Journal of Clinical and Nursing Research, 2021, Volume 5, Issue 4
http://ojs.bbwpublisher.com/index.php/JCNR
ISSN Online: 2208-3693
ISSN Print: 2208-3685

A Systematic Review of the Efficacy and Safety of Didroxyprogesterone Combined with Progesterone in the Treatment of Luteal Insufficiency-Induced Abortion

Yanjing Yang[1]*, Hongli Zhu[2]

[1]Shaanxi University of traditional Chinese medicine, Xianyang 712046, Shaanxi Province, China

[2]Affiliated Hospital of Shaanxi University of traditional Chinese medicine, Xianyang 712046, Shaanxi Province, China

Corresponding author: Yanjing Yang, 1157598640@qq.com

Abstract: ***Objective:*** To systematically evaluate the efficacy and safety of didroxyprogesterone combined with progesterone in the treatment of luteal insufficiency abortion. ***Methods:*** We searched CNKI database, VIP database, Wanfang database, PubMed database, EMBASE database and Cochrane library database for literatures on the treatment of luteal insufficiency-induced abortion with didroxyprogesterone and progesterone. Meta-analysis was performed using Revman 5.3 software after literature extraction and further quality evaluation. ***Results:*** Ten randomized controlled trial-related articles that describe studies on a total of 1145 patients, 570 in the combination group and 575 in the control group, were included. The results of meta-analysis showed that combination therapy could improve the effective rate of fetal protection (OR = 0.14, 95% CI [0.07, 0.27], P < 0.00001). The safety of the combination group was significantly higher than that of the control group (OR = 3.09, 95% CI [1.13,8.48], P = 0.03). ***Conclusion****:* To sum up, compared with the control group, the combination of progesterone and progesterone is more effective and safer in the treatment of luteal insufficiency abortion. However, the sample size of the data is relatively small and the quality of the literature is low. This conclusion still needs to be further verified in high-quality randomized controlled trials that involve large samples.

Keywords: Luteal insufficiency-induced abortion; Didroxyprogesterone; Progesterone; Meta-analysis

Publication date: July 2021; ***Online publication:*** July 30, 2021

1. Introduction

Threatened abortion is a common complication of early pregnancy, which is mainly related to the lack of luteal function in pregnant women. Luteal insufficiency-induced abortion is the main cause of early abortion due to the decrease of luteal endocrine function in pregnant women, which significantly reduces the secretion of progesterone in the blood, and cannot maintain normal function, leading to menstrual disorders and endometrial differentiation disorders [1]. Progesterone functions to maintain reproductive function. Once the progesterone level of pregnant women is below 25ng/mL, timely intervention is needed, so the main clinical treatment is to supplement progesterone [1], which is commonly used for vaginal bleeding and abdominal pain [2]. In the clinical treatment, fetal protection is the main measure for the treatment of threatened abortion [3]. The commonly used drugs are didroxyprogesterone and progesterone in different dosage forms. Dydrogesterone is a kind of natural progesterone, which causes less adverse reactions and can inhibit endometrial hyperplasia, protect and repair endometrium, and improve uterine receptivity. Progesterone can inhibit uterine excitability, and reduce embryo rejection through maternal

immune regulation. The combined use of the two drugs can effectively improve the efficiency of fetal care, ensure high level of safety, and significantly reduce the adverse reactions of patients, and its curative effect is significant. Therefore, through meta-analysis, this paper systematically evaluates the efficacy and safety of didroxyprogesterone combined with progesterone in the treatment of threatened abortion due to luteal insufficiency, so as to provide basis for clinical decision-making.

2. Data and methods

2.1. Inclusion criteria

(i) Study type: Randomized controlled trial of clinical design
(ii) Research subjects: Women that meet the diagnostic criteria of luteal insufficiency threatened abortion in Obstetrics and Gynecology department [4]
(iii) Interventions: The combined group was given progesterone, and the control group was given placebo
(iv) Outcome measures: The efficiency and safety of fetal protection

2.2. Exclusion criteria

(i) Non-randomized controlled study, conference literature, animal experiments, etc.
(ii) Individuals with other diseases and those who take drugs that may affect the statistical results of the research subjects
(iii) Subjects who do not meet the inclusion criteria
(iv) Lack of original data, etc.

2.3. Search strategy

CNKI, VIP, Wanfang, PubMed, EMBASE and the Cochrane library were searched by computer. The last search time was September 2020. The keywords are: luteal insufficiency; luteal insufficiency abortion; luteal insufficiency abortion; didroxyprogesterone; progesterone; progesterone; randomized controlled trial.

2.4. Literature screening and data extraction

Literature retrieved from each database was imported into Noteexpress software, and excel table was established for data extraction and collation. The extracted contents include: (i) basic information; (ii) intervention measures, such as sample size of combination group and control group, dosage, frequency and course of treatment of didroxyprogesterone and progesterone; (iii) outcome indicators; (iv) key elements of bias risk assessment.

2.5. Methodological quality

The methodological quality was evaluated using the Cochrane scale.

2.6 Statistical analysis

Revman 5.3 software was used for statistical analysis. Odds ratio (OR) was used for binary variables, and mean deviation (SMD) was used for continuous variables, with 95% confidence interval (CI). In this meta-analysis, Chi-squared test and I2 test were used for heterogeneity analysis. If $P \geq 0.1$ and $I2 < 50\%$, the heterogeneity was small, and fixed effect model was used for analysis. On the contrary, random effect model was used for analysis.

3. Results

3.1. Literature search results

According to the principle of Picos, 588 articles (196 from CNKI, 312 from Wanfang, 42 from VIP, none

from PubMed, none from EMBASE, 38 from Cochrane Library) were screened. After reading the full text, 10 articles that describe studies involving a total of 1145 patients, including 570 in the combination group and 575 in the control group, were included.

3.2. Basic characteristics and quality evaluation results

The basic characteristics and quality evaluation results of the included articles are shown in **Table 1** and **Figure 1**.

Table 1. Basic characteristics and quality evaluation results

Name	Year	Sample size		Age		Gestational weeks		Intervening measure		Course of Treatment (d)	Outcome indexes
		T	C	T	C	T	C	T	C		
Ouyang P [11]	2020	33	33	29.6 ± 0.5	28.6 ± 0.5	8.6 ± 0.4	9.6 ± 0.4	Control group + oral progesterone 200 ~ 300 mg/d, once or twice, dose ≤ 200 mg/time	Initial oral dose of dydrogesterone of 40 mg, followed by 10 mg every 8 hours	Transference cure	1, 2, 3, 4, 6
Zhu H [5]	2020	52	52	28 ± 3	7.8 ± 0.8	28 ± 4	7.9 ± 0.9	Control group + oral dydrogesterone, initial dose 40 mg, then take 10 mg every 8 hours	Intramuscular injection of progesterone, 20 mg/time, 1 time/d	Transference cure	1, 2, 3, 4, 6
Xu Q [8]	2019	40	40	30.3 ± 2.5	30.2 ± 2.6	9.1 ± 0.4	9.2 ± 0.5	Control group + oral dydrogesterone tablets 40 mg for the first time, then take 10 mg once every 8 hours	Intramuscular progesterone 20 mg once a day	28d	1, 2, 6
Yang X [9]	2019	100	100	28.72 ± 3.57	28.58 ± 3.82	11.21 ± 0.57	11.05 ± 0.58	Control group + oral dydrogesterone, initial 40 mg, followed by 10 mg every 8 h	intramuscular progesterone dose, 40 mg/time, 1 time/d.	Transference cure	5a, 5b, 6
Lou Y [1]	2019	47	47	28 ± 4	28 ± 4	8.2 ± 1.6	8.1 ± 1.5	Control group + intramuscular injection of 20 mg progesterone once a day	Oral dydrogesterone, initial 40 mg, followed by 10 mg every 8 h	14d	1, 2, 3, 6
Zhang C [6]	2018	120	125	24.8 ± 5.89	23.9 ± 6.21	—	—	Control group + oral dydrogesterone 10 mg/time, twice daily	Intramuscular injection of progesterone 20 ml, once daily or oral progesterone capsules, 100 mg/time, twice daily	15d	4, 6
Liu Y [2]	2018	40	40	29.72 ± 3.51	27.40 ± 3.77	6.27 ± 2.69	7.81 ± 3.02	Control group + intramuscular progesterone 40 mg each time, once a day, the dose can be changed to 20 mg after symptom relief	Oral dydrogesterone 40 mg, twice daily, changed to 10 mg after 8 h	Transference cure	1, 3, 4, 5a, 5b
Chen X [3]	2017	53	53	25.9 ± 5.4	26.8 ± 5.2	8.5 ± 1.2	7.9 ± 1.6	Control group + intramuscular injection of 20 mg progesterone once a day	Oral dydrogesterone, initial 40 mg, followed by 10 mg every 8 h	14d	1, 2, 3, 4
Wang Q [10]	2019	40	40	27.63 ± 2.43	27.51 ± 2.39	8.36 ± 1.22	8.33 ± 1.28	Control group + oral administration of progesterone tablets (20 mg/d, twice)	Oral progesterone 200 mg/d, twice	Transference cure	1, 2, 3, 5a, 5b
Peng Y [7]	2018	45	45	28.11 ± 2.96	27.04 ± 2.99	6.98 ± 1.21	7.13 ± 1.05	Control group + oral administration of dydrogesterone, 30 mg for the first time, followed by 10 mg/time, 3 times/d	Intramuscular injection of progesterone 35 mL/time, 1 time/d	15d	4, 6

T, experimental group; C, control group; 1, P; 2, E2; 3, HCG; 4, fetal effective rate; 5, symptom disappearance time (a: bleeding; b: abdominal pain); 6, safety.

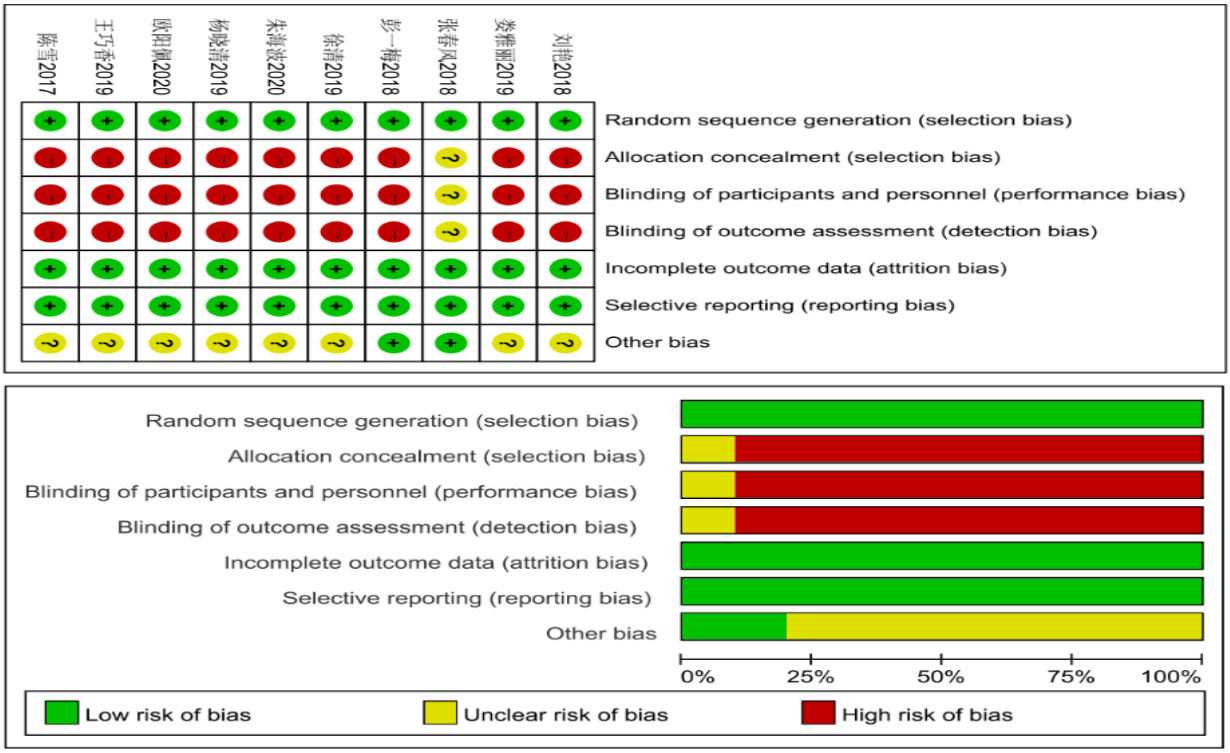

Figure 1. Basic characteristics and quality evaluation results

4. Meta-analysis

A total of 5 articles (n=625) evaluated the effective rate of fetal protection [2,3,5-7]. Heterogeneity test showed that the heterogeneity was small (P=0.24, I2=27%), so fixed effect model analysis was used. The effective rate of combined medication was higher than that of control group (OR=0.14, 95% CI [0.07,0.27], P < 0.00001), and there was statistical difference between the two groups. See **Figure 2**. Eight articles (n=959) evaluated the safety [1,5-11]. The heterogeneity test showed that the heterogeneity was large (P<0.0001, I2=79%), so the random effect model analysis showed that the safety of the combination group was significantly better than that of the control group (OR=3.09, 95% CI[1.13,8.48], P= 0.03), with statistical difference between groups, as shown in **Figure 3**.

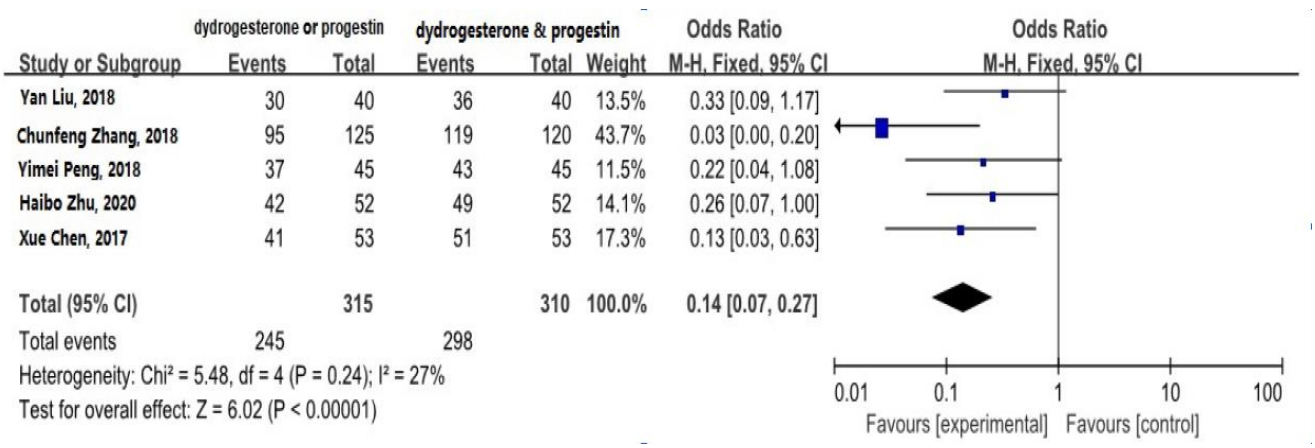

Figure 2. Effective rate of tire protection

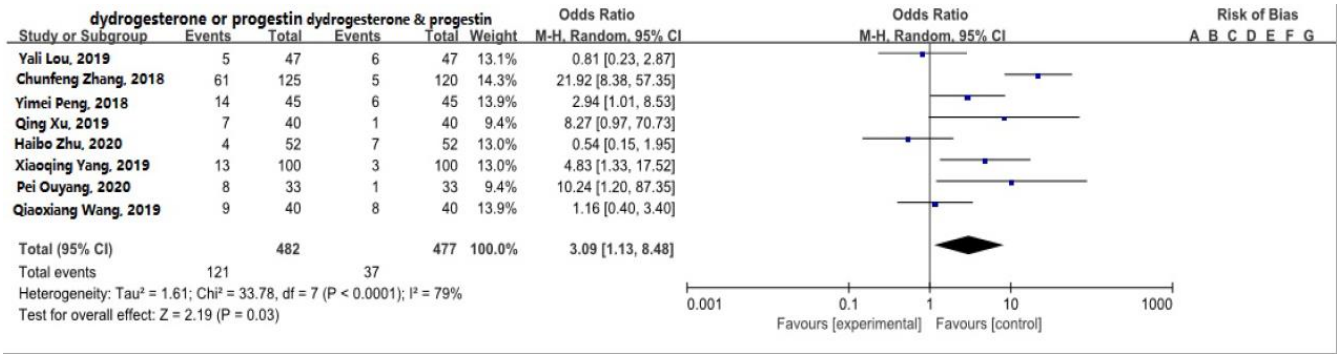

Figure 3. Security

5. Discussion

Through meta-analysis of 10 included articles, the results showed that the combination group was better than the control group in improving the efficiency and safety of fetal protection. Dydrogesterone combined with progesterone in the treatment of luteal insufficiency abortion, to a certain extent, can avoid the occurrence of serious complications in patients, so the combination of drugs is very beneficial for pregnant women [7]. Didroxyprogesterone is a natural progesterone, which is well absorbed in the body. It can reduce the rejection of the embryo through the immune regulation of the mother so as to maintain and protect pregnancy [12]. In pregnant women, the use of progesterone can reduce the excitability of the uterus and inhibit its activity [13], so as to protect the fetus in vivo and promote the growth and development of the fetus [14]. This meta-analysis shows that the clinical efficacy of diltraprogesterone combined with progesterone in the treatment of threatened abortion with luteal insufficiency is significantly improved, the hormone level of patients is significantly improved, the success rate of fetal protection is improved, and the safety is higher, which is conducive to the early recovery of patients, and is worthy of clinical promotion and application [11].

Funding

Social Development Science and Technology Project (Project name: Clinical study on the effect of electroacupuncture combined with walking through the meridian on body mass index, glucose metabolism and reproductive endocrine in patients with obese polycystic ovary syndrome; Project no.: 2016SF-362), and Special Project of Natural Science (Project name: Association of endometrial precancerous lesions with insulin resistance and adiponectin based on high incidence of diabetes mellitus; Project no.: 13JK0800)

Disclosure statement

The author declares no conflict of interest.

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