Effect of Progesterone Combined with Low Molecular Weight Heparin Sodium in the Treatment of Recurrent Miscarriage

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Abstract: **Objective:** To analyze the effect of progesterone combined with low molecular weight heparin sodium in the treatment of recurrent miscarriage. **Methods:** A total of 68 patients with recurrent miscarriage admitted to our hospital within 1 year from 2022.04 to 2023.04 were selected as research subjects, and they were divided into control group (34 cases, treated with progesterone) and observation group (34 cases, treated with low molecular weight heparin sodium combined with progesterone) according to the random number table method. The treatment effects of the two groups were analyzed. **Results:** Both groups achieved certain results after treatment, but the coagulation indexes, sex hormone levels and delivery outcomes of the observation group were better than those in the control group after treatment with progesterone combined with low molecular weight heparin sodium (P<0.05). **Conclusion:** Progesterone combined with low molecular weight heparin sodium can effectively improve the coagulation effect, regulate the level of sex hormones, and improve the outcome of childbirth in patients with recurrent miscarriage.

Keywords: Recurrent Miscarriage; Progesterone; Low Molecular Weight Heparin Sodium

Introduction

The definition of recurrent miscarriage varies from country to country, and the 2020 Chinese expert consensus believes that recurrent miscarriage can be diagnosed if two or more consecutive spontaneous abortions (pregnancy less than 28 weeks gestation, pregnancy loss of less than 1000 g of fetal weight) or biochemical pregnancy (sperm-egg combination develops into a fertilized egg but does not implant in the uterus [1]. The symptoms of early spontaneous abortion mainly include: vaginal bleeding, lower abdominal pain, discharge of pregnancy products, etc., and the symptoms of late spontaneous abortion also include cervical dilation, fetal cyst bulge, etc. Biochemical pregnancy presents with serum chorionic gonadotropin- hyperelevation but is difficult to detect. 80% of patients with early recurrent miscarriage and 90% of patients with late recurrent miscarriage can be successful after timely and standardized treatment. Reduce complications and improve quality of life [2]. Therefore, it is important to adopt reasonable and effective treatment regimens for patients with recurrent miscarriage to improve delivery outcomes. The effects of progesterone combined with low molecular weight heparin sodium in the treatment of recurrent miscarriage were investigated herein, as reported below:

1. Objects and methods

1.1 Object

A total of 68 patients with recurrent miscarriage admitted to our hospital within 1 year from 2022.04 to 2023.04 were selected as the research subjects, and they were divided into control groups (34 cases, aged 22-40 years, with an average of 29.11±1.43 years; 4-9 weeks' gestation, mean 5.14±0.31 weeks; Body weight 45-63kg, average 51.37±3.49kg; 2-6 pregnancies, with an average of 3.67±0.54; The number of miscarriages was 2-4, with a mean of 2.66±0.45) and the observation group (34 cases, age 23-39 years, mean 28.04±1.37 years; 4-8 weeks' gestation, with an average of 5.27±0.47

weeks; Body weight 44-65kg, average 52.03±3.53kg; 2-5 pregnancies, with an average of 3.54±0.41; The number of miscarriages was 2-5, with an average of 2.87±0.37). There was no significant difference in general data between the two groups (P>0.05).

Inclusion Criteria: Both groups of patients and their families were aware of the study and signed informed consent; Number of miscarriages≥2; Clinical data are complete.

Exclusion criteria: patients with diseases of the endocrine system; Patients with congenital uterine dysplasia; Patients with important organ diseases such as liver and kidney; Patients with autoimmunosuppressive diseases; Those who have contraindications or allergies to the drugs in this study; People with mental disorders; those with cognitive impairments; Drop out of the investigator halfway.

1.2 Method

Both groups were treated with basic treatment: folic acid tablets (Gansu Lan Pharmaceutical Co., Ltd., Sinopharm H62020684, specification: 5mg/tablet), vitamin E softgels (Jilin Tonghua Boxiang Pharmaceutical Co., Ltd., Sinopharm H22021633, specification: 5mg/capsule) were selected for oral administration. The doses were 10 mg / time, 1 time / day; 5mg / time, 2 times / d.

On this basis, the control group was treated with progesterone (Zhejiang Xianju Pharmaceutical Co., Ltd., Sinopharm H20041902, specification: 50mg/capsule), oral, 100mg/time, 2 times/d, and continued to be used until the end of 12 years of pregnancy.

The observation group was treated with low molecular weight heparin sodium injection (Qilu Pharmaceutical Co., Ltd., Sinopharm H20030429, specification: 5000IU/branch) on the basis of the control group, subcutaneous injection, 5000IU/time, 1 time/d, and continuous medication for 12 weekends.

1.3 Observation indicators

The two groups of coagulation function indexes were compared, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level (Fib), tissue plasminogen activator (t-PA), plasma plasminogen activator inhibitor-1 (PAI-1). Levels of sex hormones were compared between two groups, including progesterone (P), estradiol (E_2), follicle-stimulating hormone (FSH), and blood chorionic gonadotropin (HCG); The two groups were compared for birth outcomes, including miscarriage, preterm birth, term delivery, and live birth.

1.4 Statistical analysis

The SPSS20.0 software was used to statistically analyze the data, and the "$\bar{x} \pm s$" was used to indicate the measurement data, and the t-test was used for the intergroup comparison results. "n,%" was used to indicate the measurement data, and the x^2 test was used for the between-group comparisons. P<0.05 indicates that the data difference is statistically significant.

2. Results

2.1 Comparison of coagulation function indexes between the two groups

The coagulation function indexes in the observation group were significantly better than those in the control group, and the differences were statistically significant (P<0.05). As shown in Table 1:

Table 1 Comparison of coagulation indexes between the two groups ($\bar{x} \pm s$)

Groups	Number of cases	PT（s）	APTT（s）	Fib（g/L）	t-PA（AU/ml）	PAI-1（AU/ml）
Observation group	34	13.85±1.57	30.33±2.04	2.26±0.24	0.65±0.17	0.54±0.24

Control group	34	12.13±1.61	18.59±1.84	3.13±0.36	0.54±0.13	0.76±0.29
t	-	4.469	24.918	11.725	2.997	3.408
P	-	0.001	0.001	0.001	0.004	0.001

2.2 Comparison of sex hormone levels between the two groups

The levels of sex hormones in the observation group were significantly better than those in the control group, and the differences were statistically significant ($P<0.05$). As shown in Table 2:

Table 2 Comparison of sex hormone levels between the two groups ($\bar{x} \pm s$)

Groups	Number of cases	P（μg/L)	E_2（ng/L）	FSH（U/L）	HCG（mIU/ml）
Observation group	34	27.64±2.94	456.97±51.06	6.27±1.07	6882.53±711.05
Control group	34	23.15±2.23	424.03±40.13	7.86±1.27	6104.29±675.67
t	-	7.095	2.958	5.583	4.626
P	-	0.001	0.004	0.001	0.001

2.3 Comparison of delivery outcomes between the two groups

The maternal and infant outcomes in the observation group were significantly better than those in the control group, and the differences were statistically significant ($P<0.05$). As shown in Table 3:

Table 3 Comparison of maternal and infant outcomes between the two groups (n,%)

Groups	Number of cases	Abortion	Premature birth	Full-term delivery	Live birth
Observation group	34	2（5.88）	5（14.70）	26（76.47）	33（97.06）
Control group	34	8（23.53）	13（38.24）	11（32.35）	23（67.65）
x^2	-	4.221	4.836	13.339	10.119
P	-	0.040	0.028	0.001	0.001

3. Discussion

The causes of recurrent miscarriage are complex and diverse, and it is currently believed that they can be mainly divided into the following types: genetic factors, immune factors, thrombophilia, endocrine factors, anatomical factors, infectious factors, male factors, environmental factors and unknown causes. The occurrence of recurrent miscarriage may adversely affect the couple's relationship and family relationship. It may also cause excessive mental stress in the pregnant woman, affecting the pregnancy, thereby increasing the risk of miscarriage. The disease may also be passed on to the next generation [3]. The incidence of the disease is approximately 1 to 5 percent in all women of reproductive age, with older age increasing the risk [4]. Therefore, it is important to adopt reasonable and effective treatment regimens for patients with recurrent miscarriage to improve delivery outcomes.

In this study, progesterone combined with low molecular weight heparin sodium was used in patients with recurrent miscarriage, and the coagulation function indexes, sex hormone levels, and delivery outcomes in the observation group were

better than those in the control group, and the differences were statistically significant (P<0.05). It shows that it can effectively improve the coagulation function of patients, regulate their sex hormone levels, and improve the outcome of delivery. This is because progesterone is a steroid hormone secreted by the ovaries, placenta and adrenal glands, in the presence of sufficient estrogen, progesterone can make the endometrium change from proliferative phase to secretory period, providing favorable conditions for pregnant egg implantation, after fertilized egg implantation, placenta formation, can reduce the excitability of the pregnant uterus, maintain the state of pregnancy; May promote breast development and prepare for breastfeeding. This product can inhibit the release of luteinizing hormone in the anterior pituitary through negative feedback to the hypothalamus, so that the follicles cannot develop and mature, and inhibit the ovulation process of the ovaries [5]-[6]. However, long-term application can cause abnormal liver function and an increase in the incidence of ischemic heart disease; The endometrium atrophy, decreased menstrual flow, predisposing to the development of vaginal fungal infections. Therefore, consider combination with low molecular weight heparin sodium. Heparin is an anticoagulant, which is what people call blood revitalizing drugs. Low-molecular heparin has a smaller molecular weight, so subcutaneous absorption is faster and regular than heparin, bioavailability is higher, and antithrombotic effect is stronger. At the same time, thrombocytopenia and bleeding risk are lower, meaning side effects are smaller [7]. It is generally believed that the anticoagulant effect of heparin is mainly achieved through two aspects: (1) inhibition of thrombin; (2) Inhibit coagulation activity factor Xa (FXa). Both rely on the pentose layout of heparin and the antithrombin III (AT-III) linkage, which enhances the ability of heparin-linked antithrombin III to bind to thrombin and FXa. The antithrombotic effect of heparin requires not only heparin to bind to AT III, but also direct binding of heparin to thrombin, which requires heparin molecules of sufficient length (at least 18 monosaccharide length, at least 5000 D molecules). However, the direct confrontation of heparin with FXa enhances the inhibitory effect of antithrombin III on FXa, and the minimum amount required for this effect is unnecessary heparin. Low molecular weight heparin has a much lower anticoagulant effect than its anti-FXA effect due to its short fragment length, and its molecular length is mostly less than the length of 18 monosaccharides[8].

In summary, progesterone combined with low molecular weight heparin sodium treatment for patients with recurrent miscarriage can effectively improve their coagulation function, regulate their sex hormone levels, and improve labor outcomes.

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