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Atosiban Combined with Ritodrine for Late Threatened Abortion or Threatened Premature Labor Patients with No Response to Ritodrine: A Clinical Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABC 1 Shuai Fu*
DEF 1 Haitian Xie*
BCD 1,2 Yilei Zhong*
D 1 Qi Xu
B 1 Liqiong Zhu
B 1 Hanjie Mo
AG 1 Jianping Zhang
CF 1 Yinglin Liu
AG 1 Hui Chen
AD 2 Yonghong Zhong
AD 1 Jianping Tan

1 Department of Obstetrics and Gynecology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P.R. China
2 Department of Obstetrics and Gynecology, Yue Bei People's Hospital, Shaoguan, Guangdong, P.R. China

* Shuai Fu, Haitian Xie and Yilei Zhong contributed equally to this work

Corresponding Authors: Yonghong Zhong, e-mail: zyhong1104@163.com, Jianping Tan, e-mail: julietp2004@126.com

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Background: Premature labor is an important cause of infant death and long-term disability. This study aimed to explore the safety and effectiveness of combining the tocolytic agents atosiban and ritodrine to extend gestation.

Material/Methods: The study included 52 patients with late threatened abortion and threatened premature labor between $20^{0/7}$ and $33^{6/7}$ weeks' gestation who were administrated continuous tocolytic agents for 48 h. Patients were divided into a research group receiving ritodrine combined with atosiban, owing to having no response to ritodrine alone (n=30), and a control group receiving ritodrine alone (n=22). The mean infusion rate and duration of tocolytic administration, gestation extension, pregnancy outcomes, and adverse effects were recorded. Routine blood tests, including C-reactive protein, and cultures for leukorrhea, candida, and mycoplasma were performed before and 1 week after treatment.

Results: Patients receiving ritodrine with atosiban had a mean gestation extension of 42.53±31.70 days. The extension of gestation of the research group was statistically shorter than that of the control group ($P<0.05$). The fetal loss rate, newborn birth weight, and Apgar score at 1 min were similar between the 2 groups (all, $P>0.05$). The research group had a lower incidence of palpitations than the control group ($P<0.05$).

Conclusions: For patients with late threatened abortion or threatened premature labor not controlled with ritodrine alone, ritodrine combined with atosiban extends gestation and improves pregnancy outcomes. For patients with abnormal uterine contractions, routine testing for reproductive tract infection should be performed. When infection is present, anti-infective therapy should be administered.

Keywords: Abortion, Threatened • Premature Birth • Tocolytic Agents

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Background

Premature labor is an important cause of infant death and long-term disability and its incidence ranges from 5% to 15% [1]. About 40% of premature labor cases are spontaneous [2]. Proper and effective application of tocolytic agents can postpone delivery, give time for promoting fetal lung maturation, and enable the intrauterine transport [3].

In 2012, the American College of Obstetricians and Gynecologists recommended ritodrine (a β2-receptor agonist) as the first-line medication for suppressing premature contractions [4]. However, owing to the wide distribution of β2 receptors in human tissues, long-term and high-dose use of this drug can cause adverse effects such as increased heart rate, chest pain, disorder of glucose metabolism, and hypokalemia. High concentrations of β2-adrenoceptor agonists have an anti-diuretic effect, which can result in sodium and water retention and even lead to pulmonary edema [5,6].

Atosiban is an oxytocin-receptor antagonist. It is specific for oxytocin receptors and has no effects on organs without these receptors. Extensive research has shown that atosiban and indomethacin are the only 2 drugs of this drug type not associated with severe adverse drug reactions [7]. Atosiban is the first-line drug to suppress contractions in Europe, but the cost of atosiban exceeds the cost of other tocolytic drugs, such as ritodrine [8].

Currently, a single drug is primarily used to suppress contractions. An ideal tocolytic should prolong gestational weeks at a low cost without maternal and fetal adverse effects [7]. However, none of the single tocolytics meet these criteria because either their effects are not adequate or the adverse effects are not tolerable; therefore, it is necessary to consider combining different drugs [9]. However, very little is known about the combined drug use. In view of this uncertainty, we aimed to compare the effectiveness and safety of the β2-adrenoceptor agonist ritodrine combined with the oxytocin antagonist atosiban in women with late threatened abortion and threatened preterm birth.

Material and Methods

This study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [10] and retrospectively reviewed the records of 52 patients with late threatened abortion and threatened premature labor hospitalized between January 2012 and January 2019 at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China. A total of 30 patients with late threatened abortion and threatened premature labor with singleton pregnancies having no labor history and who were between $20^{0/7}$ and $33^{6/7}$ weeks' gestation were included in the analysis. The gestational age was determined by the last menstrual date. All patients initially received ritodrine (5 mL: 50 mg; Taiwan Biotech Co, Ltd, Taiwan). The patients whose contractions could not be controlled with the maximum ritodrine dosage were administrated ritodrine combined with atosiban (5 mL: 37.5 mg; Ferring GmbH, Switzerland). At the same time, 22 patients with threatened abortion or threatened premature labor who met the indications for tocolytic treatment and had received ritodrine treatment only were included as a control group (**Figure 1**).

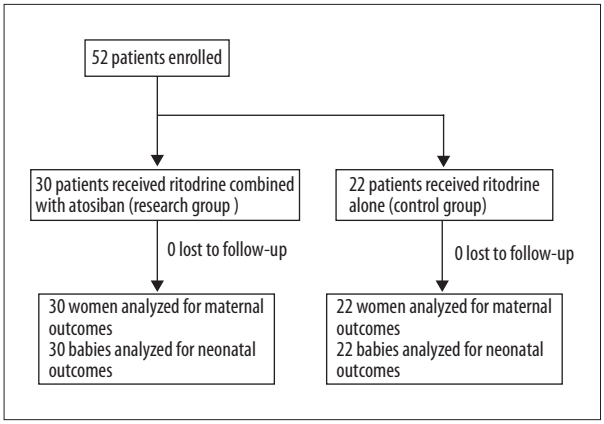

Figure 1. Study profile.

The indications for tocolytic treatment were as follows: (1) Four or more contractions every 30 min, with each contraction lasting for 30 s or more; (2) cervix shortened to ≤25 mm; (3) cervical dilatation of 1 to 3 cm; (4) no contraindications to tocolytic therapy, such as diabetes, heart disease, hyperthyroidism, gestational hypertension, and vaginal bleeding; and (5) no indications for pregnancy termination, such as fever, infection, and fetal distress.

When contractions were controlled or suppressed for 24 h with the administration of ritodrine, the dosage was reduced. However, if contractions increased within 30 min because of the dosage reduction, the dosage of ritodrine was increased and administered continuously for 48 h or more. Obvious control was defined as each contraction lasting for <30 s, with <2 regular contractions every 2 h. Complete suppression was defined as the absence of contractions, alleviations of abdominal pain or soreness of the waist, and absence of vaginal bleeding.

The indications for adding atosiban to ritodrine were as follows: (1) Four or more contractions every 30 min, with each contraction lasting for 30 s or more; (2) cervix shortening to ≤25 mm; (3) cervical dilatation of 1 to 3 cm; (4) no contraindications to tocolytic therapy, such as diabetes, heart disease, hyperthyroidism, gestational hypertension, and vaginal

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bleeding; and (5) no indications for pregnancy termination, such as fever, infection, and fetal distress.

Failure of ritodrine therapy was defined as follows: (1) Ritodrine alone was administrated for 48 h, and after adjusting to the maximum infusion rate (0.35 mg/min), the contractions were still not controlled; and (2) the infusion rate was <0.35 mg/min, but the maternal heart rate was >130 beats per min and the contractions were not controlled.

When contractions were controlled or suppressed for 24 h with the administration of atosiban combined with ritodrine, the dosage was reduced. However, if contractions increased within 30 min because of the dose reduction, the dosage of atosiban was increased and administered continuously for 48 h or more. Obvious control was defined as each contraction lasting for <30 s, with <2 regular contractions every 2 h. Complete suppression was defined as the absence of contractions, alleviation of abdominal pain or soreness of waist, and absence of vaginal bleeding.

No patients had contraindications to the use of ritodrine and atosiban. Before the administration of the tocolytics, all patients received an EGG and cardiac color Doppler ultrasound examination, and the results were normal for all patients. No patients had other obstetric complications, such as gestational diabetes, hypertension, and preeclampsia. All patients had routine blood examinations, and all had a white blood cell (WBC) count in the normal range and no fever or vaginal bleeding.

Therapeutic Regimens

For treatment with ritodrine alone, 100 mg of ritodrine was added to 500 mL of 5% glucose solution to achieve a dilution of 0.2 mg/mL. The initial intravenous infusion rate was 0.05 mg/min (5 drops/min), and then the dosage was gradually increased according to the effect on contractions, with a maximum of 0.35 mg/min (35 drops/min).

For the treatment with atosiban combined with ritodrine, atosiban was added when the infusion rate of ritodrine was at the maximum (0.35 mg/min), and the contractions were not controlled. A second intravenous line was placed on the opposite arm for the IV administration of atosiban. First, 6.75 mg of atosiban (0.9 mL/6.75 mg) was intravenously injected for over 1 min. Then, 20 mL of atosiban solution (37.5 mg/5 mL) was added to 180 mL of 0.9% sodium chloride solution. The initial rate of infusion was 24 mL/h for 3 h. After 3 h, the rate was adjusted to 8 mL/h until the contractions were controlled, followed by decreasing the infusion rate of ritodrine.

The same procedure described above was followed in patients with a maternal heart rate of >130 beats per min without the control of contractions on ritodrine alone.

Maternal-fetal Monitoring During Drug Treatment

Maternal vital signs were monitored daily. Routine blood tests including WBC, red blood cell, platelets, hemoglobin, percentage of neutrophils, C-reactive protein (CRP), and high-sensitivity CRP were done with the original matching reagents and were performed every week to monitor for indications of infection. Maternal biochemical and blood glucose examinations were performed weekly. Routine prenatal examinations including blood pressure and fetal monitoring were performed weekly. Cervical ultrasounds were performed every 2 to 4 weeks to examine cervical morphology and length. Every 4 weeks, fetal ultrasound was performed to examine fetal size. Every 4 weeks, ECG and cardiac color Doppler ultrasound were performed to determine if there were changes of cardiac function and morphology due to the drugs.

Indications for Withdrawal of Drug

There were 4 indications for the withdrawal of drug treatment: (1) At the 34th week of gestation, the tocolytic agents were stopped. If the mother and fetus were in good condition, the mother was expected to give birth naturally; (2) atosiban combined with ritodrine were at the maximum dosages and the contractions were not controlled; (3) there was any evidence of maternal infection or cardiac dysfunction; and (4) there was fetal distress or evidence of intrauterine infection.

Statistical Methods

Data were analyzed using SPSS 22.0 statistical software. The *t* test was used for analyzing quantitative data, and the χ^2 test was used for analyzing categorical data. The quantitative data of the 2 samples were normally distributed and the 2 population variances were equal. A value of $P<0.05$ was regarded as statistically significant. The odds ratio was used for all of the categorical variable.

Results

Clinical Data

The patients in the research group ranged in age from 24 to 40 years, with a mean age of 32.63 years, and the patients in the control group ranged in age from 18 to 40 years, with a mean age of 30.68 years. There was no statistically significant difference in age between the 2 groups. The average gestational age of the research group was 25.90 weeks and the average gestational age of the control group was 22.00 weeks; the difference was statistically significant ($P=0.002$). The length of drug treatment in the control group was statistically longer than that in the research groups (**Table 1**).

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Table 1. Characteristics of pregnant women at the time of admission. Continuous data are shown as mean±SD. The *t* test was used for analyzing quantitative data. *P*<0.05 was considered statistically significant.

Items	Control group (n=22)	Research group (n=30)	P
Age (years)	30.68±5.07	32.63±4.65	0.160
Gestation (weeks)	22.00±4.84	25.90±2.92	0.002*
Duration of tocolytic administration (days)	72.77±47.53	39.97±31.09	0.008*

* *P*<0.05, statistically significant.

Table 2. Indicators of infection before treatment. Categorical data are shown as a frequency (percentage) and continuous data are shown as mean±SD. The *t* test was used for analyzing quantitative data, and the χ^2 test was used for analyzing categorical data. *P*<0.05 was considered statistically significant.

Items	Control group (n=22)	Research group (n=30)	P	OR (95%CI)
White blood cell counts (×10^9/L)	10.20±3.75	11.45±2.07	0.133	–
Neutrophils (%)	70.85±9.4	78.81±6.58	0.001*	–
C-reactive protein (mg/L)	6.23±6.61	16.19±20.28	0.016	–
Leucorrhea cleanliness	1.93±0.39	2.02±0.68	0.733	–
Monilial infection (cases)	3	5	0.779	1.27 (0.27-5.97)
Mycoplasma infection (cases)	7	8	0.264	0.78 (0.23-2.61)

* *P*<0.05, statistically significant.

Table 3. Indicators of infection 1 week after treatment. Categorical data are shown as a frequency (percentage) and continuous data are shown as mean±SD. The *t* test was used for analyzing quantitative data, and the χ^2 test was used for analyzing categorical data. *P*<0.05 was considered statistically significant.

Items	Control group (n=22)	Research group (n=30)	P	OR (95%CI)
White blood cell counts (×10^9/L)	10.92±2.44	10.44±2.10	0.459	–
Neutrophils (%)	72.19±7.06	78.32±4.26	0.001*	–
C-reactive protein (mg/L)	7.76±4.98	18.41±14.81	0.001*	–
Leucorrhea cleanliness	2.05±0.52	2.09±0.38	0.681	–
Monilial infection (cases)	1	2	0.412	1.50 (0.13-17.67)
Mycoplasma infection (cases)	3	4	0.877	0.97 (0.20-4.87)

* *P*<0.05, statistically significant.

Indicators of Infection

There were no statistically significant differences in indicators of infection including WBC count, the presence of leukorrhea, and positive mycoplasma culture before treatment and 1 week after treatment between the 2 groups. The research group had a significantly higher CRP level and neutrophilic granulocyte percentage than the control group (both, *P*<0.05). Patients with the presence of leukorrhea suggesting a monilial infection were administrated clotrimazole vaginal tablets 2 times every 3 days (Canesten, 500 mg/tablet; Bayer, Germany). If the vaginal secretion test suggested mycoplasma infection, the patients were administered 4 azithromycin tablets (Zithromax, 250 mg/tablet, Pfizer PGM, France) (**Tables 2, 3**). The incidence of monilial infection (odds ratio 1.27; 95% confidence interval [CI] 0.27-5.97; *P*=0.765) was higher in the research group than in the control group, but the difference was not statistically significant. The incidence of mycoplasma infection (odds ratio 0.78; 95% CI 0.23-2.61; *P*=0.686) was lower in the research group than in the control group, but the difference was not statistically significant. After 1 week of treatment, the incidence of monilial infection (odds ratio 1.50; 95% CI 0.13-17.67; *P*=0.747) was higher in the research group than in the control group, but the difference was not statistically significant. The incidence of mycoplasma infection (odds ratio 0.97; 95% CI 0.20-4.87; *P*=0.975) was lower in the research

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Table 4. Dosage and pregnancy outcomes. Categorical data are shown as a frequency (percentage) and continuous data are shown as mean±SD. The *t* test was used for analyzing quantitative data, while the χ^2 test was used for analyzing categorical data. *P*<0.05 was considered statistically significant.

Items	Control group (n=22)	Research group (n=30)	P
Extension of gestation (days)	93.55±42.29	42.53±31.70	<0.001*
Mean infusion rate of ritodrine (drops/min)	6.68±2.46	6.67±1.92	0.980
Fetal loss rate (%)	13.64 (3/22)	26.67 (8/30)	0.257
Newborn birth weight (kg)	2.47±0.98	1.95±0.94	0.063
Apgar score at 1 minute	8.70±1.53	8.36±2.08	0.560

* *P*<0.05, statistically significant.

Table 5. Adverse drug reactions. Categorical data are shown as a frequency (percentage) and continuous data are shown as mean±SD. The *t* test was used for analyzing quantitative data, and the χ^2 test was used for analyzing categorical data. *P*<0.05 was considered statistically significant.

Items	Control group (n=22)	Research group (n=30)	P
Mean heart rate (times/min)	98.77±9.06	97.46±15.84	0.703
Palpitations (%)	68.20 (15/22)	13.30 (4/30)	<0.001*
Chest pain (%)	0.00 (0/22)	6.67 (2/30)	0.520

* *P*<0.05, statistically significant.

group than in the control group, but the difference was not statistically significant.

Dosage of Ritodrine and Pregnancy Outcomes

The mean infusion rate of ritodrine was similar between the 2 groups (*P*>0.05). The extension of gestation of the control group was significantly longer than that of the research group (*P*<0.05). The fetal loss rate, newborn birth weight, and Apgar score at 1 min were similar between the 2 groups (all, *P*>0.05) (**Table 4**). The incidence of fetal loss (odds ratio 2.30; 95% CI 0.53-9.94; *P*=0.263), was higher in the research group than in the control group, but the difference was not statistically significant.

Adverse Drug Reactions

The control group had a significantly higher rate of palpitations than did the research group (*P*>0.05) (**Table 5**).

Discussion

Premature labor is a leading cause of newborn disease and death. Newborn deaths due to premature labor account for two-thirds of all newborn deaths, including those due to congenital malformations [11]. About one-fourth of surviving newborns develop mental impairment or neurological sequelae, resulting in huge social and economic burdens. At present, the intervention for premature labor is to extend the pregnancy to 34 weeks, providing the fetal membranes are intact and the mother is in good health [12].

The proper and effective application of tocolytic agents extends gestation, allowing for fetal lung maturation [13]. Ritodrine can effectively suppress contractions but can have serious adverse effects. Atosiban is the only tocolytic agent approved by the European Medicine Agency for treatment premature labor [14]. Many studies have reported no difference in the effectiveness of atosiban and ritodrine for suppressing contractions, but atosiban has fewer adverse effects [15-17]. However, due to its high cost, atosiban is not widely used in China. It is mainly used in patients who have no response to ritodrine or have intolerable adverse effects from ritodrine.

This study showed that atosiban combined with ritodrine has certain effects in patients with late threatened abortion and threatened premature labor who have no response to ritodrine alone. The extension of gestation in the combined drug group was slightly shorter than that of the ritodrine-only group (control group). However, the fetal loss rate, newborn birth weight, and Apgar score at 1 min were similar between the 2 groups. The research group had a lower incidence of palpitations and adverse drug reactions than the control group. These results suggest that ritodrine combined with atosiban can effectively treat premature labor and suppress contractions with no adverse effects.

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At present, ritodrine combined with atosiban is not routinely used, and there is little experience using them in combination. However, their mechanisms of suppressing contractions are different, providing a theoretical basis for using them in combination. While there were no obvious adverse reactions when using ritodrine combined with atosiban in our hospital, intensive monitoring is required because of the potential of an adverse reaction [18].

It has been shown that about 40% of late abortions before the 28th week of pregnancy and 30% of premature labors before the 30th week of pregnancy are associated with infections [19]. Animal experiments and in vitro and in vivo studies have confirmed the mechanism of premature labor caused by infections is bacterial invasion in the gap between the chorion and decidua. The endotoxins and exotoxins released activate decidual cells to produce various cytokines, which activate the synthesis of prostaglandins, resulting in uterine contractions [20,21]. Interestingly, a recent study found a marked increase of CB1, anandamide, and inflammatory cytokine downregulation in human placental samples of a term delivery group, compared with those in preterm groups [22]. In addition, the proteolytic enzymes produced reduce the tensile strength of fetal membranes, decreasing collagenous fibers and increasing membrane brittleness, thus resulting in the rupture of the fetal membranes [23]. Infections can also lead to impaired function of multiple organs such as the heart, liver, and kidney, threatening the newborn's health [24].

In this study, none of the patients had a fever, and their WBC counts were in the normal range. The patients had a strong desire to continue pregnancy, and they received treatment to extend gestation and achieved good outcomes. During treatment, some patients in both groups developed candida and mycoplasma genital infections. The infection rates were obviously reduced after anti-infection therapy for only 1 week. Patients with abnormal contractions should receive examinations for reproductive tract infections, and any infections should be actively treated. The research group in this study had a significantly higher CRP level and neutrophil granulocyte percentage than the control group. This may have been due to inflammatory responses or infections at sites other than the uterus or reproductive tract. Further research examining premature labor and infection should investigate inflammatory factors such as Th1 and perform amniocentesis to obtain amniotic fluid samples to perform testing, such as an amniotic fluid smear for bacteria, amniotic liquid glucose quantification, amniotic fluid lactate dehydrogenase, and amniotic fluid IL-6 determination [25].

Conclusions

For patients with late threatened abortion or threatened premature labor that are not controlled with ritodrine alone, ritodrine combined with atosiban extends the gestation period and improves pregnancy outcomes. For patients with abnormal uterine contractions, routine testing for reproductive tract infections should be performed. If an infection is present, anti-infective therapy should be administered.

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Conflict of Interest

None.

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