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Original Article

Efficacy of atosiban combined with ritodrine in the treatment of threatened preterm labor and related risk factors of different pregnancy outcomes

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Abstract: Objective: To investigate the efficacy of atosiban combined with ritodrine in threatened preterm labor (TPL) treatment and analysis of related risk factors of different pregnancy outcomes. Methods: A retrospective study was conducted on the clinical data of 127 patients with TPL who were hospitalized in the Children's Hospital of Shanxi and Women's Health Center of Shanxi from January 2020 to November 2021. There from, 58 patients treated with ritodrine were seen as the control group (CG), and 69 treated with atosiban and ritodrine were regarded as the joint group (JG). The inhibition rate after treatment was compared, and the changes of tissue inhibitor of metalloproteinase-1 (TIMP-1), nitric oxide (NO), interleukin-6 (IL-6), and prostaglandin E2 (PGE2) in the amniotic fluid before and after treatment were assessed. The pregnancy outcomes of patients were recorded, and the risk factors of adverse pregnancy outcomes were analyzed. The full-term delivery rate, cesarean section rate and neonatal Apgar score >7 were compared, and their adverse reactions were evaluated. Results: Compared with the JG, the improvement of uterine contraction in the CG was obviously lower, and so was the inhibition rate ($P<0.05$). The rates of full-term delivery and neonatal Apgar score >7 in the CG were lower than those in the JG, while that of cesarean section was higher ($P<0.01$). After treatment, the TIMP-1 level in the amniotic fluid in the CG was markedly lower ($P<0.001$), while the NO, IL-6 and PGE2 levels were higher ($P<0.001$) as compared with the joint group. The total incidence of adverse reactions in the JG was lower than that in the CG ($P<0.05$). Logistics regression analysis revealed that age<26 and use of Atosiban combined with Ritodrine are protective factors for pregnancy outcomes, while BMI≥20 before pregnancy is a risk factor for adverse pregnancy. Conclusion: Atosiban combined with ritodrine can improve the condition of TPL patients, enhance the treatment efficacy, and reduce the occurrence of adverse pregnancy outcomes.

Keywords: Atosiban, ritodrine, threatened preterm labor, pregnancy outcome, analysis of risk factors

Introduction

Threatened preterm labor (TPL) is a common pathological condition in pregnant women [1]. Pregnant women who give birth at 28-36 weeks of gestation may experience vaginal bleeding, irregular uterine contractions, etc., and a small number of patients may also suffer shortening of the cervical canal and dilation of the cervix, which may easily lead to premature delivery [2]. Data indicate that more than 3.1 million newborns die each year due to preterm birth. Preterm birth has become the leading cause of neonatal death, and the risk of long-term adverse outcomes of survivors is also increased [3]. Premature infants have immature organ systems and are prone to various infections and complications after birth, which will adversely affect their future growth and development. Therefore, TPL patients need timely treatment to protect their fetuses [4]. With the opening of the three-child policy, the proportion of pregnant women with advanced age and multiple pregnancies has increased dramatically, which leads to a marked increase in the probability of late abortion and preterm deliv-

ery, resulting in a serious threat to the lives of mothers and infants [5]. Thus, how to avoid TPL and reduce neonatal mortality is particularly important.

The main factor of TPL is the decrease of maternal progesterone level due to various reasons, which leads to fetal rejection and uterine contractions [6]. Thus, drugs are mainly used to control maternal uterine contractions [7]. Ritodrine, a representative drug of inhibition of uterine contraction can activate adenylate cyclase, inhibit uterine smooth muscle contraction, reduce the time and degree of uterine contraction, and decrease the risk of abortion [8]. However, it has side effects on mothers and infants, especially in the cardiovascular system, which limits its clinical use [9]. As an oxytocin receptor antagonist, atosiban is a synthetic polypeptide compound modified on the basis of the structure of oxytocin. It is a competitive antagonist of the cyclic peptide oxytocin receptor on the myometrium, decidua and fetal membrane [10]. It has a remarkable improvement effect in the control of maternal uterine contractions, with fewer adverse reactions and a high drug safety [11]. Because the pharmacological mechanisms of the two drugs in preterm delivery treatment are different, it is unclear whether the combination can better inhibit uterine contractions and reduce the adverse outcomes of mothers and fetuses.

In this retrospective study, we compared the clinical efficacy of ritodrine alone and atosiban combined with ritodrine in TPL treatment, and analyzed the factors affecting the pregnancy outcomes of patients.

Methods and materials

Clinical data

A total of 127 patients with TPL who were hospitalized in the Children's Hospital of Shanxi and Women's Health Center of Shanxi from January 2020 to November 2021 were retrospectively enrolled in this study. Among them, 58 patients treated with ritodrine alone were considered as the control group (CG), and the rest 69 treated with atosiban and ritodrine were regarded as the joint group (JG). This research was approved by the Medical Ethics Committee of Children's Hospital of Shanxi and Women's Health Center of Shanxi. Ethical number: IRB-KY-2022-014.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the criteria of threatened abortion in Chinese Obstetrics and Gynecology [12]: (1) 4 or more uterine contractions every 30 min with each contraction lasting more than 30 s; (2) Cervical shortening ≤25 mm; (3) The cervix dilation of 1-3 cm; (4) Patients with complete clinical data. All of participants knew about the treatment and signed the informed consent form.

Exclusion criteria: Patients with contraindications to uterine contraction treatment, such as diabetes, heart disease, hyperthyroidism, gestational hypertension, vaginal bleeding, etc; Patients with signs of termination of pregnancy such as fever, infection, fetal distress, etc; Patients who were intolerant to the drugs; Patients with multiple pregnancies.

Sources of drugs and kits

Atosiban acetate injection (Meheco Kangli Pharma Co., Ltd., Hainan, China, SFDA Approval No. H20223012, specification: 5 mL: 37.5 mg), ritojun hydrochloride injection (Jichuan Pharmaceutical Group Co., Ltd., Jiangsu, China, SFDA Approval No. H20093498, specification: 5 mL: 50 mg), tissue inhibitor of metalloproteinase-1 (TIMP-1, ml568710-2), nitric oxide (No, ml057447), interleukin-6 (IL-6, ml028583) and prostaglandin E2 (PGE2, ml057929) kits (Shanghai Enzyme-linked Biotechnology Co., Ltd).

Treatment regimens

Patients in the CG were treated with ritodrine hydrochloride injection alone. A solution of 100 mg ritodrine hydrochloride and 500 mL of 5% glucose was prepared into 0.2 mg/mL ritodrine solution, which was then administered via intravenous drip. The optiamal dose for good uterine contractions should be selected, and the maximum dose should not exceed 0.35 mg/min.

JG patients were treated similarily to the CG plus atosiban acetate injection. The first intravenous injection of 6.75 mg of atosiban acetate was followed by an intravenous drip using 37.5

mg/5 mL injection + 5% glucose injection 180 mL. The infusion rate was 24 mL/h for the first 3 hour and 8 mL/h for the next 3 hours, with a total of 6-hours of infusion. If patients consciously developed tachycardia, increased heart rate, fetal tachycardia, etc, the drip rate should be slowed down.

Detection indexes

After disinfection of the vulva, vagina and cervix of the patient, the vagina was dilated with a speculum, and 5 mL of amniotic fluid was extracted by needle-free injection. After anticoagulation treatment, the supernatant was collected by centrifugation at 1500 g for 10 min, placed in a clean EP tube, labele, and stored at -70°C for use. dThe TIMP-1, NO, IL-6 and PGE2 levels in amniotic fluid were tested by ELISA method, strictly based on the instructions of kits.

Outcome measures

Main outcome measures: The inhibition rate of patients after treatment was compared; The changes of TIMP-1, NO, IL-6 and PGE2 in the amniotic fluid of patients before and after treatment were assessed. Pregnancy outcomes of patients were counted, and risk factors for adverse pregnancy outcomes were analyzed.

Secondary outcome measures: The clinical data were compared between both groups. The full-term delivery rate, cesarean section rate and the rate of neonatal Apgar score >7 were compared between both groups. Premature delivery, neonatal asphyxia and neonatal death were regarded as adverse pregnancy outcomes, which were compared between both groups.

Evaluation criteria of uterine contraction inhibition rate

Complete inhibition: After intervention, abdominal pain, low back pain and other symptoms and signs of PTL were relieved, and there was no vaginal bleeding. Obvious inhibition: There were still uterine contractions after intervention, but the duration was less than 30 s/time and the frequency was less than 2 times/h. No inhibition: After intervention, the uterine contraction still lasted more than 30 s/time, and the frequency was more than 4 times/h. The rate of effective uterine contraction inhibition = complete inhibition rate + obvious inhibition rate.

Statistical analysis

The collected data were analyzed using SPSS 20.0 software, and then visualized via GraphPad Prism 8 software. The counting data was expressed by n (%) and analyzed using chi-square test. The measurement data were expressed by mean ± standard deviation and assessed by t-test. There from, independent sample t-test was used for inter-group comparison, and paired t-test was used for intra-group comparison. Logistics regression was conducted to investigate the risk factors of adverse pregnancy outcomes. $P<0.05$ was regarded as statistical significance.

Results

Baseline data of patients

The baseline data of both groups were compared. It revealed that there was no marked difference in age, pre-pregnancy BMI, number of pregnancies, education level and family income between the two groups ($P>0.05$, **Table 1**).

Comparison of inhibition rate of uterine contraction

By comparing the inhibition rate of uterine contraction between both groups, we found that the inhibition rate in uterine contraction in the CG was lower than that in the JG ($P<0.05$, **Table 2**).

Comparison of full-term delivery rate, cesarean section rate and neonatal Apgar score

The full-term delivery rate, cesarean section rate and neonatal Apgar score were compared between both groups. The full-term delivery rate and rate of infants with neonatal Apgar score >7 in the CG were lower than those in the JG, while the rate of cesarean section in the CG was higher than that in JG ($P<0.01$, **Table 3**).

Changes of TIMP-1, NO, IL-6 and PGE2 in amniotic fluid

The TIMP-1, NO, IL-6 and PGE2 levels in amniotic fluid of both groups were tested before and after treatment. The results revealed that the

Table 1. Baseline data of patients

Factor	Control group (n=58)	Joint group (n=69)	*P* value
Age (year)			0.761
≥26 (n=77)	36	41	
<26 (n=50)	22	28	
Gestational weeks			0.952
≥30 (n=50)	23	27	
<30 (n=77)	35	42	
Pre-pregnancy BMI (kg/m^2)			0.760
≥20 (n=61)	27	34	
<20 (n=66)	31	35	
Number of pregnancies			0.589
Primipara (n=58)	28	30	
Multipara (n=69)	30	39	
Education level			0.299
≥ high school (n=86)	42	44	
<high school (n=41)	16	25	
Average household income (month/yuan)			0.843
≥6000 (n=47)	22	25	
<6000 (n=80)	36	44	
History of abortion			0.879
Yes (n=56)	26	30	
No (n=71)	32	39	

Note: BMI, Body mass index.

Table 2. Inhibition rate of uterine contraction

Group	Complete inhibition	Obvious inhibition	No inhibition	Complete inhibition rate
Control group (n=58)	18	23	17	41 (70.69)
Joint group (n=69)	28	33	8	61 (88.40)
χ^2/Z value		-1.982		6.256
P value		0.048		0.012

Table 3. Analysis of full-term delivery rate, cesarean section rate and neonatal Apgar score

Group	Full-term delivery	Cesarean section rate	Neonatal Apgar>7
Control group (n=58)	38 (65.52)	13 (22.41)	40 (68.96)
Joint group (n=69)	63 (91.30)	5 (7.24)	63 (91.30)
χ^2 value	12.870	6.172	10.260
P value	0.001	0.013	0.001

levels had no marked differences before treatment (all P>0.05). The TIMP-1 level decreased after treatment in both groups, while the levels of the other three increased (all P<0.001). Furthermore, after treatment, the TIMP-1 level in the amniotic fluid in the CG was lower than that in the JG (P<0.001), while the NO, IL-6 and PGE2 levels in the CG were higher (all P<0.001, **Figure 1**).

Comparison of adverse reactions

The adverse reactions during the treatment were compared between the two groups. There were no remarkable differences in palpitation, gastrointestinal reaction, dizziness and nausea (all P>0.05). Nevertheless, the total incidence of adverse reactions in the JG was lower than that in the CG (P<0.05, **Table 4**).

Statistics of pregnancy outcomes and analysis of risk factors

In this research, we conducted statistical analysis on the pregnancy outcomes of pregnant women. The pregnancy outcomes of patients were counted, and the number of premature births and neonatal asphyxia in the CG was higher than that in the JG (P<0.05, **Table 5**).

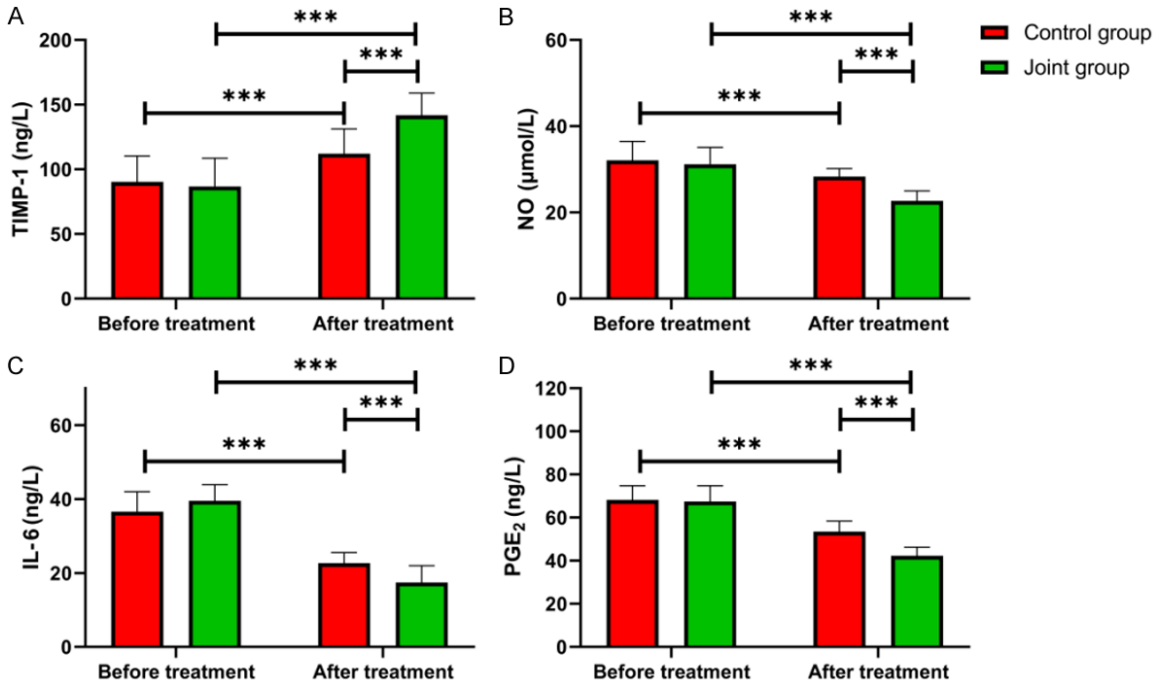

Figure 1. Changes of TIMP-1, NO, IL-6 and PGE2 in amniotic fluid. A. Changes of TIMP-1 in amniotic fluid before and after treatment in both groups; B. Changes of NO in amniotic fluid before and after treatment in both groups; C. Changes of IL-6 in amniotic fluid before and after treatment in both groups; D. The PGE2 level in amniotic fluid of both groups before and after treatment. Note: TIMP-1, Tissue inhibitor of metalloproteinase-1; NO, Nitric oxide; IL-6, Interleukin-6; PGE2, Prostaglandin E2. ***P<0.001.

Table 4. Comparison of adverse reactions

Group	Palpitation	Gastrointestinal reaction	Dizziness and nausea	Total incidence
Control group (n=58)	3	2	5	10
Joint Group (n=69)	1	1	2	4
χ^2 value	1.432	0.545	1.981	4.208
P value	0.231	0.460	0.159	0.040

Table 5. Statistics of pregnancy outcomes

Group	Premature delivery	Neonatal asphyxia	Neonatal death	Adverse pregnancy outcomes
Control group (n=58)	9	6	5	20
Joint group (n=69)	3	1	2	6
χ^2 value	4.595	4.787	1.981	12.870
P value	0.032	0.028	0.159	0.001

Then, patients were divided into two groups based on the adverse pregnancy outcomes (**Table 6**): normal pregnancy group (n=101) and adverse pregnancy group (n=26). Logistic regression analysis found that gestational weeks, number of pregnancies, education level, average household income, abortion history, TIMP-1, NO, IL-6, and PGE2 were not risk factors for poor pregnancy outcome. Whereas age <26 years old and joint therapy were protective factors for adverse pregnancy outcomes, and pre-pregnancy BMI ≥20 was a risk factor for adverse pregnancy (**Tables 7** and **8**, P<0.01). ROC curve showed that the combined detection had high clinical value in predicting adverse pregnancy outcomes (**Figure 2**).

Table 6. Assignment table

Factor	Assignment
Age	≥26 year =1; <26 year =0
Gestational weeks	≥30 weeks =1; <30 weeks =0
Pre-pregnancy BMI	≥20 (kg/m^2) =1; <20 (kg/m^2) =0
Number of pregnancies	Primipara =1; Multipara =0
Education level	≥ high school =1; < high school =0
Average household income	≥6000 yuan =1; <6000 yuan =0
Abortion history	Yes =1; No=0
Treatment regimens	Control group =1; Joint group =0
Pregnancy outcomes	Normal pregnancy outcome =1; Adverse pregnancy outcomes =0
TIMP-1 (ng/L)	Data are continuous variables using raw data
NO (μmol/L)	Data are continuous variables using raw data
IL-6 (ng/L)	Data are continuous variables using raw data
PGE2 (ng/L)	Data are continuous variables using raw data

Note: BMI, Body mass index; TIMP-1, Tissue inhibitor of metalloproteinase-1; NO, Nitric oxide; IL-6, Interleukin-6; PGE2, Prostaglandin E2.

Table 7. Analysis of risk factors of adverse pregnancy outcomes

Factor	Normal pregnancy outcomes (n=101)	Adverse pregnancy outcomes (n=26)	*P* value
Age (year)			0.018
≥26 (n=77)	56	21	
<26 (n=50)	45	5	
Gestational weeks			0.314
≥30 (n=50)	42	8	
<30 (n=77)	59	18	
Pre-pregnancy BMI (kg/m^2)			0.004
≥20 (n=61)	42	19	
<20 (n=66)	59	7	
Number of pregnancies			0.087
Primipara (n=58)	50	8	
Multipara (n=69)	51	18	
Education level			0.220
≥ high school (n=86)	71	15	
< high school (n=41)	30	11	
Average household income (month/yuan)			0.863
≥6000 (n=47)	37	10	
<6000 (n=80)	64	16	
History of abortion			0.813
Yes (n=56)	44	12	
No (n=71)	57	14	
Treatment schemes			0.001
Control group (n=58)	38	20	
Joint group (n=69)	63	6	
TIMP-1 (ng/L)	86.96±20.65	93.53±22.08	0.157
NO (μmol/L)	31.50±4.50	31.81±3.49	0.743
IL-6 (ng/L)	38.35±4.96	37.71±5.42	0.565
PGE2 (ng/L)	67.74±6.91	67.94±7.37	0.898

Note: BMI, Body mass index; TIMP-1, Tissue inhibitor of metalloproteinase-1; NO, Nitric oxide; IL-6, Interleukin-6; PGE2, Prostaglandin E2.

Table 8. Multivariate analysis

Factor	β	SE	χ^2	*P* value	OR value	95% CI	
						Lower limit	Upper limit
Age	-1.274	0.584	4.761	0.029	0.28	0.089	0.878
Pre-pregnancy BMI	1.542	0.532	8.411	0.004	4.676	1.649	13.259
Treatment schemes	-1.732	0.541	10.269	0.001	0.177	0.061	0.51

Note: BMI, Body mass index.

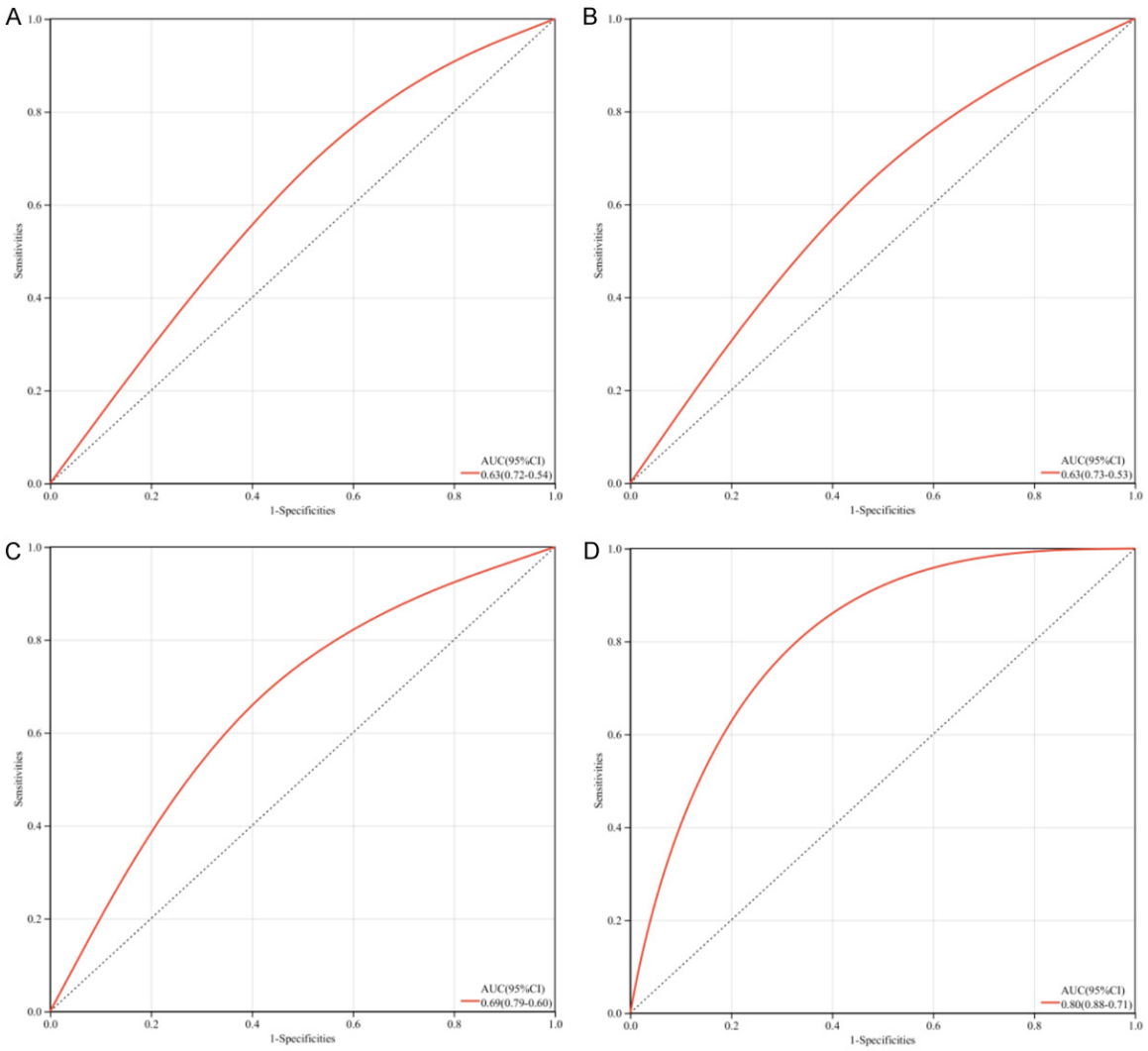

Figure 2. ROC curve of age, pre-pregnancy BMI, treatment regimens and combination indexes in predicting adverse pregnancy outcomes. A. ROC curve of age in predicting adverse outcomes of patients; B. ROC curve of pre-pregnancy BMI in predicting adverse outcomes of patients; C. ROC curve of treatment regimens in predicting adverse outcomes of patients; D. ROC curve of combined indicators in predicting adverse outcomes. Note: BMI, Body mass index.

Discussion

TPL is defined as delivery between 28 and less than 37 weeks of gestation and is a common pregnancy complication [13]. Recent studies have found that TPL is related to factors such as fetal development, pregnancy complicated by other diseases, increased or decreased amniotic fluid, previous history of preterm birth or multiple pregnancies [14]. With the two-child

and three-child policy, the incidence of TPL has continued to grow [15]. Drug therapy is the common clinical treatment, but there is still controversy about the choice of drugs in clinical practice.

In this research, we compared the efficacy of ritodrine alone and atosiban combined with ritodrine in TPL treatment. We found that the inhibition rate of uterine contraction in the JG was better than that in the CG after treatment, which indicated that the combination of the two drugs could improve the uterine contraction inhibition rate. What's more, we also discovered that the number of premature infants after combined treatment was significantly lower than that of the control group. Fu et al. [16] also verified that atosiban combined with ritodrine effectively reduced the risk of preterm birth. Ritodrine is a β-receptor agonist, which can effectively activate adenylate cyclase in uterine smooth muscle cells, inhibit the release of calcium ions in uterine muscle cells, and reduce uterine activity in patients, thereby prolonging the pregnancy period and protecting fetuses [17]. However, ritodrine has side effects on mothers and infants, which will increase the adverse reactions of patients [18]. Atosiban is a synthetic peptide that acts as an oxytocin receptor antagonist and can bind to oxytocin receptors to reduce the frequency and tension of uterine contractions and relax uterine smooth muscle, thereby inhibiting uterine contractions. It can effectively prolong the pregnancy of patients, improve their tolerance, and effectively reduce the premature birth rate [19, 20]. The combined use of the two drugs can inhibit uterine contractions faster and more effectively, increase the gestational age of fetus, and protect the health of mothers and babies.

TIMP-1 is a specific inhibitor that is in equilibrium during the pregnancy cycle and when the balance is broken, it will induce the weakening of fetal membrane tension and the increase in cervical dilatation, which may easily lead to premature birth [21]. Elevated NO is generally seen in infectious diseases, and may also be affected by exogenous NO. In the term of preterm labor, the intrauterine pressure increases, and the uterine wall and lower uterine segment are susceptible to mechanical expansion, manifested in the production of endothelin and inflammatory factors and elevation of NO level [22]. IL-6 is an essential inflammatory factor secreted and produced by various cells, which can stimulate the myometrium, decidua, and chorionic cells to produce more PGE2, induce uterine contractions, and initiate premature labor [23]. PGE2 promotes cervical ripening and labor induction; it is also a prostaglandin, and changes in its level can reflect the progress of TPL [24]. The changes of TIMP-1, NO, IL-6 and PGE2 were examined before and after treatment in this study. The results revealed that after treatment, the TIMP-1 level in the amniotic fluid of the CG was lower than that of the JG, while the levels of the other three in the CG were higher. This also shows from a side view that the combination therapy can adjust the homeostasis and reduce the risk of premature birth in patients.

In the end, we analyzed the risk factors for adverse pregnancy outcomes in patients. Specifically, age<26 years old and combination therapy were protective factors for adverse pregnancy outcomes, while pre-pregnancy BMI<20 was a risk factor for adverse pregnancy. With the implementation of the government's fertility policy, there are more and more pregnant women at advanced ages. With the increase of age, various functions of the female body decline to varying degrees, and women are prone to premature birth with signs of irregular uterine contractions and dilation of the cervix during gestational weeks 28-37 [25]. Earlier research has shown that BMI>24 kg/m^2 is a risk factor for preterm birth [26], and our study found that ≥20 kg/m^2 may lead to adverse pregnancy outcomes, which shows that weight is relevant to maternal adverse pregnancy outcomes. Finally, we determined that the combination therapy could reduce the adverse pregnancy outcomes of patients through the regression equation. Besides, ROC analysis showed that combined detection of the above indicators could serve as a potential reference for predicting adverse pregnancy outcomes in patients.

We retrospectively determined that atosiban combined with ritodrine improved the treatment efficacy of TPL and reduced adverse pregnancy outcomes in patients. Nevertheless, the present study still has some limitations. Since no data were collected from women with multiple pregnancies, it was not possible to determine whether the model had the same predic-

tive value for patients with multiple pregnancies. Second, it is equally vague to us whether there is a difference in the effect of atosiban alone versus atosiban in combination with ritodrine. Hence, we hope to collect more cases and observe more treatment protocols in subsequent studies to complement our research trials.

In conclusion, atosiban combined with ritodrine can enhance the treatment efficacy and reduce the occurrence of adverse pregnancy outcomes in TPL patients.

Disclosure of conflict of interest

None.

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