

Original Article

Clinical efficacy of atosiban treatment in late abortion and preterm labour of twin pregnancy

Ya-Juan Xu*, Li-Min Ran*, Xiao-Hua Luo, Shan-Shan Zhai, Zhong-Yuan Zhou, Ying-Ying Zhang, Yue-Hua Liu, Juan Peng, Li-Dan Ren, Teng Hong, Rui Liu

Department of Obstetrics, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China. *Equal contributors.

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Abstract: The objective of this study was to investigate the clinical efficacy and adverse events of treatment with the oxytocin receptor antagonist atosiban in late abortion and preterm labour of twin pregnancy. A total of 60 pregnant women with twin pregnancy who experienced late abortion and preterm labour were randomly divided into two groups: the first group included 30 cases of a short course of treatment (18 hours), and the second group included 30 cases of a long course of treatment (45 hours). The treatment efficacy, adverse events and pregnancy outcomes for the pregnant women in the two groups were compared, and the treatment efficacy for the pregnant women with different cervical lengths (CLs) was analysed. The rates of the 48 h and 7 d effective tocolysis for the long course of treatment group were significantly superior to the same rates for the short course of treatment group, and the differences were statistically significant ($P < 0.05$). The comparison of the safety between the two groups showed no statistically significant differences ($P > 0.05$). When the program of the short course of treatment was employed, the rates of the 48 h and 7 d effective tocolysis of the group with $CL \geq 20$ mm were significantly superior to the same rates for the group with $CL < 20$ mm, and the differences were statistically significant ($P < 0.05$). When the program of the long course of treatment was employed, the rates of the 48 h and 7 d effective tocolysis of the group with $CL \geq 20$ mm and the group with $CL < 20$ mm showed no significant difference ($P > 0.05$). In addition, a total of 101 cases of neonates survived, with 19 cases of death. Atosiban can effectively extend the pregnancy time for twin pregnancy with late abortion and preterm labour. The long course of the treatment program was more effective and performed better for the cases in which $CL < 20$ mm. The long course of treatment did not increase the adverse events for the mothers and infants.

Keywords: Twin pregnancy, atosiban, preterm labour, pregnancy outcome

Introduction

With the development of assisted reproductive technology, the proportion of pregnant women with twin pregnancy has increased. Twin pregnancy is a high-risk pregnancy, and preterm labour is the most common complication of twin pregnancy, which is also the main cause of neonatal morbidity and mortality. The incidence of preterm labour in twin pregnancy is almost 50% [1]. Currently, the application of tocolytic agents is the primary method for preventing preterm labour; it provides ample time for transportation and the opportunity to apply corticosteroids to pregnant women [2]. Currently, the Royal College of Obstetrics and Gynaecology (RCOG) recommends atosiban as the primary drug for anti-preterm labour. During

the treatment of preterm labour, tocolytic agents and other miscarriage prevention drugs showed a high risk for pregnant women with twin pregnancy, which may cause pulmonary edema and heart failure [3, 4]. In this study, we treated the late abortion and preterm labour of twin pregnancy with atosiban to investigate the treatment efficacy and safety of atosiban in the late abortion and preterm labour of twin pregnancy.

Subjects and methods

Subjects

Hospitalized pregnant women with twin pregnancy in 24-33 weeks of gestation who showed signs of late abortion and preterm labour from

Atosiban treatment for twin pregnancy

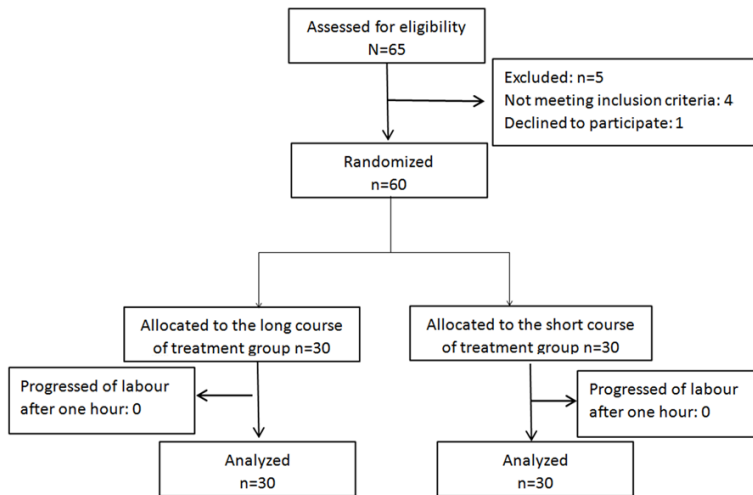


Figure 1. The flow chart for patients recruitment.

June 2011 to June 2015 were selected as the research subjects in this study. The inclusion criteria were as follows: (1) cases in which women experienced regular contractions with durations ≥ 30 s and frequencies ≥ 4 times/30 min and (2) cases in which women showed cervical canal regression $\geq 50\%$. The exclusion criteria were as follows: premature rupture of membranes, cervix ≥ 3 cm, vaginal bleeding, preeclampsia, gestational hypertension, severe maternal disease, foetal growth restriction, foetus with chromosomal disorders, insufficient amount of amniotic fluid, and chorioamnionitis. A total of 60 cases were randomly divided into two groups (a flow chart for patient recruitment was shown in **Figure 1**): the first group contained 30 cases of a short course of treatment (18 hours), and the second group contained 30 cases of a long course of treatment (45 hours). All groups included pregnant women who showed no contraindication for a continuous pregnancy and the application of a tocolytic agent. This study was approved by the ethics committee of the Third Affiliated Hospital of Zhengzhou University, and all patients provided informed consent for participation.

Transvaginal ultrasound measurement of cervical length

(1) Transvaginal ultrasound was performed after emptying the bladder. (2) The probe was placed in the interior fornix of the vagina, and excessive force was avoided. (3) At the standard sagittal plane, the image was enlarged to a minimum of 75% of the full screen, and the

straight distance from the inner cervix to the outer cervix was measured to obtain the shortest value of three successive measurements.

Atosiban regimen

Atosiban is the product of Ferring (Sweden) Pharmaceuticals Ltd. The 18 hour-program (short course of treatment) was as follows: first, a dose of 6.75 mg was intravenously injected with a speed greater than 1 min; second, an atosiban injection of 20 ml (specification of 7.5 mg/ml) in 180 ml of 0.9% sodium chloride

injection or 5% glucose injection was administered by intravenous infusion at the speed of 300 $\mu\text{g}/\text{ml}$ for 3 h; and, last, the same injection was administered at the speed of 100 $\mu\text{g}/\text{min}$ until the desired effect of inhibiting uterine contractions was achieved. The total time was approximately 18 h. The 45-hour program (long course of treatment) was as follows: first, a dose of 6.75 mg was intravenously injected with a speed greater than 1 min; second, an atosiban injection of 40 ml in 360 ml of 0.9% sodium chloride injection or 5% glucose injection was administered by intravenous infusion at a speed of 300 $\mu\text{g}/\text{ml}$ for 3 h; and, last, the same injection was administered by 100 $\mu\text{g}/\text{min}$ until the desired effect of inhibiting uterine contractions was achieved. The total time was approximately 45 h. The pregnant woman who showed progress of labour was considered to be given the rescue tocolytic observation and treatment if the following conditions occurred after one hour: (1) the frequency of contractions was increased or no change occurred and (2) the cervical dilation increased by 1 cm. Repeated treatment can be provided to pregnant women with recurrent symptoms of preterm labour after a successful inhibition of contractions. All pregnant women admitted to the hospital underwent a course of corticosteroid therapy.

Outcome measures

(1) The treatment efficacy and safety of the extended gestational age for 48 h and 7 d between the short course of treatment group

Table 1. General information about the long course of treatment group and the short course of treatment group

	Long course of treatment (n=30)	Short course of treatment (n=30)	P value
Maternal age (year)	30.86±4.42	30.70±5.57	0.901
Primipara (case)	19	16	0.432
History of preterm delivery (case)	3	5	0.704
Average gestational age at admission (week)	28.40±2.44	28.59±2.63	0.784
Pregnancy with assisted reproductive technology (case)	7	10	0.39
Average cervical length (mm)	23.83±10.85	22.27±9.18	0.553
Cervical length (CL)			
≥20 mm (case)	16	17	0.795
<20 mm (case)	14	13	

Table 2. Comparison of the treatment efficacy between the two groups

Group	n (case)	48 h effective ^① (n, %)	7 d effective (n, %)
Short course of treatment group	30	22, 73.3	14, 46.7
Long course of treatment group	30	29, 96.7	24, 80.0
χ^2		4.706	6.504
P		0.030	0.007

Note: ^①corrected χ^2 test.

and the long course of treatment group were compared. (2) The efficacies in contraction suppression between the group with CL ≥20 mm and the group with CL <20 mm for either the long course of treatment program or the short course of treatment program were compared. (3) The condition during the delivery, the post-natal situation, and the neonatal morbidity and mortality were observed and analysed.

Criteria of efficacy and safety

Effective tocolysis: after the treatment, contractions and cervical dilation gradually ceased with continuous pregnancy of more than 48 h. Ineffective tocolysis: after the treatment, contractions were not weakened and delivery occurred within 48 h. Safety: any possible adverse events were included, such as nausea, vomiting, tremors, tachycardia, hypotension, headache, pulmonary edema, haemorrhage, and deep venous thrombosis.

Statistical analysis

The data were analysed using SPSS 17.0 software. The counting data were represented as percentages. The χ^2 test or the Fisher's exact

test was performed. The measurement data were represented as $\bar{x} \pm s$, and the comparison between the groups was performed using the t test. Difference with $P < 0.05$ were considered to be statistically significant.

Results

General information about the pregnant women in the long course of treatment group and the short course of treatment group

The comparison of the maternal age, number of pregnancies, gestational age, history of preterm delivery, number of pregnancies with assisted reproductive technology, and cervical length showed no statistically significant difference between the two groups ($P > 0.05$) (Table 1).

Efficacy of the drug treatment

Among the 60 cases of pregnant women with twin pregnancy who received the atosiban treatment, 85.0% (51/60) of the women did not deliver within 48 hours and 63.3% (38/60) of the women did not deliver within 7 days. The gestation was prolonged for a minimum of 15 hours and a maximum of 74 days. The comparison of the efficacy for the short course of treatment and the long course of treatment is shown in Table 2. The results of the χ^2 test suggested that the rates of the 48 h and 7 d effective contraction suppression in the long course of treatment group were significantly superior to the same rates in the short course of treatment

Table 3. Comparison of the efficacy between the two CL groups for the long course of treatment

Cervical length	n (case)	48 h effective (n, %)	7 d effective (n, %)
<20 mm	14	13, 92.9	10, 71.4
≥20 mm	16	16, 100.0	14, 87.5
P		0.467	0.378

Note: Fisher's exact test.

Table 4. Comparison of the efficacy between the two CL groups for the short course of treatment

Cervical length	n (case)	48 h effective ^① (n, %)	7 d effective ^② (n, %)
<20 mm	13	7, 53.8	2, 15.4
≥20 mm	17	15, 88.2	12, 70.6
P		0.049	0.004

Note: ^①Fisher's exact test for 48 h, $P=0.049<0.05$; ^②Fisher's exact test for 7 d, $P=0.004<0.05$.

group, and the differences were statistically significant ($P<0.05$).

Safety of the treatment in the short and long course of the treatment groups

In the long course of treatment group, one case of headache and nausea was reported and one case of palpitation and chest tightness was reported, which did not affect the treatment. In the short course of treatment group, one case of nausea was reported and one case of pruritus was reported, which did not affect the treatment. The incidence of adverse events for the two groups showed no statistically significant differences (6.7% vs. 6.7%, $P>0.05$).

Efficacy of the treatment in the pregnant women with different cervical lengths

In the 30 cases of pregnant women who received the long treatment, 16 cases showed CL ≥20 mm and 14 cases showed CL <20 mm. The results of the comparison in the efficacy of atosiban treatment between the two cases are listed in **Table 3**. The rates of the 48 h and 7 d effective tocolysis with two different cervical lengths showed no statistically significant differences.

In the 30 cases of pregnant women who received the short course of treatment, 17

cases showed CL ≥20 mm and 13 cases showed CL <20 mm. The results of the comparison of the efficacy of the atosiban treatment between the two types of CL are listed in **Table 4**. The rates of the 48 h and 7 d effective tocolysis with CL ≥20 mm were significantly superior to the same rates with CL <20 mm, and the differences were statistically significant.

Pregnancy outcome

Among the 60 cases, nine pregnant women experienced natural labour and 51 patients underwent caesarean section. The cases with intrapartum uterine inertia accounted for 11.7% (7/60) of the cases. Postpartum haemorrhage did not occur after the injection of carboprost tromethamine. Delivery occurred with a gestational age of <28 weeks in 17 cases, a gestational age from 28-34 weeks in 29 cases, and a gestational age of ≥34 weeks in 14 cases. The pregnancy outcome showed 101 cases of neonatal survivals and 19 deaths (17 cases in which the gestational age was <28 weeks, one case in which a woman died of intestinal obstruction, and one case in which a patient died of septicemia). The morbidity rates for the 101 survived neonates are listed in **Table 5**.

Discussion

Status of treatment in late abortion and pre-term labour of twin pregnancy

Preterm birth is a major cause of neonatal morbidity and mortality. Therefore, the prevention of preterm birth is an important factor in improving the prognoses of perinatal infants. The interventions for the late abortion and premature labour of twin pregnancy include cervical cerclage, hospitalization and bed rest, prophylactic oxytocin inhibitor, and prophylactic pessary. As cervical cerclage may increase the risk of premature labour for twin pregnancy, it is not recommended [5]. Insufficient evidence is available to prove that hospitalization, bed rest and pessary can reduce the neonatal morbidity and mortality [6]. In the treatment of preterm labour, the application of a tocolytic agent to inhibit uterine contractions is capable of postponing delivery until the completion of a course of corticosteroid treatment, which provides ample time for the prevention of neonatal idiopathic respiratory distress syndrome and the transportation of pregnant women to a facility

Table 5. Morbidity rates of the survived neonates

	Short course of treatment group N=52 (n, %)	Long course of treatment group N=49 (n, %)	χ^2	P
Respiratory distress syndrome	27, 51.9	31, 63.3	1.327	0.249
Neonatal asphyxia	14, 26.9	17, 34.7	0.716	0.397
Hyperbilirubinemia	19, 36.5	17, 34.7	0.037	0.847
Myocardial injury	22, 42.3	18, 36.7	0.328	0.567
Neonatal brain injury	10, 19.2	11, 22.4	0.159	0.690
Neonatal intracranial haemorrhage	9, 17.3	9, 18.4	0.019	0.889
Neonatal pneumonia	9, 17.3	10, 20.4	0.159	0.690
Neonatal pulmonary haemorrhage	4, 7.7	2, 4.1	0.120	0.729
Bronchial dysplasia	5, 9.6	7, 14.3	0.526	0.468
Caput succedaneum	1, 1.9	0, 0	0	1.000
Intestinal obstruction	0, 0	1, 2.0	0.001	0.976
Congenital heart disease	2, 3.8	1, 2.0	0	1.000

with an intensive care unit for neonatal infants [6].

The most commonly used tocolytic agents are β_2 adrenergic receptor agonists, Ca^{2+} channel blockers, prostaglandins and oxytocin receptor antagonists. The oxytocin receptor antagonist atosiban is the only contraction inhibitor that is specifically employed in the uterus; its application in the treatment of preterm labour has received an increasing amount of attention. Its mechanism is to compete the oxytocin receptors on the myometrium, decidua, and foetal membranes with oxytocin, which can reduce the effect of oxytocin. A decrease in the calcium level in muscle cells may inhibit uterine contraction [7]. As atosiban is highly specific to the uterus, it is safe and causes a significantly lower incidence of cardiovascular side effects compared with other tocolytic agents.

In a study of atosiban for single pregnancy, Shim et al. [8] discovered that, compared to ritodrine, the 7 day tocolytic efficacy of atosiban was significantly better, whereas the incidence of adverse events of atosiban in pregnant women was significantly lower than the incidence of adverse events of ritodrine. Compared with a single pregnancy, the risk of adverse events, such as pulmonary edema, for the pregnant women with twin pregnancy was higher with the application of a tocolytic agent. Thus, the tocolytic drug must be carefully selected. Kashanian et al. compared atosiban and the calcium channel blocker nifedipine for the rescue treatment of preterm labour and concluded that atosiban is safe and effective, with fewer

adverse events, which can be employed in premature labour patients with heart disease and multiple pregnancy [9].

Assessment of efficacy, safety and perinatal outcome of atosiban treatment for late abortion and preterm labour in pregnant women with twin pregnancy

For the pregnant women with late abortion and preterm labour that failed the ritodrine treatment or other tocolytic drug therapy or showed some adverse events, Tan et al. [10] discovered that atosiban can significantly prolong the gestation time with a satisfactory pregnancy outcome in the patient. The efficacy of the tocolytic agent in twin pregnancy lacks sufficient evidence. The results of this study showed that the rates of the 48 h and 7 d effective tocolysis of atosiban in the 60 cases of pregnant women with twin pregnancy were 85.0% (51/60) and 63.3% (38/60), respectively. Thus, for the pregnant women with twin pregnancy, atosiban can effectively inhibit contractions, which has an important significance in delaying delivery for patients with preterm labour until the completion of a course of corticosteroid treatment. Currently, the atosiban treatment programs in China include a long course of treatment and a short course of treatment (i.e., an 18 h program and a 45 h program). As the cost of the atosiban treatment is expensive, an optimal treatment program is expected to achieve cost-effective results. This study determined that the short-term and long-term efficacies of the long course of treatment group were superior to those of the short course of treatment group. From an

economic perspective, Wex et al. [11] determined that atosiban can save 13 million euros per year in Italy due to its efficacy and its safety to the mothers and infants compared to β_2 -adrenergic receptor agonists. Therefore, the long course of treatment program of atosiban can be considered to be a cost-effective method of treatment.

Romero et al. [12] compared atosiban with a placebo and determined that their safety levels were equivalent. The application of an oxytocin inhibitor can prevent immediate premature birth, but the drug showed adverse events for the mother and infant; thus, this maintenance medication is not recommended in most countries. However, the American College of Obstetricians and Gynecologists (ACOG) indicated that atosiban can be employed as the only oxytocin inhibitor as maintenance medication based on its safety. This study revealed that the long course of treatment did not increase the adverse events for pregnant women with twin pregnancy, which confirmed the safety of atosiban. The mechanism of atosiban is to antagonize the oxytocin receptors; atosiban may cause postpartum haemorrhage. The high tension of uterine muscle in twin pregnancy can easily cause postpartum uterine inertia. In this study, the incidence of uterine inertia during labour and delivery accounted for 11.7% (7/60) of cases, with no case of postpartum haemorrhage. However, the sample size of this study is small, and a placebo control group was not set up. In future studies, the correlation of atosiban and uterine inertia will be investigated. This study determined that the main complications in newborns for the 60 cases of pregnant women with twin pregnancy after an atosiban treatment included neonatal respiratory distress syndrome, neonatal hyperbilirubinemia, neonatal asphyxia, and myocardial injury; these incidences were consistent with the incidences reported in the literature [13]. Thus, it is believed that atosiban does not increase the risk of neonatal complications.

Tocolytic efficacy of atosiban in pregnant women with late abortion and preterm labour for different cervical lengths

Studies have shown that changes in cervical length can predict the occurrence of preterm labour [14]. Pregnant women with CL <25 mm

are at a high risk of preterm labour. The guidelines of preterm labour in China indicated that a tocolytic agent can be applied to pregnant women with regular uterine contractions and CL <20 mm based on vaginal ultrasound measurement or that medication can be administered according to the CL changes based on the dynamic monitoring [1]. Charlotte Clock et al. [15] discovered that the occurrence of regular contractions with progressive cervical shortening at a gestational age from 23-34 weeks suggests an increased risk of preterm delivery. Therefore, a tocolytic agent should be applied to these pregnant women. For pregnant women with twin pregnancy with signs of late abortion and preterm labour in this study, the atosiban treatment was applied when progressive regression of the cervical length was observed during monitoring. We discovered that the rates of the 48 h and 7 d effective tocolysis in the group with CL $\geq$ 20 mm for the short course of treatment program were significantly superior to the same rates in the group with CL <20 mm, and the differences were statistically significant ($P < 0.05$). For atosiban as a treatment for late abortion and preterm labour, the efficacy of medication for women with CL $\geq$ 20 mm was significantly better than the efficacy of medication for women with CL <20 mm. Therefore, the cervical length is also an important indicator of the therapeutic efficacy of an oxytocin inhibitor. For pregnant women with twin pregnancy who show signs of late abortion and preterm labour, the cervical length could be routinely measured to control the timing of medication. When progressive shortening of the cervical length is observed, treatment should be provided as early as possible to achieve a better tocolytic effect and improve the perinatal outcome of the new-born. This study determined that the rates of the 48 h and 7 d effective tocolysis for the long course of treatment program between the groups with CL $\geq$ 20 mm and CL <20 mm were not significantly different ($P > 0.05$); thus, when a significantly shortened cervix is observed, the long course of treatment program of atosiban can be applied to improve the tocolytic efficacy.

This study determined that the efficacy of the long course of treatment program was better and that the tocolytic efficacy with cervical lengths over 20 mm is better. Thus, the medication timing can be controlled based on the

cervical length, which is monitored by ultrasound. When the cervical length is determined to be less than 20 mm, the long course of treatment program should be selected to achieve an efficient tocolytic result, extend the gestational age and improve the perinatal outcome. Compared with other tocolytic agents, the use of atosiban is expensive in China; thus, it primarily serves as a remedial treatment when other tocolytic agents fail or show adverse events. However, as twin pregnancy is a high-risk pregnancy with a high incidence of miscarriage and premature delivery, extra attention should be given to the miscarriage prevention process. Due to the safety and efficacy of atosiban in twin pregnancy, atosiban can be employed as a primary treatment for late abortion and preterm labour in twin pregnancy to reduce the adverse consequences of tocolysis.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ya-Juan Xu, Department of Obstetrics, The Third Affiliated Hospital of Zhengzhou University, No. 7 Front Kangfu Street, Er'qi District, Zhengzhou 450052, Henan Province, China. Tel: 86-371-66903961; Fax: 86-371-66903961; E-mail: xuyajuanzz@sina.com

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