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Original Article

Effect of dydrogesterone and progesterone on threatened miscarriage due to corpus luteum insufficiency

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Abstract: Objective: To investigate the efficacy and safety of dydrogesterone and progesterone in the treatment of threatened miscarriage due to corpus luteum insufficiency. Methods: A prospective cohort study was designed and a total of 1,285 patients with threatened miscarriage due to corpus luteum insufficiency were recruited, in which 665 participants received dydrogesterone treatment (dydrogesterone group), and the other 620 received progesterone treatment (progesterone group). The time for clinical symptom relief, changes of sex hormone levels in serum, the rate of miscarriage prevention, delivery outcome, and adverse effects were compared between the two groups. XGBoost algorithm was applied to analyze the factors impacting the efficacy and safety of each treatment. Results: There was no significant difference regarding the time for clinical symptom relief and the rate of miscarriage prevention between the two groups (P>0.05, RR=1.01, 95% CI: 0.97-1.06, P=0.566). However, after 4 weeks of treatment, compared with the progesterone group, the level of sex hormones was significantly upregulated, while the preterm birth rate (9.65% vs. 14.04%), the postpartum hemorrhage rate (3.10% vs. 5.62%), and the incidence of adverse effects (17.44% vs. 32.58%) were considerably reduced in the dydrogesterone group (all P<0.05). XGBoost algorithm analysis demonstrated that dydrogesterone treatment was correlated with a lower incidence of preterm birth rate, postpartum hemorrhage, and adverse effects, ranking the 3rd, 2nd and 1st, respectively, in the weight of dependent variables. Conclusion: Compared with progesterone, dydrogesterone can improve the delivery outcome and demonstrate a higher safety in the treatment of threatened miscarriage due to corpus luteum insufficiency.

Keywords: Threatened miscarriage, dydrogesterone, progesterone, efficacy, XGBoost, influencing factors

Introduction

Threatened miscarriage is a common disease during early pregnancy, with a morbidity of 30% to 40%, which could develop into a complete miscarriage or dystocia without timely treatment [1]. Many pathogenic factors contribute to the threatened miscarriage, of which lacking progestogens due to the endocrine dysfunction of corpus luteum is one of the main culprits [2, 3]. Therefore, supplementation of progestogens is a primary therapeutic strategy for the treatment of threatened miscarriage due to corpus luteum insufficiency, among which progesterone and dydrogesterone are the leading medications in clinical practice [3-6]. Progesterone is an endogenous progestogen sex hormone secreted by the corpus luteum. Supplementation of progesterone is a direct way to elevate progesterone levels caused by insufficient corpus luteum secretion, which is involved in the treatment of threatened miscarriage [7]. Dydrogesterone is an analog of the progestogen, which is highly similar to endogenous progesterone in terms of the structure, function, and biological characteristics [5]. In recent years, dydrogesterone has been widely used in the treatment of threatened miscar-

riage and assisted reproductive technology, showing promising outcomes [8].

However, currently, golden standard for the pharmaceutical dosage and the treatment course of dydrogesterone is not available in clinical practice. On the other hand, an accurate methodology for the judgment of luteal function is absent. So far, there is still a lack of high-quality and evidence-based research regarding the clinical efficacy and safety of dydrogesterone treatment [5, 8]. In addition, there are few studies reporting the safety of dydrogesterone in the treatment of threatened miscarriage due to corpus luteum insufficiency [9, 10]. XGBoost algorithm is an extended variant of boosting, which can be used as an effective prediction model for uneven data sets and is able to process highly diversified descriptors and complex feature spaces [11, 12]. In this study, we designed a prospective cohort study to compare the effect of droprogesterone and progesterone in the treatment of threatened miscarriage due to corpus luteum insufficiency, applied the machine learning XGBoost algorithm to analyze the clinical data of 1,285 patients, and established a model to accurately evaluate the safety and efficacy of dydrogesterone in the treatment of threatened miscarriage.

Materials and methods

Patients

A total of 1,285 patients treated in the outpatient of the Sixth People's Hospital of Zhuji from January 2013 to December 2017 with threatened miscarriage due to corpus luteum insufficiency were recruited in this study. Among them, 665 received dydrogesterone treatment (dydrogesterone group), and 620 received progesterone treatment (progesterone group). Inclusion criteria: ① Patients showed symptoms of early pregnancy, which was confirmed by B-ultrasound, urine hCG test, and history of menopause. ② The gestational week was between the 6th to 10th week. ③ Patients were diagnosed with threatened miscarriage due to corpus luteum insufficiency [13]. ④ Patients were administered dydrogesterone or progesterone soft capsules. Exclusion criteria: ① Patients were diagnosed with ectopic pregnancy. ② Patients were combined with severe heart, liver, lung, kidney, and other organ disorders. ③ Patients had a history of recurrent miscarriage. ④ Patients were allergic to the target drug. ⑤ Patients and their family members were not willing to prevent the miscarriage. ⑥ Patients had poor treatment compliance or incomplete clinical data.

Ethics statement

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Sixth People's Hospital of Zhuji. All patients were informed and signed the consent form.

Treatment methods

Dydrogesterone group was treated with Dydrogesterone tablets (Abbott Healthcare, Netherlands). The first oral dose was 40 mg, and the subsequent oral dose was 10 mg/time, 3 times/day, 2 weeks as a course of treatment. Except for patients whose pregnancy was terminated, the rest patients were treated till 12 weeks of gestation.

Progesterone group was treated with progesterone soft capsules (Zhejiang Pharmaceutical Co., Ltd., China) orally, 0.1 g/time, 2 times/day, 2 weeks as a course of treatment. Except for patients whose pregnancy was terminated, the rest were treated till 12 weeks of gestation.

Measurements of sex hormone levels

Before treatment and 4 weeks after treatment, 4 mL of fasting peripheral venous blood was collected from the patients in two groups in the early morning, followed by centrifugation for 15 min (3,000 r/min) to isolate the supernatant for testing. Electrochemiluminescence (ECL) method was applied to quantify the levels of estradiol (E2), human chorionic gonadotropin (HCG), and progesterone (P). E2, HCG, and P kits were purchased from Wuhan Mingde Biotechnology Co., Ltd., China.

Follow-up

All patients were followed up till the end of gestation. The adverse effects during the treatment were recorded, and patients' gestation and delivery outcome, including the gestational week of delivery, delivery method, and complications during delivery were also recorded.

Evaluation criteria

① Successful miscarriage prevention: gestation ≥28 weeks was considered as successful, and less than 28 weeks or no gestational week information was regarded as unsuccessful. ② Preterm birth: gestation ≥28 weeks, but less than 37 weeks was considered as preterm birth [14].

XGBoost algorithm analysis

Establishment of XGBoost algorithm analysis database: ① Data collection: the clinical data of 1,285 patients with threatened miscarriage due to corpus luteum insufficiency were collected, including the patients' general information, testing data, and medication data. ② Establishment of the database: the above data were filtered and preprocessed to create an XGBoost analysis database.

Variable system set-up: Target variables and condition variables were set up. Target variables include the success rate of miscarriage prevention, preterm birth, postpartum hemorrhage, and the incidence of adverse effects. Condition variables include indicators such as general information of the patients, pregnancy information, medication regimen, combined medication, and testing information.

XGBoost algorithm was adopted to establish an evaluation model for the safety and efficacy of dydrogesterone in the treatment of threatened miscarriage: ① The above two types of data were imported, respectively. ② All discontinuous variables were processed to reduce the dimensionality via principal component analysis (PCA) and other methods to preliminarily filter important variables. ③ Different parameter combinations were iterated and tested using grid search method to refine the important factors for endpoints. ④ Finally, the data were extracted, constructed via decision tree, and processed by correlation analysis to establish an evaluation model for the safety and efficacy of dydrogesterone in the treatment of miscarriage.

Outcome measurements

The primary outcome measurements included the success rate of miscarriage prevention, delivery outcome, incidence of adverse effects, and the results of XGBoost analysis in the two groups. The secondary outcome measurements included the time for clinical symptom relief in the two groups and serum sex hormone levels before and after treatment.

Statistical analysis

SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) software was applied for the statistical analysis. The count data were presented as the number (n, %) and analyzed by χ^2 test. The quantitative data with normal distribution were presented as mean ± standard deviation ($\bar{x}$ ± sd). The comparison between the two groups was conducted by independent sample t-test, while the comparison before and after treatment within the same group was carried out by paired t-test. The significance level was defined by two-sided α=0.05. P<0.05 indicated the statistically significant difference.

Results

General information of the two groups of patients

A total of 1,285 patients with threatened miscarriage due to corpus luteum insufficiency were recruited in this study, of which 665 patients received dydrogesterone treatment as dydrogesterone group, and the other 620 patients were given progesterone soft capsules as progesterone group. There was no significant difference in terms of age, gestational week, parity, pregnant times, number of single births, proportion of habitual abortion history, and number of cases of hypertension during pregnancy between the two groups of patients (P>0.05, **Table 1**).

Efficacy

The clinical symptoms of the two groups of patients were significantly improved after receiving dydrogesterone or progesterone treatment for about 4 days. There was no significant difference in terms of time for low-back pain relief, time for abdominal pain relief, and hemostasis time between the two groups (P>0.05, **Table 2**). After 4 weeks of treatment, the levels of serum sex hormones were significantly increased in the two groups as compared with those before treatment (P<0.001). Of note, the levels of HCG, E2, and P were significantly higher in the dydrogesterone group

Table 1. Comparison of general information of the two groups of patients

Category	Dydrogesterone group (n=665)	Progesterone group (n=620)	χ^2/t	P
Age ($\bar{x}$ ± sd, years)	27.6±5.6	28.0±5.8	1.256	0.209
Gestational weeks ($\bar{x}$ ± sd, weeks)	8.1±1.4	8.2±1.5	1.233	0.218
Parity (n (%))			2.724	0.256
≤1	302 (45.41)	310 (50.00)		
2	223 (33.53)	192 (30.97)		
≥3	140 (21.05)	118 (19.03)		
Pregnant times (n (%))			0.957	0.620
≤1	125 (18.80)	130 (20.97)		
2	442 (66.47)	402 (64.84)		
≥3	98 (14.74)	88 (14.19)		
Number of single birth (n (%))	505 (75.94)	483 (77.90)	0.696	0.404
Hypertension during pregnancy (n (%))	85 (12.78)	72 (11.61)	0.409	0.523

Table 2. Relief time of clinical symptoms in the two groups of patients

Group	Case	Time for low-back pain relief (d)	Time for abdominal pain relief (d)	Hemostasis time (d)
Dydrogesterone group	665	4.15±1.20	3.83±1.32	3.79±1.06
Progesterone group	620	4.20±1.37	3.92±1.41	3.87±1.21
t		0.694	1.179	1.257
P		0.488	0.239	0.209

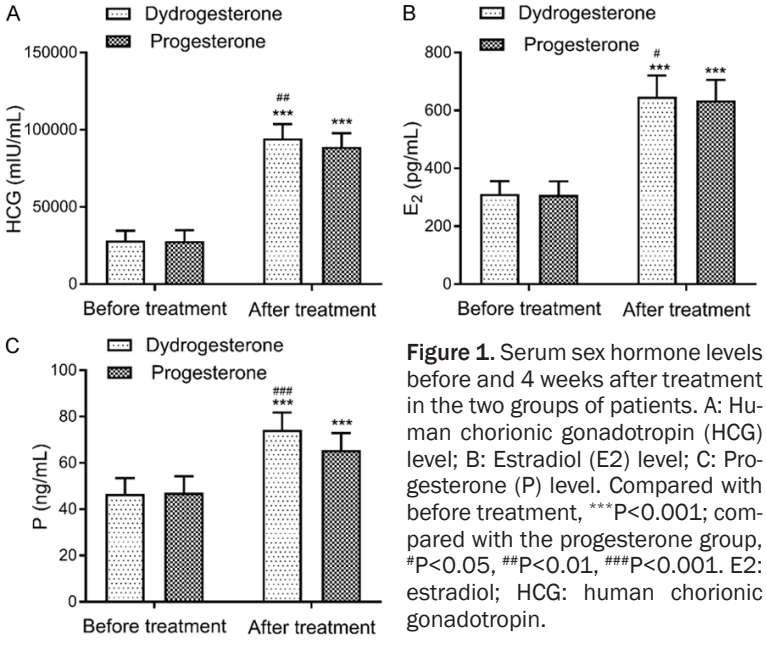

Figure 1. Serum sex hormone levels before and 4 weeks after treatment in the two groups of patients. A: Human chorionic gonadotropin (HCG) level; B: Estradiol (E2) level; C: Progesterone (P) level. Compared with before treatment, ***P<0.001; compared with the progesterone group, #P<0.05, ##P<0.01, ###P<0.001. E2: estradiol; HCG: human chorionic gonadotropin.

than those of the progesterone group (P<0.05, **Figure 1**).

The success rate of miscarriage prevention and delivery outcome in the two groups of patients

Among the 665 patients in the dydrogesterone group, miscarriage was successfully prevented in 580 cases while 85 cases failed, with a success rate of 87.22%. Among the 620 patients in the progesterone group, miscarriage was successfully prevented in 534 cases while 86 cases failed, with a success rate of 86.13%. There was no significant difference regarding the rate of miscarriage prevention between the two groups of patients (RR=1.01, 95% CI: 0.97-1.06, P=0.566). Compared with the progesterone group, the preterm birth rate (9.65% vs. 14.04%) and postpartum hemorrhage rate (3.10% vs. 5.62%) were significantly lower in the dydrogesterone group. However, there was no significant difference in terms of the occurrence of placenta previa, placental adhesion, and premature rupture of fetal membranes between the two groups of patients (P>0.05, **Table 3**).

Table 3. Comparison of delivery outcomes between the two groups of patients (n, %)

Category	Dydrogesterone group (n=580)	Progesterone group (n=534)	χ^2	P
Preterm birth	56 (9.66)	75 (14.04)	5.163	0.023
Complications during delivery				
Postpartum hemorrhage	18 (3.10)	30 (5.62)	4.264	0.039
Placenta previa	9 (1.55)	13 (2.43)	1.119	0.290
Placental adhesion	6 (1.03)	10 (1.87)	1.380	0.240
Premature rupture of fetal membranes	28 (4.83)	35 (6.55)	1.554	0.213

Table 4. Comparison of the incidence of adverse effects between the two groups of patients (n, %)

Category	Dydrogesterone group (n=665)	Progesterone group (n=620)	χ^2	P
Nausea	36 (5.41)	56 (9.03)	6.321	0.012
Headache	55 (8.27)	74 (11.94)	4.772	0.290
Breast tenderness	10 (1.50)	8 (1.29)	0.106	0.745
Breast induration	15 (2.26)	64 (10.32)	36.188	<0.001
Total incidence (%)	116 (17.44)	202 (32.58)	39.477	<0.001

Safety evaluation

The major adverse effects during treatment included nausea, headache, breast tenderness, and breast induration. Compared with the progesterone group, the total incidence of adverse effects was significantly reduced in the dydrogesterone group (P<0.001, **Table 4**).

Establishment of variables via XGBoost analysis

XGBoost data pool was constructed by using the clinical data of 1,285 patients. A total of 1,114 cases successfully achieved miscarriage prevention and 171 cases failed. There were 1,154 cases of normal delivery and 131 cases of preterm birth. There were 48 cases of postpartum hemorrhage and 318 cases of adverse effects, with a total incidence of 24.75%. A total of 665 cases were treated with dydrogesterone and 620 cases were treated with progesterone. The combined medication included 15 kinds of Chinese medicines such as multivitamins, Baotai Wuyou Tablet, nifedipine, etc. A total of 10 parameters including white blood cell count, red blood cell count, lymphocyte population and hematocrit were included in the test, in which only the data of early pregnancy were included. The size of final data unit was 1,285×40 (**Table 5**).

XGBoost analysis results

The XGBoost analysis was performed with "successful miscarriage prevention", "preterm birth", "postpartum hemorrhage", and "incidence of adverse effects" as the target variables, and the top 10 variables based on variable importance scores were selected. The results showed that the importance of dydrogesterone in the influencing factors of preterm birth, postpartum hemorrhage, and incidence of adverse effects ranked the 3rd, 2nd, and 1st, respectively, in patients with threatened miscarriage due to corpus luteum insufficiency (**Table 6**).

Discussion

When the corpus luteum function is insufficient, the secretion of maternal progesterone and other progestogens are not enough, which cannot effectively inhibit the frequent contractions of the uterus and the immune rejection of embryonic antigens, leading to the threatened miscarriage [13, 15]. Therefore, normal corpus luteum function plays important roles in the successful implantation of the zygote, maintenance of gestation, and normal embryonic development. Thus, the most direct and effective treatment strategy is the supplementation of progestogens [16].

In this study, we designed a prospective cohort study to evaluate the efficacy of dydrogesterone and progesterone in the treatment of threatened miscarriage due to corpus luteum insufficiency. The results demonstrated that there is no significant difference regarding the time for symptom relief and miscarriage prevention between the dydrogesterone group and the progesterone group, which may be due to

Table 5. Establishment of variables via XGBoost analysis

Variable	Category	Variable description
Target variable		
Miscarriage prevention	Categorical variable	1 successful miscarriage prevention, 0 unsuccessful miscarriage prevention
Preterm birth	Categorical variable	0 normal delivery, 1 preterm birth
Postpartum hemorrhage	Categorical variable	0 no hemorrhage, 1 hemorrhage
Adverse effects	Continuous variable	Unit: %
General information		
Age	Continuous variable	Unit: year
Marriage	Categorical variable	Unmarried, married, divorced, other
Occupation	Categorical variable	Others, staff, unemployed, national civil servant, professional and technical personnel, freelancer, worker
Medical history	Categorical variable	Endometrial abnormalities, appendectomy, penicillin allergy
Pregnant information		
Pregnancy times	Continuous variable	Number of previous pregnancies
Parity	Continuous variable	Number of past delivery
Number of fetuses	Continuous variable	Number of fetuses in this pregnancy
Hypertension during pregnancy	Continuous variable	0 no hypertension, 1 hypertension
Previous pregnant history	Categorical variable	Artificial abortion, spontaneous abortion, fetal arrest, medical abortion
Body weight gain during pregnancy	Continuous variable	Unit: kg
Treatment strategy		
Medication	Categorical variable	1 dydrogesterone, 0 progesterone soft capsules
Course of treatment	Continuous variable	The course of taking dydrogesterone or progesterone soft capsules
Combined medication		
Multivitamins	Categorical variable	1 yes, 0 no
Baotai Wuyou Tablet	Categorical variable	1 yes, 0 no
Ritodrine hydrochloride	Categorical variable	1 yes, 0 no
Nifedipine	Categorical variable	1 yes, 0 no
Testing data		
White blood cell count_early pregnancy	Continuous variable	Unit: ×10^9/L
Red blood cell count_early pregnancy	Continuous variable	Unit: ×10^9/L
Eosinophil population_late pregnancy	Continuous variable	Unit: %
Basophil population_late pregnancy	Continuous variable	Unit: %

Table 6. Ranking of the importance of factors affecting the outcome of miscarriage prevention

Variable importance ranking	Successful miscarriage prevention	Preterm birth	Postpartum hemorrhage	Incidence of adverse effects
1	Parity	Parity	Hypertension during pregnancy	Dydrogesterone treatment
2	Pregnant times	Pregnant times	Parity	Age
3	Hematocrit	Dydrogesterone treatment	Dydrogesterone treatment	Course of treatment
4	Baotai Wuyou Tablet	Hypertension during pregnancy	Nifedipine	Nifedipine
5	Hypertension during pregnancy	Parity	Pregnant times	Hypertension during pregnancy
6	Age	Past pregnant history	Past pregnant history	Ritodrine hydrochloride
7	Course of treatment	Baotai Wuyou Tablet	Hematocrit	Monocyte population
8	Lymphocyte population	Course of treatment	Baotai Wuyou Tablet	Baotai Wuyou Tablet
9	White blood cell count	Body weight gain during pregnancy	Course of treatment	Lymphocyte population
10	Monocyte population	Age	Parity	Multivitamins

the fact that both treatment approaches could stimulate estrogen secretion and inhibit uterine smooth muscle contraction. However, progesterone has a slower onset of action but a rapid inactivation by the liver after uptake by the body, resulting in a very short half-life and poor efficacy in some patients [17]. Studies have also reported that long-term use of progesterone may cause adverse effects such as muscle twitches and gastrointestinal discomfort, leading to limited clinical applications [18]. In our study, serum sex hormone levels were elevated and the preterm birth rate was significantly reduced in patients treated with dydrogesterone. Manuck has also reported that dydrogesterone could effectively reduce the preterm birth rate [19]. Hudic et al. have revealed that dydrogesterone treatment could effectively upregulate the levels of the blocking factor and interleukin (IL)-10 in pregnant women with a high risk of preterm birth, and regulate the ratio of Th1/Th2 to extend the gestational period [20]. In addition, the rate of postpartum hemorrhage and adverse effects were significantly reduced in the dydrogesterone group of this study. Other studies have also demonstrated that dydrogesterone could effectively reduce the incidence of hypertension and preeclampsia during pregnancy, which may be one of the mechanisms by which dydrogesterone could reduce the incidence of preterm birth and postpartum hemorrhage [21, 22]. Compared with progesterone soft capsules, the advantages of dydrogesterone in the treatment of patients with threatened miscarriage due to corpus luteum insufficiency include: ① As a progesterone analog, dydrogesterone can be quickly absorbed via oral administration, and has a higher affinity and specificity for progesterone receptors; ② It can be orally administered, with few adverse effects and higher medication compliance; ③ It demonstrates a good immunomodulatory effect, effectively reduces maternal immune response to embryos, and promotes embryo implantation; ④ It can inhibit the synthesis and release of prostaglandins in the endometrium and provide a favorable environment for embryo development [23-25].

We further adopted the machine learning XGBoost algorithm to evaluate the efficacy and safety of dydrogesterone. Through the analysis of the correlation between the patients' clinical data and endpoints after treatment, the important factors related to these endpoints were discovered, and the evaluation model for the safety and efficacy of dydrogesterone in the treatment of threatened miscarriage was established, which greatly improved the reliability of our data. The results revealed that dydrogesterone treatment was correlated with a lower incidence of preterm birth, postpartum hemorrhage, and adverse effects, ranking 3rd, 2nd, and 1st, respectively, in the weight of dependent variables.

In summary, compared with progesterone, dydrogesterone can significantly improve the delivery outcome, showing a higher safety in the treatment of threatened miscarriage due to corpus luteum insufficiency.

Disclosure of conflict of interest

None.

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