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Original Article

Efficacy of atosiban combined with ritodrine on spontaneous threatened preterm birth and its effect on PAF and fFN levels

Rui Wang[1], Juandi Liu[2], Yuan Qiao[3], Xiaojing Wang[4], Jianhong Chen[4], Ying Ma[4]

Departments of [1]Obstetrics, [2]Gynaecology, Northwest Women and Children's Hospital, No. 1616, Yanxiang Road, Yanta District, Xi'an 170061, Shaanxi, China; [3]Obstetric Intensive Care Unit, Northwest Women and Children's Hospital, No. 1616, Yanxiang Road, Yanta District, Xi'an 170061, Shaanxi, China; [4]Department of Obstetrics, Baoji Maternal and Child Health Hospital, No. 2, East Section of Xinjian Road, Weibin District, Baoji 721000, Shaanxi, China

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Abstract: Objective: To explore the efficacy of Atosiban combined with Ritodrine treatment on spontaneous threatened preterm birth and its effect on platelet-activating factor (PAF) and fetal fibronectin levels. Methods: Medical records from 120 patients with threatened preterm birth admitted to Baoji Maternal and Child Health Hospital from October 2020 to December 2021 were collected for this retrospective analysis. A total of 56 patients treated with Ritodrine alone were taken as the control group (CG), and the other 64 patients given combined treatment of Atosiban and Ritodrine were seen as the observation group (OG). Indexes of uterine contraction inhibition rate, pregnancy prolongation time, onset time, adverse reactions and pregnancy outcomes were compared between the two groups; in addition, the levels of inflammatory factors as well as PAF and fFN before and after treatment were detected and compared between two groups. Results: Compared with the CG, the uterine contraction inhibition rate as well as the pregnancy prolongation time in the OG were evidently higher (all $P<0.05$); the time of the disappearance of uterine contraction in the OG was significantly shorter ($P<0.05$); the rate of full-term delivery and neonatal 1-min Apgar score in the OG were obviously higher ($P<0.05$); and the incidence of total adverse reactions in the OG was markedly lower ($P<0.05$). However, there was no significant difference observed in the neonatal asphyxia rate and the number of fetuses between the two groups ($P>0.05$). After treatment, the OG was observed with markedly lower level of inflammatory factors C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) than the CG ($P<0.05$); levels of PAF and fFN decreased significantly in both two groups ($P<0.05$), and the levels in the OG were comparatively lower as compared to the CG ($P<0.05$). The areas under the ROC curve for PAF and fFN to predict pregnancy outcome were 0.766 and 0.757, respectively. Conclusion: Atosiban combined with Ritodrine evidently improves the therapeutic efficacy in patients with threatened preterm labor, reduces the occurrence of adverse pregnancy outcomes as well as the levels of PAF and fFN.

Keywords: Atosiban, Ritodrine, spontaneous threatened preterm birth, PAF, fFN

Introduction

Preterm birth refers to a birth that takes place more than three weeks before the baby's estimated due date, that is, less than 37 weeks of gestation. Statistically, 8-11% of all pregnancies in the world are premature, which has become the main cause of perinatal mortality and morbidity in developed countries [1, 2]. Premature infants suffer from poor prognosis and are vulnerable to disability even if they survive, such as respiratory diseases, cognitive impairment, blindness and deafness, as well as complications, including motor and sensory impairments, learning difficulties, and behavioral problems during development, which bring great physical and mental stress to the families [3, 4].

Threatened preterm labor is defined as persistent uterine contractions between 20 and 37 weeks of gestation, along with pelvic pressure, back pain, increased vaginal discharge, menstrual pain, bleeding, and shortening of the cer-

vix [5]. Due to the uterine contractions, treatment for women with threatened preterm labor includes the administration of tocolytics to temporarily suppress uterine contractions and prolong the pregnancy, gaining more time for the maturity of fetal lungs [6].

Ritodrine, a β2-receptor agonist, is the first-line treatment drug for premature labor, which inhibits uterine contraction by increasing the β2-receptor excitability in uterine smooth muscle, thereby prolonging the pregnancy period of patients [7]. However, β2 receptors are widely distributed in the human body and can easily activate the β1 receptors of the heart, which lead to an increase in the heart rate of pregnant women. Its long-term usage can also cause adverse reactions such as glucose metabolism disorders, affecting the safety of mothers and babies. Therefore, the dosage and medication time need to be controlled based on the maternal situation [8]. Atosiban, an oxytocin receptor antagonist with high specificity to the uterus, can inhibit the uterine contraction effect of oxytocin, prevent premature birth, and is of high safety [9]. Platelet-activating factor (PAF) and fetal fibronectin (fFN) have been found to be related to premature birth and some neonatal diseases and even have a certain predictive value for the occurrence and progression of the disease in animal experiments and clinical studies [10, 11]. However, more research is needed to verify the specific changes in the treatment of threatened preterm birth.

In view of this, this study aimed to analyze the clinical effect of Ritodrine combined with Atosiban in the treatment of spontaneous threatened preterm birth, and to observe their effects on the levels of PAF and fFN.

Methods and information

General information

Medical records from 120 patients with threatened preterm birth admitted to Baoji Maternal and Child Health Hospital from October 2020 to December 2021 were collected for this retrospective analysis. A total of 56 patients treated with Ritodrine alone were taken as the control group (CG), with an average age of (27.98±1.02) years old and an average gestational age of (29.64±1.37) weeks; the other 64 patients were given the combined treatment of Atosiban and Ritodrine were seen as the observation group (OG), with an average age of (27.19±1.83) years old and gestational age of (29.30±1.33) weeks. This study was conducted after being reviewed and approved by the Medical Ethics Committee of our hospital.

Inclusion and exclusion criteria

Inclusion criteria: Patients clinically diagnosed with threatened preterm birth [12]; patients with gestational period of 28-37 weeks; patients who gave consent to the given treatment; patients with complete medical records.

Exclusion criteria: Patients with intrauterine infection; patients with severe unstable blood pressure levels; patients combined with hyperthyroidism, heart disease, etc.; patients with cervical dilation >2 cm; patients with allergy to the drugs used in this study; patients who had received treatment to promote fetal lung maturation after admission to the hospital before changing to treatment plan.

Treatment methods

The CG patients were treated with Ritodrine (manufacturer: Xindong Biotechnology Co., Ltd.; approval number: HC20080024). Briefly, 50 mg Ritodrine was dissolved in 50 ml of 5% glucose solution for intravenous pumping, and the speed was adjusted according to the uterine contractions, which did not exceed 21 ml/h. When uterine contractions stopped, intravenous infusion was maintained for 18 hours, with a total intake of <2000 ml.

The OG was treated with Atosiban injection (manufacturer: Hainan Zhonghe Pharmaceutical Co., Ltd.; approval number: 20150201) on the basis of care in the CG. First, 6.75 mg single-dose Atosiban injection was injected intravenously for more than 1 min, followed by continuous infusion of a high-dose diluted 5 ml:37.5 mg Atosiban injection (300 μg/min) for 3 hours. Finally, the diluted 5 ml:37.5 mg Atosiban injection was given at a low dose for 45 hours, and the treatment time did not exceed 48 hours.

Observation indicators

(1) The uterine contraction inhibition rate of the two groups were compared and categorized:

Table 1. Baseline data of two groups

	Observation Group (n = 64)	Control Group (n = 56)	t/X^2	P
Age (years)	27.19±1.83	27.34±2.04	0.425	0.672
Gestational Week (Week)	29.30±1.33	29.64±1.37	1.378	0.171
Weight (kg)	63.12±4.98	63.32±5.04	0.218	0.828
Cervical canal length (cm)	3.44±0.41	3.52±0.34	1.154	0.251
Childbirth history			1.139	0.286
primipara	29 (45.31)	20 (35.71)		
multipara	35 (54.69)	36 (64.29)		
History of cesarean section	10 (15.63)	5 (8.93)	1.224	0.269
History of miscarriage	20 (31.25)	21 (37.50)	0.519	0.471
Gestational diabetes	18 (28.13)	12 (21.43)	0.714	0.398
Premature rupture of membranes	14 (21.88)	10 (17.86)	0.301	0.583
Polyhydramnios	26 (40.63)	20 (35.71)	0.305	0.581
Placental abruption	16 (25.00)	16 (28.57)	0.195	0.659

complete inhibition of uterine contractions (complete disappearance of backache, abdominal pain, vaginal bleeding and uterine contractions and other symptoms); effective inhibition of uterine contractions (improved symptoms and signs of uterine contraction with frequency less than 2 times/h and duration of <30 s/time); ineffective inhibition of uterine contractions (no improvement in symptoms and signs, with uterine contraction frequency ≥2 times/h and contraction time ≥30 s/time). The total effective rate of uterine contraction inhibition = (complete inhibition + effective inhibition)/total number of cases × 100% [13]. (2) The prolonged pregnancy time and the time to the disappearance of uterine contractions were compared between the two groups. (3) The pregnancy outcomes of the two groups after treatment were compared and observed, including conditions of term birth, preterm birth, Neonatal Apgar score at 1 min, number of fetuses, and neonatal asphyxia. (4) The adverse reactions of the two groups were compared and observed. (5) 4 ml of venous blood was drawn after the patient was admitted to the hospital and after the treatment, respectively. After centrifugation at a low speed (3 000 rpm, radius 15 cm, time 5 min), the levels of PAF and fFN as well as inflammatory factors C-reactive protein (CRP), TNF-α, IL-6, were detected by ELISA. Kits for PAF and fFN were purchased from abcam (ab2878790) and Wuhan Fein Bio (EH4158), and those for C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were from Wuhan Fein Bio (EH0099, EH0302, AQ-H0201), respectively. Levels of PAF, fFN and inflammatory factor levels before and after treatment were compared between the two groups. (6) Levels of PAF and fFN were compared between preterm and full-term patients. The value of PAF and fFN in predicting pregnancy outcome was detected by ROC curve.

Statistical methods

SPSS20.0 (Chicago SPSS Co., Ltd.) statistical analysis software was used for statistical analysis of the collected data. The enumeration data was presented by rate (%) and analyzed by chi-square test, denoted by X^2, and the measurement data was expressed by mean ± standard deviation (Means ± SD), and all measurement data conformed to normal distribution. Inter-group comparison and intra-group comparison was carried out with Student t-test and Paired t-test respectively, expressed as t. $P<0.05$ was taken as the significance level. ROC curve was used to detect the value of PAF and fFN levels in predicting pregnancy outcomes.

Results

Baseline data of patients

There were no significant differences observed between two groups in terms of age, gestational age, weight, cervical length, birth history, cesarean section, miscarriage history, gestational diabetes, premature rupture of membranes, polyhydramnios, or placental abruption, indicating the comparability between two groups (**Table 1**).

Table 2. The uterine contraction inhibition rate of the two groups

	Observation Group (n = 64)	Control Group (n = 56)	X^2	P
Complete inhibition of uterine contractions	38 (59.38)	23 (41.07)	4.003	0.045
Effective inhibition of uterine contractions	22 (34.38)	23 (41.07)	0.571	0.450
Ineffective inhibition of uterine contractions	4 (6.25)	10 (17.86)	3.905	0.048
Total effective rate of uterine contraction inhibition	60 (93.75)	46 (82.14)	3.905	0.048

Table 3. Comparison of the treatment efficacy between two groups

	Prolonged pregnancy time (d)	Time to the disappearance of contractions (h)
Observation Group (n = 64)	26.23±3.44	14.39±2.13
Control Group (n = 56)	20.74±3.16	18.25±2.68
t	9.058	8.782
P	<0.001	<0.001

Table 4. Pregnancy outcome of the two groups of patients

	Observation Group (n = 64)	Control Group (n = 56)	X^2/t	P
Full term delivery	52 (81.25)	36 (64.29)	4.395	0.036
Premature birth	12 (18.75)	20 (35.71)	4.395	0.036
Neonatal asphyxia	2 (3.13)	6 (10.71)	2.765	0.096
Neonatal 1 min Apgar score	8.47±0.59	8.07±0.42	4.299	<0.001
Number of fetuses			0.978	0.323
Singleton	59 (92.19)	54 (96.43)		
Multiple births	5 (7.81)	2 (3.57)		

Comparison of the uterine contraction inhibition rate between two groups

By comparing the effect of uterine contraction inhibition between the two groups, it was found that the complete inhibition rate of uterine contractions and the total effective rate of uterine contraction inhibition in OG were both evidently higher than those in CG (P<0.05, **Table 2**).

Comparison of the application effects

Compared with CG, it was found that the prolonged pregnancy time in OG was evidently longer (P<0.05), while the time to the disappearance of uterine contractions was markedly shorter (P<0.05), as shown in **Table 3**.

Comparison of pregnancy outcomes after treatment

By observing the pregnancy outcomes of the two groups of patients after treatment, it was found that the full-term delivery rate and neonatal 1 min Apgar score in OG were significantly higher than that in CG (both P<0.05), but there was no significant difference in the neonatal asphyxia rate and the number of fetuses between the two groups (both P>0.05, **Table 4**).

Comparison of adverse reactions between the two groups

The incidence of total adverse reactions in OG (7.81%) was evidently lower than that in CG (21.43%) (P<0.05, **Table 5**).

Inflammation levels before and after treatment in the two groups

There was no significant difference in the expression levels of CRP, TNF-α and IL-6 between the two groups before treatment. However, after the treatment, those levels in the two groups were both markedly decreased, and OG harvested significantly lower levels as compared with the CG (all P<0.001), as shown in **Figure 1**.

Table 5. Adverse reactions of two groups of patients

	Observation Group (n = 64)	Control Group (n = 56)	X^2	P
Headache	2 (3.13)	5 (8.93)		
Chest pain	1 (1.56)	3 (5.36)		
Nausea	1 (1.56)	2 (3.57)		
Tachycardia	1 (1.56)	2 (3.57)		
Total adverse reactions	5 (7.81)	12 (21.43)	4.554	0.033

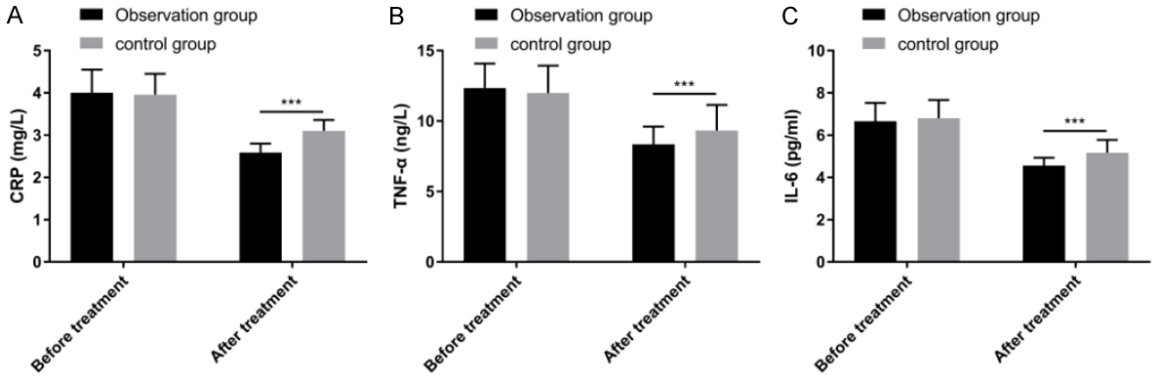

Figure 1. Inflammation levels before and after treatment in the two groups of patients. A. After treatment, the CRP level of the observation group was significantly lower than that of the control group (P<0.001). B. After treatment, the level of TNF-the observation group was significantly lower than that of the control group (P<0.001). C. After treatment, the level of IL-6 in the observation group was significantly lower than that in the control group (P<0.001). CRP: C-Reactive Protein; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6.

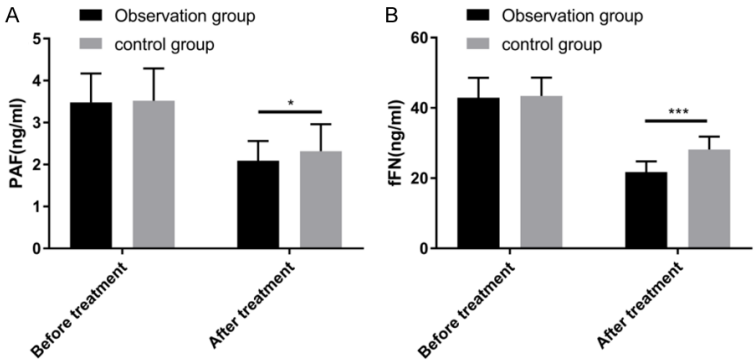

Figure 2. The levels of PAF and fFN in the two groups before and after treatment. A. After treatment, the level of PAF in the observation group was significantly lower than that in the control group (P<0.001). B. After treatment, the fFN level of the observation group was significantly lower than that of the control group (P<0.001). PAF: Platelet-Activating Factor; fFN: Fetal Fibronectin.

PAF and fFN levels before and after the treatment in two groups

No significant difference was observed in PAF and fFN levels between the two groups before treatment (P>0.05); yet after treatment, the levels of those in the two groups were both evidently decreased (all P<0.05), and OG harvested markedly lower levels than those in CG (all P<0.05, **Figure 2**).

The predictive value of PAF and fFN on pregnancy outcomes

After comparison, it was found that the levels of PAF and fFN in patients with full-term delivery were markedly lower than those in patients with preterm birth (P<0.05). ROC curve was used to detect the value of PAF and fFN levels in predicting the pregnancy outcome of patients, and it was found that the areas under the curves of PAF and fFN were 0.766 and 0.757, respectively (**Figure 3**).

Discussion

In recent years, the incidence of threatened preterm birth has shown a continuous upward

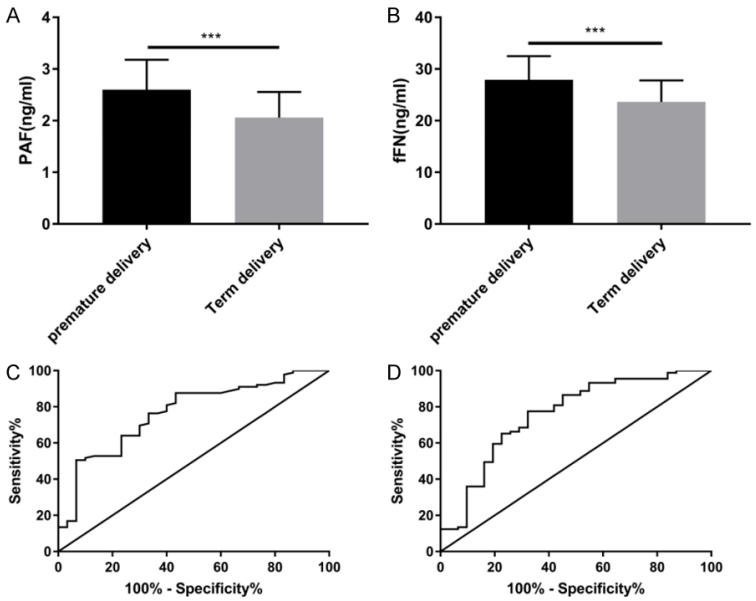

Figure 3. Predictive value of PAF and fFN for pregnancy outcome. A. The PAF of preterm delivery patients was significantly higher than that of full-term delivery patients (P<0.001). B. The fFN of preterm patients was significantly higher than that of full-term patients (P<0.001). C. The ROC curve of PAF in predicting the pregnancy outcome; the AUC was 0.766 at a cut-off value of 2.59 with the best sensitivity and specificity of 87.64% and 56.67%, respectively. D. The ROC curve of fFN in predicting the pregnancy outcome; the AUC was 0.757, at a cut-off value of 26.45 with the best sensitivity and specificity of 77.53% and 67.74%, respectively. PAF: Platelet-Activating Factor; fFN: Fetal Fibronectin.

trend, which is mostly related to factors of unfavorable living environment, lifestyle and dietary habits. Preterm birth has a great implication on fetal outcomes and is an important cause of fetal death [14, 15]. Ritodrine is an option for threatened preterm labor, which reduces the frequency and intensity of uterine contractions. However, long-term use of large dose of Ritodrine may cause a series of side effects to the mother including increased heart rate and chestpain [16, 17].

Results of this study showed that, compared with CG, the complete inhibition rate of uterine contractions and the total effective rate of uterine contraction inhibition in OG were significantly higher, as well as its prolongation time of pregnancy; OG held significantly shorter time to the disappearance of uterine contractions and lower adverse reaction rate. It suggested that Atosiban combined with Ritodrine could inhibit uterine contractions faster and more effectively in the treatment of threatened preterm labor, prolong the gestational age of pregnancy to protect the health of both mothers and babies, and improve the quality of obstetric fertility without raising the side effects. This may due to that Atosiban is a synthetic peptide substance with fast onset and short half-life that can quickly reach the ideal blood concentration with high specificity. It can directly act on the uterus, competitively bind to the oxytocin receptors on the myometrium and decidua, reduce the synthesis of prostaglandins and the ability of uterine muscle contraction, so it is of better effect in inhibiting uterine contractions [18, 19]. Inflammation has always been one of the main causes of initiating and contributing to preterm birth [20]. Gomez's study [21] also claimed that inflammatory responses increased the risk of adverse pregnancy outcomes in preterm delivery women. At the same time, Kim's study [22] also showed that Atosiban could not only keep uterine contractions, but also inhibit the inflammatory response during preterm birth. In our study, we also compared the inflammatory factors of the two groups before and after the treatment, and found that they were markedly decreased in both groups after treatment, and the levels of these three in OG were significantly lower compared to CG, suggesting that Atosiban combined with Ritodrine had a better anti-inflammatory effect.

Afterwards, we observed the pregnancy outcomes of the two groups of patients after treatment, and found that, compared with CG, the full-term delivery rate of OG was markedly higher and the premature birth rate was evidently lower, but the neonatal asphyxia rate and the number of fetuses of the two groups was not significantly different, and the 1-min Apgar score of newborns in OG was higher evidently, all indicating that the combined treatment can improve the pregnancy outcomes, promote fetal development and increase full-term rate. This is because Atosiban can interact with uterine smooth muscle oxytocin receptors, which can effectively prolong the gestational age of

pregnancy by inhibiting uterine contractions [23]. The research of Nathanielsz et al. [24] showed that atoxeban could pass through the placenta but had no effect on the mother's heart rate and fetal oxygenation. In the study of Fu et al. [25], Atosiban combined with Ritodrine was also used in the treatment of patients with late threatened abortion and threatened preterm labor, and the gestational age of pregnancy was prolonged in patients treated with combination therapy, but there were no significant differences in fetal loss rate, neonatal birth weight, and 1 min Apgar score between the two groups, which may be related to the sample type and small sample size of the subjects.

fFN is an extracellular matrix glycoprotein enriched in the maternal-fetal interface of the amniotic membrane, between the chorion and decidua, and is mainly produced by amniocytes and cytotrophoblasts. Under normal circumstances, the content of fFN in cervicovaginal secretions is very low; however, inflammation, infection, or mechanical injury would promote the release of fFN into cervicovaginal fluid or peripheral venous blood [26]. PAF, a potent proinflammatory mediator synthesized by a variety of cells including neutrophils, monocytes, macrophages, platelets, and endothelial cells, can targetedly stimulate nuclear factor-κB activation and inflammatory cytokines in uterine cells, and promote uterine activation and transition to a contractile state [27, 28]. Our study found that levels of PAF and fFN in two groups both decreased evidently after the treatment, and those indexes in OG were markedly lower than those in CG. Moreover, they were also found to be notably higher in preterm patients than full-term patients. The value of PAF and fFN levels in predicting the pregnancy outcome of patients was detected by ROC curve, and the areas under the PAF and fFN curves were 0.766 and 0.757, respectively, suggesting that these two indicators are of good predictive value for the pregnancy outcome of patients with spontaneous threatened preterm birth. Park et al. [29] evaluated the value of fFN in cervical vaginal fluid in diagnosing preterm labor in their research, and found that the sensitivity and specificity of fFN were 33% and 95%, respectively, indicating it was a good marker for diagnosing preterm labor, but its diagnostic value was lower than that of IL-6 and IL-17 ficity.

In this study, the efficacy of Atosiban combined with Ritodrine in the treatment of spontaneous threatened preterm birth was observed, as well as its effect on the levels of PAF and fFN, but there are still some limitations. First of all, our study focused on the changes in levels of PAF and fFN, but the specific mechanism still needs to be explored in more animal experiments. Secondly, few studies emphasize on the impact on premature infants, and we hope to refine our conclusions by conducting related studies in the future.

In conclusion, Atosiban combined with Ritodrine can significantly improve the therapeutic effect, reduce the incidence of adverse preterm birth, and reduce the levels of PAF and fFN in patients with threatened preterm birth.

Disclosure of conflict of interest

None.

Address correspondence to: Ying Ma, Department of Obstetrics, Baoji Maternal and Child Health Hospital, No. 2, East Section of Xinjian Road, Weibin District, Baoji 721000, Shaanxi, China. Tel: +86-0917-3251887; E-mail: Mayingdoctor@126.com

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