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*Original Article*

# Comparison of the efficacy of phloroglucinol versus ritodrine hydrochloride in preventing miscarriage and adverse reactions

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**Abstract:** Objective: To analyze the efficacy of phloroglucinol versus ritodrine hydrochloride in preventing miscarriage and adverse reactions (ARs). Methods: A retrospective analysis was conducted on 211 patients with threatened abortion or premature birth who were admitted to the Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine between July 2019 and July 2021. The control group (n=57) received ritodrine hydrochloride, while the observation group (n=154) was treated with phloroglucinol. We compared the overall therapeutic efficacy, time to symptom resolution, cessation of uterine contractions, success rate of miscarriage prevention, and full-term pregnancy rate between the two groups. Estrogen levels, including serum progesterone (P), estradiol (E2), and human chorionic gonadotropin (hCG), were measured and compared before and after treatment using ELISA. Additionally, neonatal outcomes, such as birth weight, Apgar scores, and umbilical arterial blood gas parameters [pH value, partial pressure of oxygen ($PaO_2$), and partial pressure of carbon dioxide ($PaCO_2$)], were evaluated and compared between the groups. Finally, the incidence of ARs during treatment was assessed and compared. Results: Compared to the control group, the observation group had higher effective rate of treatment, success rate of miscarriage prevention, and a full-term pregnancy rate (all $P<0.05$). The times to symptom resolution and cessation of uterine contractions were markedly shorter in the observation group than those in the control group (both $P<0.05$). After treatment, levels of serum P, $E_2$, and hCG in the observation group were significantly higher than those of the control group (all $P<0.05$). Additionally, the body weight, Apgar scores, pH value, and $PaO_2$ of the neonates in the observation group were higher, while $PaCO_2$ and the incidence of ARs were lower compared to the control group (all $P<0.05$). Conclusion: For threatened abortion or threatened premature labor, phloroglucinol is more effective than ritodrine hydrochloride for clinical intervention and treatment.

**Keywords:** Miscarriage protection, phloroglucinol, ritodrine hydrochloride, efficacy, adverse reactions

## Introduction

Vaginal bleeding or abdominal pain occurring before the 28th week of pregnancy without the expulsion of pregnancy conceptus is classified as a threatened abortion if the pregnancy can be continued after treatment. Premature birth refers to the termination of pregnancy between 28 and 36+6 weeks of gestation. The occurrence of these conditions is often associated with factors such as weak maternal constitution, trauma, fatigue, uterine contractions, and the separation of the gestational sac from the uterine body. These conditions represent common pathologicstates in pregnancy, accounting for approximately 5-10% of all pregnancies [1, 2].

In recent years, the incidences of threatened miscarriage and threatened preterm birth have been on the rise, which is attributed to increased work-related stress among women and environmental pollution. For pregnant women at less than 28 weeks' gestational age, each additional day of delaying birth can increase neonatal survival rates by 3% [3]. However, many patients with threatened miscarriage and threatened preterm labor opt to terminate their pregnancies due to concerns about adverse outcomes, which can result in complications such as birth

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canal injuries and reproductive system infections, potentially leading to infertility [4, 5]. Thus, prevention of preterm birth is crucial for reducing perinatal mortality and improving the quality of life for newborns.

The fundamental principle in the treatment of preterm labor is to inhibit uterine contractions and prolong the gestational age [6]. Ritodrine hydrochloride, a tocolytic agent, is commonly used in obstetrics and gynecology. It is effective on spastic smooth muscle with minimal impact on normal muscle and no antagonistic effect on choline [7]. Phloroglucinol, another tocolytic, typically alleviates maternal abdominal distension, has a mild effect on the fetus, and is associated with few side effects [8]. Phloroglucinol is a myotropic, non-atropine, pure smooth muscle antispasmodic agent that reduces bleeding by relieving uterine smooth muscle spasm. It has demonstrated good efficacy in the clinical management of threatened abortion [9].

However, current clinical treatment for threatened abortion often relies on empirical medication, and there is an ongoing debate about the optimal regimen among commonly used drugs. Although both phloroglucinol and ritodrine hydrochloride are widely used in clinical practice, comparative studies evaluating their efficacy are scarce.

In this study, we included 211 patients with threatened abortion or preterm labor who were admitted between July 2019 and July 2021. We analyzed the efficacy of phloroglucinol and ritodrine hydrochloride in preventing miscarriage and assessed the adverse reactions (ARs) associated with their use. Our goal was to provide more reference data for the management of patients and contribute to reducing the miscarriage rate and improving the pregnancy success rate.

## Materials and methods

### *Clinical data*

A retrospective analysis was conducted on 211 cases of threatened miscarriage or premature birth admitted between July 2019 and July 2021 to the Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine. Patients were divided into two groups based on their therapeutic regimen: the control group, consisting of 57 cases treated with ritodrine hydrochloride, and the observation group, consisting of 154 cases treated with phloroglucinol.

Inclusion criteria: (1) Patients who meet the criteria for threatened abortion or threatened premature birth [10] (since ritodrine hydrochloride is used for pregnancies >20 weeks, all cases selected in this study are >20 weeks). (2) Patients with complete case data.

Exclusion criteria: (1) Patients allergic to the drugs concerned. (2) Presence of vaginal bleeding due to placenta previa, hydatidiform mole, or other intrauterine diseases. (3) Patients with serious systemic diseases such as uterine or ovarian tumors, or reproductive tract malformations. (4) Patients with severe cognitive impairment, mental illness, or obvious memory impairment. (5) Patients with liver and kidney dysfunction. (6) Patients with poor medication compliance.

This experiment was approved by the ethics committee of the Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine and complies with the Declaration of Helsinki.

### *Treatment plans*

Upon admission, both groups underwent the same basic treatment, including left lateral rest, oxygen inhalation, symptomatic treatment, and general supportive care, with no abnormalities detected on routine electrocardiography.

In addition to basic treatment, patients in the control group received intravenous ritodrine hydrochloride (Xindong Biotechnology Co., Ltd., HC20080024) at a dose of 100 mg combined with 500 ml of 5% glucose injection (patients with diabetes received sodium chloride injection instead). The initial infusion rate was 5 drops/min, adjusted according to uterine contractions. Routine ECG monitoring was performed for 2 hours, and the infusion rate was increased by 0.05 mg/min every 10 minutes, up to a maximum rate of 40 drops/min. After uterine contractions were inhibited, infusion was stopped for 12-24 hours. Subsequently, oral ritodrine tablets (Xindong Biotechnology

Co., Ltd., HC20160013) were administered half an hour before stopping the infusion for maintenance: 10 mg every 2 hours on day 1; 20 mg every 4 hours on day 2; 20 mg every 6 hours on day 3; 20 mg every 8 hours on day 4; and 20 mg every 12 hours on day 5. The medication was discontinued once the uterine contractions ceased completely, and was reinitiated if contractions recurred.

Patients in the observation group were administered an intravenous phloroglucinol injection (Nanjing Hengsheng Pharmaceutical Co., Ltd., 40 mg/vial, approved by Chinese medicine: H20046766). Two vials (80 mg) were combined with 500 ml of 5% glucose injection, typically infused over 2 hours. The infusion rate was adjusted based on uterine contractions. If 200 mg effectively relieved the contractions, infusion was stopped on the same day. If the contractions were not relieved, an additional 200 mg was administered, not exceeding 400 mg per day. If relief was not achieved after two injections, alternative medications were considered.

*Observation indexes*

(1) Overall Therapeutic Efficacy: The overall therapeutic efficacy of the two groups was evaluated and compared. It was categorized as: Markedly effective: Reduced or completely eliminated uterine contractions and vaginal bleeding within 24 hours of medication. Effective: Reduced vaginal bleeding and uterine contractions after 24 hours of medication, with pregnancy continuing for more than 48 hours. Ineffective: Contractions were not relieved or even strengthened after 48 hours of medication, necessitating a switch to other drugs or termination of pregnancy. The total effective rate of treatment was calculated as follows: Total effective rate of treatment = (number of markedly effective cases + number of effective cases)/total case number × 100%.

(2) Symptom Resolution and Uterine Contraction Cessation: The time to symptom resolution and the time to cessation of uterine contractions were compared between the two groups.

(3) Pregnancy Success Rate and Term Pregnancy Rate: The pregnancy success rate and term pregnancy rate were compared.

(4) Neonatal Outcomes: The neonatal body weight and Apgar scores (range: 0-10, with 8-10 indicating normal, 4-7 indicating mild asphyxia, and 0-3 indicating severe asphyxia) were compared [11].

(5) Estrogen Levels: Enzyme-linked immunosorbent assay (ELISA) was used to detect and compare the estrogen levels before and after treatment, including serum progesterone (P) (Abcam, ab108670), estradiol (E2) (Abcam, ab285329), and chorionic gonadotropin (hCG) (Abcam, ab100533) levels.

(6) Umbilical Artery Blood Gas Indexes: The umbilical artery blood gas indexes of the newborns were compared. Before the newborn's first breath, two hemostatic forceps were used to clamp the umbilical cord approximately 20 cm from the fetal end. 1 mL of umbilical artery blood was drawn with a heparinized syringe for immediate inspection of pH value, partial pressure of oxygen ($PaO_2$), and partial pressure of carbon dioxide ($PaCO_2$) using a blood gas analyzer.

(7) ARs: The ARs during treatment were evaluated and compared, including tachycardia, chest tightness, nausea and vomiting, and hypokalemia.

*Statistical methods*

Statistical analysis and figure plotting were performed using SPSS 19.0 and GraphPad Prism 8, respectively. The sample size was calculated using the formula: $N=Z^2 \times (P \times (1-P))/E^2$, where Z is the confidence interval, n is the sample size, d is the sampling error range, and σ is the standard deviation, generally taken as 0.5.

The $\chi^2$ test was used for the analysis of enumerated data described as the number of cases and percentage (%). Mean ± standard deviation was used to indicate measured data. Intergroup comparisons and comparisons before and after treatment were conducted using Student's t-test and paired t-test, respectively, and a post hoc test (LSD/t) was also performed. A *P* value <0.05 indicated statistical significance.

## Results

*Comparison of general information*

No significant differences were observed between the control group and observation group in terms of age, BMI, and gestational week,

**Table 1.** Comparison of general data

| Factor | Observation Group (n=154) | Control Group (n=57) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Age (years) | | | 2.172 | 0.141 |
| ≤29 | 77 (50.00) | 22 (38.60) | | |
| >29 | 77 (50.00) | 35 (61.40) | | |
| BMI ($kg/m^2$) | | | 0.057 | 0.812 |
| ≤23 | 78 (50.65) | 28 (49.12) | | |
| >23 | 76 (49.35) | 29 (50.88) | | |
| Gestational Week | 30.24±1.27 | 30.38±1.12 | 0.733 | 0.464 |
| Disease type | | | 0.094 | 0.760 |
| Threatened Miscarriage | 82 (53.25) | 29 (50.88) | | |
| Threatened Prematurity | 72 (46.75) | 28 (49.12) | | |
| Pregnancy | | | 0.013 | 0.908 |
| ≤1 | 112 (72.73) | 41 (71.93) | | |
| >2 | 42 (27.27) | 16 (28.07) | | |
| Vaginal Bleeding Time (d) | | | 1.828 | 0.176 |
| ≤3 | 84 (54.55) | 37 (64.91) | | |
| >3 | 70 (45.45) | 20 (35.09) | | |
| Number of Miscarriages | | | 2.666 | 0.103 |
| ≤1 | 131 (85.06) | 43 (75.44) | | |
| >2 | 23 (14.94) | 14 (24.56) | | |

**Table 2.** Comparison of therapeutic efficacy

| Efficacy | Observation Group (n=154) | Control Group (n=57) | t | P |
|---|---|---|---|---|
| Markedly Effective | 98 (63.64) | 20 (35.09) | - | - |
| Effective | 46 (29.87) | 22 (38.60) | - | - |
| Ineffective | 10 (6.49) | 15 (26.32) | - | - |
| Effective Rate | 144 (93.51) | 42 (73.68) | 15.65 | <0.001 |

indicating that the subjects were comparable (all P>0.05, **Table 1**).

*Comparison of therapeutic efficacy*

The number of patients with markedly effective, effective, and ineffective treatments in the observation group were 98, 46, and 10, respectively. In the control group, these numbers were 20, 22, and 15, respectively, resulting in a significantly lower total effective rate than in the observation group (P<0.05, 93.51% *vs.* 73.68%, **Table 2**).

*Comparison of duration of symptom disappearance and cessation of uterine contractions*

The duration of symptom disappearance and cessation of uterine contractions in the observation group were (52.1±0.99) hours and (30.04±1.07) hours, respectively, while in the control group, they were (53.09±1.04) hours and (31.19±0.98) hours, respectively. Statistically, both indexes in the observation group were markedly shorter compared to the control group (both P<0.05, **Table 3**).

*Comparison of pregnancy success and term pregnancy rates*

The pregnancy success rate and full-term pregnancy rate in the observation group were 93.51% and 91.23%, respectively. In the control group, these rates were 79.87% and 52.63%, respectively. The full-term pregnancy rate of the observation group was significantly higher than that of the control group (P<0.05, **Table 4**).

*Comparison of estrogen levels before and after treatment*

Before treatment, there were no significant differences in the levels of P, $E_2$, or hCG between the two groups (P>0.05). After treatment, the levels of these indicators in both groups were markedly elevated, with the up-regulation in the observation group being more significant (P<0.05, **Figure 1**).

*Comparison of neonatal body weight and Apgar scores*

The weight and Apgar scores of the neonates in the observation group were (3.33±0.23) kg and 9.61±0.24, respectively. In the control group, these values were (2.71±0.23) kg and 9.03±0.26, which were markedly lower than those in the observation group (both P<0.05, **Table 5**).

*Comparison of umbilical artery blood gas indexes*

The umbilical artery blood pH, $PaO_2$, and $PaCO_2$ levels of neonates in the observation group

**Table 3.** Comparison of duration of symptom disappearance and cessation of uterine contractions

| Factors | Observation Group (n=154) | Control Group (n=57) | t | P |
|---|---|---|---|---|
| Duration of symptom disappearance (h) | 52.1±0.99 | 53.09±1.04 | 6.362 | <0.001 |
| Duration of cessation of uterine contractions (h) | 30.04±1.07 | 31.19±0.98 | 7.087 | <0.001 |

**Table 4.** Comparison of pregnancy success and term pregnancy rates [n/(%)]

| Factors | Observation Group (n=154) | Control Group (n=57) | $\chi^2$ | P |
|---|---|---|---|---|
| Pregnancy Success Rate | 144 (93.51) | 52 (91.23) | 0.327 | 0.567 |
| Pregnancy Term Rate | 123 (79.87) | 30 (52.63) | 15.49 | <0.001 |

were 7.41±0.05, (60.42±0.26) mmHg, and (41.29±0.28) mmHg, respectively. In the control group, these values were 7.29±0.05, (57.25±0.28) mmHg, and (43.32±0.24) mmHg, respectively. The data showed higher umbilical artery blood pH and $PaO_2$ and lower $PaCO_2$ levels in the observation group compared to the control group (all P<0.05, **Table 6**).

*Comparison of ARs*

Tachycardia, chest tightness, nausea and vomiting, and hypokalemia were observed in 0, 1, 0, and 0 case in the observation group, respectively. In the control group, these numbers were 7, 1, 0, and 1, respectively. The incidence of ARs was significantly higher in the control group than in the observation group (P<0.001, 15.79% vs. 0.65%, **Table 7**). All patients with ARs were relieved after symptomatic treatment.

## Discussion

Threatened miscarriage or threatened premature birth arises from a variety of complex factors that are often linked to pregnancy-related conditions and poor lifestyle habits. Primary clinical manifestations include uterine contractions, irregular abdominal pain, and minor vaginal bleeding [12]. If not promptly and properly treated, these conditions can adversely affect the nervous system of preterm infants and may even result in neonatal death [13]. The cornerstone of treatment for threatened miscarriage or threatened preterm birth is the suppression of uterine contractions. Intravenous infusion of magnesium sulfate is widely used for this purpose in clinical practice. However, its application is accompanied by numerous side effects, and it is limited in dose and concentration due to the risk of toxicity. These limitations increase pain and risk for patients, complicating clinical management [14, 15].

Phloroglucinol is a myotropic antispasmodic drug that is categorized as a non-atropine or non-papaverine agent. It acts directly on the smooth muscle of the urinary and reproductive systems, effectively alleviating spasms without significantly affecting normal muscle function, and it does not exhibit antagonistic effects on choline receptors [16]. The administration of phloroglucinol has been shown to significantly relieve the sensation of abdominal bulging and bloating in pregnant women. Moreover, it has minimal impact on the fetus and does not cause significant side effects. It is also gentle to the maternal cardiovascular system, as it is less likely to induce hypotension or tachycardia [17].

Ritodrine hydrochloride, a strong β2-adrenergic receptor agonist, consists primarily of benzyl hydroxyephedrine hydrochloride. It acts directly on the myometrium, binding to β2 receptors on uterine smooth muscle cells and activating adenylyl cyclase. This activation increases intracellular cyclic adenosine monophosphate (cAMP) levels and decreases intracellular calcium ion concentrations, leading to inhibition of uterine smooth muscle contraction [18].

While both phloroglucinol and ritodrine hydrochloride are widely used in clinical settings, comprehensive comparative studies on their efficacy and safety are limited. In this study, the therapeutic efficacy of these two drugs was compared. The results demonstrated that the observation group, which received phloroglucinol, exhibited significantly higher treatment efficacy, a greater success rate of pregnancy preservation, and a higher full-term pregnancy rate compared to the control group, which

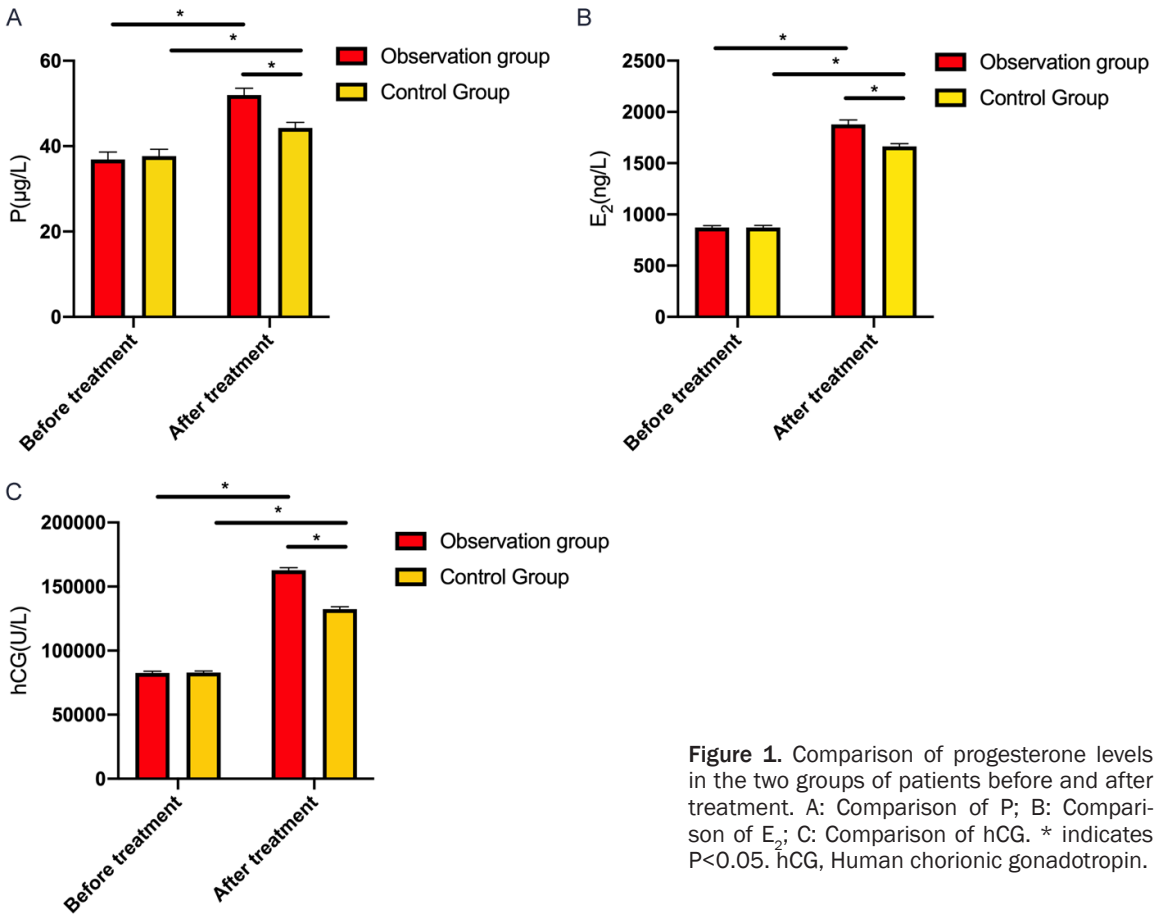


**Figure 1.** Comparison of progesterone levels in the two groups of patients before and after treatment. A: Comparison of P; B: Comparison of $E_2$; C: Comparison of hCG. * indicates P<0.05. hCG, Human chorionic gonadotropin.

**Table 5.** Comparison of neonatal body weight and Apgar scores

| Factor | Observation Group (n=154) | Control Group (n=57) | t | P |
|---|---|---|---|---|
| Neonatal Weight (kg) | 3.33±0.23 | 2.71±0.23 | 17.39 | <0.001 |
| Apgar Score | 9.61±0.24 | 9.03±0.26 | 15.24 | <0.001 |

**Table 6.** Comparison of umbilical artery blood gas indexes

| Factor | Observation Group (n=154) | Control Group (n=57) | t | P |
|---|---|---|---|---|
| pH | 7.41±0.05 | 7.29±0.05 | 15.48 | <0.001 |
| $PaO_2$ (mmHg) | 60.42±0.26 | 57.25±0.28 | 77.01 | <0.001 |
| $PaCO_2$ (mmHg) | 41.29±0.28 | 43.32±0.24 | 48.52 | <0.001 |

$PaO_2$, Partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

received ritodrine hydrochloride. Additionally, the time to symptom relief and cessation of uterine contractions was shorter in the observation group, indicating that phloroglucinol was more effective in managing threatened abortion or threatened preterm labor.

Furthermore, the gestational age at delivery was significantly longer in the observation group, and the neonatal birth weight and Apgar scores at 1 minute post-birth were notably higher than those in the control group. These findings suggest that phloroglucinol can extend the gestational age closer to full term, thereby supporting intrauterine fetal development, improving neonatal birth weight and Apgar scores, and reducing the risk of neonatal asphyxia.

Blood gas analysis is the gold standard for evaluating acid-base status in the body. The umbilical cord contains one umbilical vein and two umbilical arteries. The umbilical vein delivers nutrient- and oxygen-rich blood to the fetus, serving as a crucial conduit for the fetus to

**Table 7.** Comparison of adverse reaction rate [n, (%)]

| Adverse reaction | Observation Group (n=154) | Control Group (n=57) | $\chi^2$ | P |
|---|---|---|---|---|
| Tachycardia | 0 | 7 (12.28) | - | - |
| Chest Tightness | 1 (0.65) | 1 (1.75) | - | - |
| Nausea and Vomiting | 0 | 0 | - | - |
| Hypokalemia | 0 | 1 (1.75) | - | - |
| The Incidence of Adverse Reactions | 1 (0.65) | 9 (15.79) | 20.72 | <0.001 |

obtain oxygen and nutrients from the maternal blood [19]. Blood with high carbon dioxide concentrations and metabolites flows from the fetus to the placental villi by the umbilical arteries, allowing umbilical arterial blood oxygen levels to accurately reflect fetal oxygenation [20]. In our study, we observed that the pH and $PaO_2$ levels in the neonatal umbilical arterial blood of the observation group were significantly higher, and the $PaCO_2$ levels were markedly lower, compared to those in the control group. This indicates that phloroglucinol has a lesser impact on fetal blood gas and provides better intrauterine oxygenation than ritodrine hydrochloride. This may be due to the fact that phloroglucinol lacks anticholinergic effects, does not interfere with the normal physiologic functions of pregnant women, and helps maintain stable hemodynamics, thereby reducing its impact on the fetus [21, 22].

Additionally, estrogen and progesterone deficiencies are critical factors in threatened abortion or threatened preterm birth [23]. Studies [24] have shown that P can inhibit uterine contractions, promote reproductive system development, and support pregnancy continuation. hCG promotes the production of progesterone in the first trimester, enhances estrogen secretion, and reduces oxytocin levels, thereby inhibiting uterine contractions and preventing miscarriage. $E_2$, a form of estrogen secreted by the corpus luteum, promotes endometrial hyperplasia. Therefore, low levels of these hormones can indicate a risk of miscarriages.

Our study results demonstrated that serum levels of P, $E_2$, and hCG in both groups were significantly higher post-treatment compared to pretreatment levels, with the increases being more pronounced in the observation group than in the control group. This suggests that phloroglucinol is more effective than ritodrine in enhancing estrogen levels in patients. Although previous studies have not directly linked phloroglucinol to improved progesterone levels in patients with threatened abortion, our findings might be explained by the absence of significant ARs to the drug. By inhibiting uterine contractions, phloroglucinol provides a stable hormonal environment, allowing hormone levels to recover gradually. However, this hypothesis requires further investigation. Moreover, the incidence of adverse drug reactions was significantly lower in the observation group compared to the control group, suggesting that phloroglucinol treatment has a better safety profile than ritodrine hydrochloride.

In conclusion, phloroglucinol was better than ritodrine hydrochloride in treating threatened abortion or threatened premature labor, as it could lower the incidence of adverse clinical reactions, improve the pregnancy rate, and shorten the time to symptom disappearance. Additionally, pregnant women showed good tolerance and high acceptance of phloroglucinol, making it an effective drug for clinical intervention and treatment of threatened abortion or threatened premature birth. This also provides a new therapeutic approach and method that is worthy of clinical use.

## Disclosure of conflict of interest

None.

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