, thus fostering a conducive environment for embryo implantation [2].

Given the distinctive pathological factors present in patients with recurrent miscarriages, it becomes imperative to pursue symptomatic treatments targeting immune factors to enhance clinical efficacy [3]. This study stemmed from this premise, undertaking a controlled trial wherein a lymphocyte immunotherapy regimen was introduced and its practical value explored in patients with recurrent biochemical pregnancy loss. A total of 100 cases were studied from January 2015 to January 2016.

2. Materials and methods

2.1. General information

This study utilized patients with recurrent biochemical pregnancy loss as observation subjects for a retrospective analysis of relevant data, with 100 cases screened and enrolled from January 2015 to January 2016. Upon enrollment, patients were categorized into groups based on treatment plans: an observation group and a control group, each comprising 50 patients. Various treatment measures were implemented, including conventional tocolysis combined with lymphocyte immunotherapy for the observation group and conventional tocolysis treatment alone for the control group.

In the observation group, the age range was 22 to 42 years, with an average age of 30.24 ± 2.36 years. The distribution of miscarriage frequency was as follows: 26 cases with 2 miscarriages, 8 with 3 miscarriages, and 16 with 4 or more miscarriages. Patients in the control group were aged 22 to 45 years, with an average age of 30.33 ± 2.28 years. The distribution of miscarriage frequency in this group was 20 cases with 2 miscarriages, 12 with 3 miscarriages, and 18 with 4 or more miscarriages.

The collected data were uniformly analyzed, and the results were analyzed using information technology (SPSS 22.0 system). Permission for comparability was obtained, and data was expressed as $P > 0.05$. The research content was compiled, reported, approved by the ethics committee, and filed.

Inclusion criteria:

(1) Patients with complete clinical record data and no missing information.
(2) Patients with a history of spontaneous abortion, with two or more occurrences.
(3) Patients without reproductive tract malformations.
(4) Patients with husbands exhibiting normal sperm quality during physical examination.
(5) Patients with normal/regular menstruation at the time of enrollment.
(6) Patients with normal chromosome screening results.
(7) Patients who were fully informed of the research process, participated voluntarily, and exhibited good compliance.
(8) Patients who provided informed consent and written documentation.

Exclusion criteria:

(1) Patients with endocrine and autoimmune system disorders/abnormalities.
(2) Patients with reproductive system diseases, such as reproductive tract infections, abnormalities, chromosomal abnormalities, etc.
(3) Patients with previous pregnancies or a history of abortion prevention treatment.
(4) Patients with allergies/contraindications to the treatment techniques and drugs involved in the study.
(5) Patients who were unable to fully cooperate in completing the study due to other reasons.

2.2. Methods

Patients in the control group received routine tocolysis treatment along with progesterone (Shanghai General Pharmaceutical Co., Ltd.; National drug approval number: H31021401; specification: 1 mL: 20 mg). The dosage was 20 mg administered via intramuscular injection once daily until the 12th week of pregnancy.

Building upon this regimen, patients in the observation group underwent lymphocyte immunotherapy with the cooperation of their husbands. Venous blood (from the upper limb's elbow) was drawn in a quantity of 20 mL and mixed with an anticoagulant. In a sterile environment, a lymphocyte suspension was prepared by rinsing with physiological saline (0.9%) three times. The lymphocytes were then diluted to maintain a concentration of 2–3 × 10^7/mL and administered to the patient. The injections were administered into the inner buttocks region, with a radial injection technique. Subsequent injections were administered every two weeks following the initial injection, for a total of four injections, continuing until the 12th week of pregnancy.

2.3. Observation indicators

(1) Pregnancy outcome: The follow-up period is set to 12 months, during which the pregnancy outcomes of patients after completing the treatment course are recorded. A successful pregnancy is defined as lasting at least 20 weeks, with prenatal examinations (ultrasound) confirming the presence of a viable fetal heartbeat [4].

(2) Serum factor levels: According to the research design, two detection points are defined to assess the patient's serum factor levels: time one, before treatment (at the last prenatal check-up), and time two, after treatment (at the first follow-up examination). The evaluated factors include interferon-γ (IFN-γ), interferon-8 (IFN-8), and regulatory proteins (BANTES).

(3) Treatment safety: Throughout the study period, the treatment process was monitored by the responsible nurse, who recorded any adverse events, including nausea, vomiting, bleeding, and breast tenderness.

2.4. Statistical analysis

This project employs computer-assisted statistical analysis using SPSS 20.00 software. The software is configured to execute standardized statistical procedures: for categorical data, the chi-squared test method is used and expressed as %, while for continuous data, the *t*-test method is employed and expressed as mean ± standard deviation (SD). Input data are assumed to follow a normal distribution, and if the output yields $P < 0.05$, it indicates significant differences in the analyzed data.

3. Results

3.1. Pregnancy outcome

Table 1 shows that the observation group had a higher successful pregnancy rate and a lower miscarriage rate than the control group ($P < 0.05$).

Table 1. Comparison of pregnancy outcomes [*n* (%)]

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, the IFN-γ levels in the observation group were lower than those in the control group, while the levels of IL-8 and BANTES in the observation group were higher than those in the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Assessment of serum factor levels before and after treatment (mean ± SD)

Group	IFN-γ (ng/L)		IL-8 (pg/L)		BANTES (ng/L)	
	Before	After	Before	After	Before	After
Observation group ($n = 50$)	358.45 ± 58.56	248.42 ± 32.18*	310.24 ± 51.5	589.54 ± 82.27*	220.23 ± 64.1	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

*Compared with this group before treatment, $P < 0.05$

3.3. Treatment safety

Table 3 shows that there was no statistically significant difference in the total incidence of adverse events between the two groups ($P > 0.05$).

Table 3. Treatment safety assessment [n (%)]

Group	Nausea	Vomiting	Bleeding	Breast tenderness	Overall incidence rate (%)
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 loss are complex and primarily linked to the patient's compromised antigen recognition ability and diminished antigen responsiveness following recurrent miscarriages. Typically, insufficient maternal secretion of blocking antibodies weakens the stimulation of fetal surface antigens and compromises antibody regulation, ultimately resulting in unsuccessful pregnancies. Consequently, immune factors have emerged as a novel therapeutic approach for recurrent biochemical pregnancy loss [5].

Currently, progesterone supplementation is the primary treatment for recurrent biochemical pregnancy loss. Natural progesterone, secreted by the ovarian corpus luteum, promotes the normal implantation of fertilized eggs and possesses immunosuppressive properties, facilitating a reduction in maternal immune response [6]. However, when used alone, its efficacy is limited, particularly in patients with inadequate blocking antibodies. Therefore, clinical recommendations advocate combining progesterone with other immunotherapy techniques to enhance efficacy [7].

Lymphocyte immunotherapy represents a novel approach in obstetrics and gynecology treatment.

Peripheral blood lymphocytes from the paternal lineage are extracted and injected into the mother to stimulate the production of matching blocking antibodies, thereby enhancing the body's immune tolerance, suppressing embryonic immune disorders, and promoting successful pregnancies [8]. Following lymphocyte immune intervention, allogeneic antigen components bind to trophoblasts, acting on surface HLA antigens to block maternal immune cell attacks, thereby maintaining normal pregnancies and increasing successful pregnancy rates [9].

In patients with recurrent pregnancy loss, elevated IFN-γ levels and heightened responses in dendritic cells promote natural killer cell toxicity, impacting embryonic trophoblasts and vascularization. Serum IL-8 impedes cellular immunity activation, hinders the immune process of T lymphocytes, and strengthens the immune tolerance of maternal cells, while BANTES manifests lymphocyte immune balance, blocking immune responses and reducing antigen-stimulation-induced rejection [10]. Lymphocyte immunotherapy effectively enhances immune responses and maintains lymphocyte immune balance, yielding favorable outcomes [11].

Furthermore, lymphocyte immunotherapy is highly safe, as it does not necessitate additional medications or adversely affect physiological functions. It does not increase toxicity or side effects, making it well-received by patients [12].

In a study by Yang *et al*. [13], active immunotherapy was implemented for patients with recurrent miscarriage, yielding a pregnancy success rate of 83.30%. Without active immunotherapy, the pregnancy success rate was 44.00%, with a statistically significant difference. This underscores the positive impact of immunotherapy on patients with recurrent miscarriage, consistent with the findings of this study.

In summary, the introduction of lymphocyte immunotherapy technology for patients with recurrent biochemical pregnancy loss significantly improves pregnancy success rates, regulates serum-related factor levels, and ensures treatment safety. Its substantial value warrants clinical practice and application.

Disclosure statement

The authors declare no conflict of interest.

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