

## Original Article

# Efficacy of progesterone with different administrations in treatment of patients with early threatened abortion and its effects on serum progesterone level

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**Abstract:** Objective: This paper aims to explore the efficacy of progesterone with different administrations in the treatment of patients with early threatened abortion. Methods: Altogether 124 patients with early threatened abortion were retrospectively analyzed, and divided into an intramuscular injection group (progesterone was intramuscularly injected) (n = 62) and an oral medication group (progesterone was orally administrated) (n = 62) according to different administrations. The two groups of patients were observed and compared with respect to efficacy, incidence of complications during pregnancy, incidence of adverse side effects, perinatal outcomes, serum progesterone levels before and after treatment, fetal heart rate changes, and clinical efficacy. Results: After treatment, progesterone levels in the intramuscular injection and oral medication groups were significantly higher than those before treatment ( $P < 0.001$ ), and the level after treatment in the intramuscular injection group was slightly higher than that in the oral medication group ( $P > 0.05$ ). The difference in the incidence of complications during pregnancy between the intramuscular injection group (6.45%) and the oral medication group (14.52%) was not statistically significant ( $P > 0.05$ ). There was no statistically significant difference between the two groups in terms of the incidence of adverse side effects after treatment ( $P > 0.05$ ), the incidence of infants with low Apgar score, perinatal malformation, fetal distress, full-term low-birth weight infants and cases of live-born infants (all  $P > 0.05$ ). The total effective rate in the intramuscular injection group was higher than that in the oral medication group ( $P > 0.05$ ). After treatment, the fetal heart rates in the intramuscular injection and oral medication groups were significantly higher than those before treatment ( $P < 0.001$ ), and the rate after treatment in the intramuscular injection group was higher than that in the oral medication group ( $P > 0.05$ ). Conclusion: Both the intramuscular injection and the oral administration of progesterone are effective for patients with early threatened abortion, without significant adverse effects on perinatal outcomes and fetal heart rate. Therefore, progesterone with different administrations can be chosen for the treatment of early threatened abortion according to patients' conditions.

**Keywords:** Progesterone, early threatened abortion, progesterone level, efficacy

## Introduction

Early spontaneous abortion is a common complication during early pregnancy, and early threatened abortion occurs within the first 12 weeks of pregnancy with the incidence of about 15% [1, 2]. Abortion is caused by many factors, such as abnormal increase of blood glucose, thyroid dysfunction and unhealthy living habits [3-5]. Studies show that pregnancy is affected by genetic factors, immune factors, chromosome abnormalities, and dyscrinism during pregnancy, etc. Pregnancy hormones such as pro-

gesterone and estrogen maintain pregnancy [6-8]. Progesterone deficiency is an important reason for early spontaneous abortion [9, 10].

Progesterone, as a natural progestin widely used in the treatment of early threatened abortion, safely provides exogenous progesterone supplements for pregnant women [11]. The intramuscular injection of progesterone has been widely used due to its rapid onset and remarkable effect, but the long-term injection results in redness and discomfort of the skin at the injection site [12, 13]. In recent years, the

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oral administration of progesterone has been gradually applied to the treatment of patients with early threatened abortion, and its efficacy is similar to that of the intramuscular injection [14]. However, the effects of oral progesterone on serum progesterone level have been rarely studied. Therefore, the efficacy of progesterone with different administrations in the treatment of patients with early threatened abortion and its effects on serum progesterone level were explored.

## Information and methods

### General information

A total of 124 patients diagnosed with early spontaneous abortion in Linyi Central Hospital from February 1, 2015 to May 1, 2018 were retrospectively analyzed and divided into the intramuscular injection and oral medication groups (n = 62) according to different administrations. Patients in the oral medication group were orally administrated with progesterone, aged 22-40 years old with an average age of  $26.1 \pm 7.1$  years old. Patients in the intramuscular injection group were intramuscularly injected with progesterone, aged 22-38 years old with an average age of  $26.8 \pm 6.9$  years old.

Inclusion and exclusion criteria: (1) Patients diagnosed with early spontaneous abortion and treated in Linyi Central Hospital were included, referring to the diagnostic criteria for spontaneous abortion of the World Health Organization [15]. The included subjects had no abortion caused by chromosome abnormalities, anatomic abnormalities, dyscrinism, reproductive system infections and autoimmune diseases. (2) Patients with contraindications to the drugs used in this study were excluded; patients with hypertension, hepatitis B virus infection, gallstones, AIDS and various blood diseases; pregnant women with a history of abnormal pregnancy. The included subjects and their families signed an informed consent form in advance. This study was approved by the Ethics Committee of Linyi Central Hospital.

### Administration

Patients in the intramuscular injection and oral medication groups were kept in bed for rest after admission and not allowed to have sex during this period. They were routinely treated with oral vitamin E and folic acid. Patients in

the intramuscular injection group were intramuscularly injected with progesterone solutions (Tianjin Kingyork Group Co., Ltd., specification: 20 mg), 20 mg/time and once daily for 1 week. Patients in the oral medication group were orally administrated with progesterone capsules (Zhejiang Asen Pharmaceutical Co., Ltd., specification: 100 mg), 100 mg/time and twice daily for 2 weeks.

### Outcome measures

In the intramuscular injection and oral medication groups, serum progesterone levels before and 2 weeks after treatment were detected using enzyme-linked immunosorbent assay (ELISA, Shanghai Yu Bo Biotech Co., Ltd.). Complications (diabetes, hypertension, pre-eclampsia, placenta previa, heart disease during pregnancy and placental abruption) during pregnancy were recorded. Fetal heart rate changes before and after treatments were recorded. Adverse side effects during pregnancy were recorded. Perinatal outcomes (live-born infants, infants with low Apgar score, macrosomia, perinatal malformation, fetal distress and full-term low-birth weight infants) were recorded. Patients' adverse drug reactions were reported to attending doctors in time for treatment. The clinical efficacy after treatment was compared between the two groups.

### Efficacy evaluation

Cure indicated that patients' adverse symptoms during pregnancy such as abdominal pain and vaginal bleeding disappeared, and B-type ultrasonic doppler diagnostic apparatus showed normal fetal development. Effectivity indicated that the adverse symptoms were significantly improved, and the apparatus showed normal fetal development which was consistent with the gestational weeks. Invalidity indicated that the adverse symptoms were aggravated or not improved, and the apparatus showed abnormal fetal development, stopped development or abortion. The total effective rate = (cured + effective cases)/total cases \* 100%.

### Statistical methods

SPSS19.0 (Bizinsight Information Technology Co., Ltd, Beijing) was used for statistical analysis. Count data were expressed by the number of cases/percentage (n, %) and tested by  $\chi^2$ .

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**Table 1.** Comparison of general information

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	t/ $\chi^2$	P
Age (year)	26.8 ± 6.9	26.1 ± 7.1	0.557	0.579
BMI (kg/m <sup>2</sup> )	18.57 ± 3.05	19.11 ± 2.78	1.030	0.305
Alcohol intake			0.290	0.590
Yes	29 (46.77)	32 (51.61)		
No	33 (53.23)	30 (48.39)		
Smoking			0.041	0.839
Yes	16 (25.81)	17 (27.42)		
No	46 (74.19)	45 (72.58)		
Thyroid function				
FT3 (pmmol/L)	4.75 ± 0.98	4.70 ± 0.59	0.344	0.731
FT4 (pmmol/L)	12.26 ± 2.71	11.40 ± 4.82	1.225	0.223
TSH ( $\mu$ IU/mL)	1.79 ± 0.55	2.01 ± 0.79	1.800	0.074
Blood routine				
Hb (gm/dl)	11.45 ± 1.43	10.78 ± 2.68	1.737	0.085
RBC (*10 <sup>12</sup> /L)	4.29 ± 0.39	4.20 ± 0.38	1.301	0.196
PLT (*10 <sup>9</sup> /L)	147.44 ± 22.16	151.74 ± 25.82	0.995	0.322
Liver function				
ALT (U/L)	22.25 ± 10.49	20.50 ± 8.75	1.009	0.315
AST (U/L)	19.65 ± 8.46	17.50 ± 7.10	1.533	0.128

Note: BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; TSH: thyroid stimulating hormone; Hb, hemoglobin; RBC, red blood cell; PLT, blood platelet; ALT, alanine aminotransferase; AST, aspartate amino transferase.

Measurement data were expressed by mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ), and independent samples t test was used for comparison between groups at the same time point, paired t test for comparison before and after treatment within groups.  $P < 0.05$  indicates a statistically significant difference.

## Results

### Comparison of general information

There was no statistically significant difference between the intramuscular injection and oral medication groups in age, body mass index (BMI), blood routine, indexes of thyroid function and liver function (all  $P > 0.05$ ). More details are shown in **Table 1**.

### Comparison of efficacy after treatment

The total effective rate in the intramuscular injection group was higher than that in the oral medication group ( $P > 0.05$ ). More details are shown in **Table 2**.

### Comparison of progesterone level before and after treatment

Before treatment, there was no statistically significant difference in the progesterone level between the intramuscular injection and oral medication groups ( $P > 0.05$ ). After treatment, the levels in the two groups were significantly higher than those before treatment (both  $P < 0.001$ ), and the level after treatment in the intramuscular injection group was higher than that in the oral medication group ( $P > 0.05$ ). More details are shown in **Table 3** and **Figure 1**.

### Comparison of incidence of complications and adverse side effects during pregnancy

**Incidence of complications during pregnancy:** The total incidence of complications during pregnancy in the intramuscular injection group was 6.45%, lower than 14.52% in the oral medication group ( $P > 0.05$ ). More details are shown in **Table 4**.

**Incidence of adverse side effects during pregnancy:** There was no statistically significant difference in incidence of adverse side effects during pregnancy between the intramuscular injection and oral medication groups ( $P > 0.05$ ). More details are shown in **Table 5**.

### Comparison of perinatal outcomes

The incidence of infants with low Apgar score, perinatal malformation, fetal distress and full-term low-birth weight infants in the intramuscular injection group was lower than that in the oral medication group ( $P > 0.05$ ). More details are shown in **Table 6**.

### Comparison of fetal heart rate changes

Before treatment, there was no statistically significant difference in the fetal heart rate between the intramuscular injection and oral medication groups ( $P > 0.05$ ). After treatment, the fetal heart rates in the two groups were significantly higher than those before treatment (both  $P < 0.001$ ), and the rate after treatment

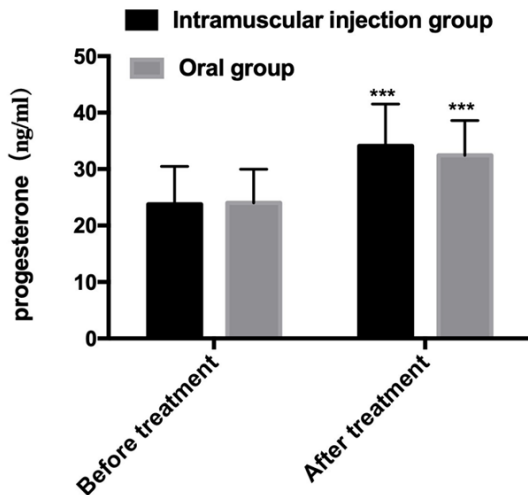
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**Table 2.** Comparison of efficacy after treatment

Groups	n	Cure	Effective	Invalid	Total effective rate
Intramuscular injection group	62	22 (35.48)	36 (58.06)	4 (6.46)	58 (93.55)
Oral medication group	62	20 (32.26)	36 (58.06)	6 (9.68)	56 (90.32)
$\chi^2$					0.435
P					0.510

**Table 3.** Comparison of progesterone level before and after treatment

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	t	P
Before treatment	23.76 ± 6.73	24.01 ± 5.98	0.219	0.827
After treatment	34.12 ± 7.39	32.44 ± 6.15	1.376	0.171
t	8.161	7.738		
P	< 0.001	< 0.001		



**Figure 1.** Comparison of progesterone level before and after treatment. Compared with the group before treatment, \*\*\*P < 0.001.

in the intramuscular injection group was higher than that in the oral medication group (P > 0.05). More details are shown in **Table 7**.

## Discussion

Early spontaneous abortion can be caused by the following factors. One is that insufficient nutrition provided by the mother leads to arresting of fetal development. The other is that pregnant women's abdomen is squeezed and collided, which results in abnormal fetal position or unhealthy fetal development [16, 17]. The pregnancy of pregnant women is often judged through the changes of progesterone

level, whose great decline directly affects the pregnancy [18, 19]. A study shows that maternal progesterone is closely related to immune responses in the reproductive tract caused by fetal antigens, and the antigens are inhibited through the endometrial tissue binding to progesterone [20]. According to a previous study, adequate progesterone supplementation for pregnant women greatly reduces the incidence of early threatened ab-

ortion [21]. Progesterone is a natural progestin widely recognized and used in the prevention or treatment of early threatened abortion [22]. Currently, progesterone is orally administered and intramuscularly injected for treatment. In order to minimize the incidence of abortion, the efficacy of progesterone with different administrations in the treatment of patients with early threatened abortion and its effects on serum progesterone level were explored in this study.

In this study, the results of efficacy comparison showed that the total effective rate in the intramuscular injection group was slightly higher than that in the oral medication group, which may be caused by insufficient sample size. A similar study shows that the efficacy of the intramuscular injection of progesterone is similar to that of the oral administration for patients with early threatened abortion [23]. Therefore, the efficacy of the intramuscular injection of progesterone is slightly higher than that of the oral administration, but on the whole, both of the two administrations are effective for patients with early threatened abortion, with similar efficacy. According to the comparison of progesterone level before and after treatment, there was no statistically significant difference in the progesterone level between the intramuscular injection and oral medication groups before treatment. After treatment, the levels in the two groups were significantly higher than those before treatment, and the level after treatment in the intramuscu-

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**Table 4.** Comparison of incidence of complications during pregnancy

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	$\chi^2$	P
Diabetes	1 (1.61)	2 (3.23)	0.342	0.559
Hypertension	2 (3.23)	3 (4.84)	0.208	0.648
Preeclampsia	0 (0.00)	2 (3.23)	2.033	0.154
Placenta previa	1 (1.61)	1 (1.61)	0.000	1.000
Heart disease during pregnancy	0 (0.00)	0 (0.00)	0.000	1.000
Placental abruption	0 (0.00)	1 (1.61)	1.008	0.315
Total	4 (6.45)	9 (14.52)	2.148	0.143

**Table 5.** Comparison of incidence of adverse side effects during pregnancy

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	$\chi^2$	P
Gastrointestinal reaction	0 (0.00)	2 (3.23)	2.033	0.154
Breast distending pain	2 (3.23)	3 (4.84)	0.208	0.648
Liver and kidney damage	1 (1.61)	1 (1.61)	0.000	1.000
Dizziness	2 (3.23)	2 (3.23)	0.000	1.000
Total	6 (9.68)	8 (12.90)	0.322	0.570

**Table 6.** Comparison of perinatal outcomes

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	$\chi^2$	P
Low Apgar score infants	1 (1.61)	2 (3.23)	0.342	0.559
Fetal macrosomia	1 (1.61)	1 (1.61)	0.000	1.000
Perinatal malformation	0 (0.00)	1 (1.61)		0.315*
Fetal distress	1 (1.61)	2 (3.23)	0.342	0.559
Full-term low-birth weight infants	1 (1.61)	3 (4.84)	1.033	0.309

Note: \*Fisher's Exact Test.

**Table 7.** Comparison of fetal heart rate changes

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	t	P
Before treatment	103.67 ± 10.37	102.85 ± 10.29	0.442	0.659
After treatment	120.38 ± 11.46	118.26 ± 10.57	1.071	0.284
t	8.224	7.846		
P	< 0.001	< 0.001		

lar injection group was slightly higher than that in the oral medication group. A large number of studies confirmed that serum progesterone can be used as an important monitoring index for abnormal placental function during pregnancy [24]. Therefore, the intramuscular injection or the oral administration of progesterone

can supplement the progesterone required by patients with early threatened abortion and improve their placental function during pregnancy.

According to the comparison of the incidence of complications and adverse side effects during pregnancy, the total incidence of complications during pregnancy in the intramuscular injection group was slightly lower than that in the oral medication group, but there was no statistically significant difference between the two groups in the incidence of adverse side effects during pregnancy. Complications during pregnancy are a sign of early threatened abortion and seriously endanger the safety of pregnant women and their fetuses [25]. At present, there is still controversy over the adverse side effects of progesterone with different administrations during pregnancy, which has been rarely studied. Therefore, this paper has a higher reference value than existing studies on progesterone for treatment. Thus, it is believed that for patients with early threatened abortion,

the efficacy of the intramuscular injection of progesterone is similar to that of the oral medication for preventing and reducing the incidence of complications during pregnancy. However, the results of this study showed that the intramuscular injection was better than the oral administration in this aspect. According to

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the comparison of the incidence of perinatal adverse events and fetal heart rate changes, the incidence of infants with low Apgar score, perinatal malformation, fetal distress and full-term low-birth weight infants in the intramuscular injection group was lower than that in the oral medication group. After treatment, the fetal heart rates in the two groups were significantly higher than those before treatment, and the rate after treatment in the intramuscular injection group was higher than that in the oral medication group, but without statistically significant difference. Therefore, the effect of the intramuscular injection of progesterone is similar to that of the oral administration on perinatal outcomes, and reasonable dose can improve the fetal heart rate. A similar study shows that the effect of the intramuscular injection of progesterone is similar to that of the oral administration on perinatal outcomes, but the two administrations are effective without significant difference [26].

There are still deficiencies in this study. For example, the patients' treatment satisfaction was not recorded and they had regional characteristics. These deficiencies may affect the research results. Therefore, the patients will be regularly followed up in the later period according to their data, to improve this study.

In conclusion, both the intramuscular injection and the oral administration of progesterone are effective for patients with early threatened abortion, without significant adverse effects on perinatal outcomes and with similar effects on the fetal heart rate. Therefore, progesterone with different administrations can be chosen for the treatment of early threatened abortion according to patients' conditions.

### Disclosure of conflict of interest

None.

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