European Review for Medical and Pharmacological Sciences 2016; 20: 1881-1887

Evaluation of the efficacy of atosiban in pregnant women with threatened preterm labor associated with assisted reproductive technology

Y.-J. XU, L.-M. RAN, S.-S. ZHAI, X.-H. LUO, Y.-Y. ZHANG, Z.-Y. ZHOU, Y.-H. LIU, L.-D. REN, T. HONG, R. LIU

Department of Obstetrics, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China

Abstract. – OBJECTIVE: The present study aimed to investigate the effectiveness of atosiban in treating women with threatened preterm labor who had become pregnant through assisted reproductive technology (ART) and the corresponding pregnancy outcomes.

PATIENTS AND METHODS: Seventy pregnant women with threatened preterm labor after ART were randomly divided into two groups, with 35 cases in the atosiban group and 35 in the ritodrine group. The post-treatment effects and the corresponding pregnancy outcomes were observed.

RESULTS: The efficacy of extending gestational age by 48 hours was significantly higher in the atosiban group than in the ritodrine group ($p<0.05$), whereas the efficacy of extending gestational age by seven days was the same in the two groups ($p>0.05$). There was no significant difference between the atosiban and ritodrine groups in the average gestational age at birth ($p<0.05$). The occurrence of side effects in the pregnant women was higher in the ritodrine group than in the atosiban group ($p<0.05$), although the prevalence of abnormal fetal heart rate was not significantly different ($p>0.05$). Both the perinatal mortality rate and the prevalence of neonatal asphyxia were significantly lower in the atosiban group than in the ritodrine group ($p<0.05$). When the medication was applied at a gestational age of fewer than 28 weeks, the perinatal mortality rate and the prevalence of neonatal pneumonia were significantly lower in the atosiban group compared with the ritodrine group ($p<0.05$). When the first drug administration was at a gestational age of 28 weeks or later, the need for neonatal pediatric treatment was significantly reduced in the atosiban group relative to the ritodrine group. Independent of when the drug administration was initiated, there were no significant differences between the atosiban and ritodrine groups in the occurrences of neonatal asphyxia, acute respiratory distress syndrome (ARDS), neonatal brain injury, or neonatal sepsis ($p>0.05$).

CONCLUSIONS: Administration of atosiban has a comparatively better effect than that of ritodrine on pregnant women who underwent ART and is safe and effective at preventing immediate preterm birth. Atosiban is significantly better than ritodrine at reducing the rates of perinatal mortality and neonatal pneumonia, and the perinatal outcomes for those who began to use atosiban at a gestational age of fewer than 28 weeks were even better.

Key Words

Assisted reproductive technology, Preterm birth, Atosiban, Ritodrine.

Introduction

The upper limit for preterm labor is universally defined all over the world as childbirth at less than 37 weeks of pregnancy, but the lower limit is set at different gestational ages in different countries. Many developed countries and regions have set 20 or 24 weeks of pregnancy as the lower limit, but China has chosen 28 weeks[1]. Preterm birth is one of the main causes of perinatal illness and death. Assisted reproductive technology (ART) has become an important means for treating infertility in recent years. Studies inside and outside of China indicate that the incidence of preterm birth is significantly higher among women who underwent *in vitro* fertilization-embryo transplantation (IVF-ET) than in those with natural pregnancies[2,3]. The IVF-ET procedure has thus emerged as a new high-risk factor in the etiology of preterm birth[4], but the pregnancy outcomes in such cases with threatened preterm birth are not entirely clear. This study analyzed the pregnancy outcomes of pregnant women who had undergone ART and were treated with atosiban for threatened preterm birth at the Third Affiliated Hospital of Zhengzhou University.

Corresponding Author: Ya-Juan Xu, MD; e-mail: cnzzzsl@163.com

Patients and Methods

Clinical Data of Patients

Seventy pregnant women who had undergone ART and were diagnosed with the threat of preterm labor and consequently hospitalized at the Third Affiliated Hospital of Zhengzhou University between June 2011 and June 2015 were selected and randomly divided into two groups, with 35 cases in the atosiban treatment group and 35 in the ritodrine treatment group. The inclusion criteria were as follows: (1) uterine contractions (duration ≥30 seconds, rate ≥4 times/30 minutes), a cervical canal length of less than 20 mm by transvaginal ultrasound measurement, or progressive shortening of the endocervical canal length; (2) patient age ≥18 years old; (3) gestational age 26 to 33 weeks plus 6 days. The exclusion criteria included vaginal bleeding; severe preeclampsia or hypertension; fever (body temperature >37.5°C); urinary tract infection; abnormalities in the fetus, placenta, or amniotic fluid (e.g., fetal malformations, chorioamnionitis, polyhydramnios, fetal growth restriction, or placenta previa); serious maternal diseases (e.g., cardiovascular disease, hyperthyroidism, diabetes, pheochromocytoma, or asthma attacks); and any contraindication to β-receptor agonists.

Drug Administration Methods

A first dose of 6.75 mg atosiban (Ferring Pharmaceuticals, Switzerland: Tractocile) was specified and intravenously injected in under one minute. Next, 20 ml of atosiban solution (7.5 mg/ml) was added to 180 ml of 0.9% sodium chloride or 5% glucose and intravenously infused at 300 μg/ml for three hours. Thereafter, a 100 μg/min drip rate was used until the expected uterine contraction-inhibiting effect was achieved. The entire course of a single treatment did not exceed 45 hours, and the total amount did not exceed 330 μg.

In the second group, 100 mg of ritodrine (Biotech Co., Ltd., Taiwan, China: Anpo) was added to a 5% glucose solution for intravenous infusion. The drip rate was closely observed and adjusted through a controllable infusion device or by altering the number of drops per minute. Initially, the drip rate was controlled to achieve a dosage of 0.05 mg/min, increasing by 0.05 mg/min (increase of 5 drops/min) every 10 minutes until the expected effect was achieved. The drip rate was generally maintained at 0.15 mg/min to 0.35 mg/min (15-35 drops/min) until at least 12 to 18 hours after the uterine contractions stopped. The treatment effects, adverse reactions, and perinatal results of each group of pregnant women were observed.

Upon admission into the hospital, each pregnant woman was immediately given a single course of glucocorticoid treatment. This medication was discontinued in those women with more than 3 cm cervical dilation or a ruptured fetal membrane. The patients in the two groups did not use a combination of medications. In certain cases, the atosiban or ritodrine treatment was repeated in pregnant women who experienced a recurrence of preterm birth symptoms after the uterine contractions had been successfully inhibited.

Observation Indicators

1) The efficacy of the two treatments in extending the gestational age by 48 hours or by seven days and the average gestational age at birth. For a treatment to be deemed 'effective', application of the medication had to be followed by a gradual cessation of uterine contractions and cervical dilation, with continuation of the pregnancy for more than 48 hours. The treatment was considered 'ineffective' in those cases in which uterine contractions did not weaken and for whom childbirth occurred within 48 hours. 2) Potential adverse reactions in the mother or fetus included the following: tachycardia, constipation, nausea, headache, tremor, hypotension, anxiety, and difficulty breathing in the mother; tachycardia and abnormal fetal heart rate (FHR) in the fetus; 3) Perinatal prognosis included the following: average body weight of the newborn, perinatal mortality (defined as fetal death, stillbirth, or death within seven days of birth for all singleton pregnancies born at a gestational age ≥28 weeks), neonatal asphyxia rate (Apgar score of 1 minute ≤7 points), the need for pediatric treatment for the newborn (neonatal asphyxia, aspiration pneumonia, decreased responsiveness, preterm birth, swallowing syndrome, birth defects, jaundice, gastrointestinal bleeding), acute respiratory distress syndrome (ARDS), neonatal brain injury, neonatal pneumonia, and neonatal sepsis.

Statistical Analysis

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The enumerated data were analyzed as percentages by the chi-square test. The measurement data are expressed as $x \pm s$ and were compared using *t*-tests or corrected *t'*-tests, with $p<0.05$ considered statistically significant.

Table I. Comparison of the protective effects of atosiban and ritodrine on the fetus in pregnant women who had undergone ART

	Atosiban group (n=35 cases)	Ritodrine group (n=35 cases)	p
Age of the pregnant women (years)	31.51±5.00	31.60±5.08	0.943
Primipara (cases, %)	32 (91.4%)	31 (88.6%)	1.000
Premature rupture of the fetal membrane (cases, %)	10 (28.6%)	12 (34.3%)	0.607
Singleton pregnancy (cases, %)	12 (34.3%)	15 (42.9%)	0.461
Gemellary pregnancy (cases, %)	23 (65.7%)	20 (57.1%)	0.461
Gestational age at 1st drug administration (weeks)	28.53±1.74	28.89±2.19	0.448
Less than 28 weeks (cases, %)	18 (51.4%)	16 (45.7%)	0.632
28-33+6 weeks (cases, %)	17 (48.6%)	19 (54.3%)	0.632
Average length of the cervical canal (CL) (cases, %)			
CL>20 mm	18 (51.4%)	12 (34.3%)	0.147
CL≤20 mm	17 (48.6%)	23 (65.7%)	0.147
Infertility reasons (cases)			
Fallopian tube obstruction	6	7	0.759
Polycystic ovary syndrome	8	10	0.584
Endometriosis	2	5	0.426
Oligo-asthenozoospermia	10	9	0.788
Other reasons/unknown reasons for infertility	9	4	0.142
48-hour efficacy (cases, %)	30 (85.7%)	22 (62.9%)	0.029
7-day efficacy (cases, %)	20 (57.1%)	15 (42.9%)	0.232
Average gestational age at birth (weeks)	32.43±3.93	31.27±3.81	0.213

Results

Comparison of the Protective Effects of Atosiban and Ritodrine on the Fetus in Women who had Become Pregnant Through ART

Compared with ritodrine, atosiban was significantly more effective at extending the gestational age by 48 hours ($p<0.05$). However, there were no significant differences between the two groups in basic clinical information, the seven-day protective effect on the fetus, or the average gestational age at birth ($p>0.05$) (Table I).

Comparison of the Safety of Atosiban and Ritodrine Administration in Pregnant Women Who Had Undergone ART

The incidence of side effects in the pregnant women was higher in the ritodrine group than in the atosiban group ($p<0.05$). However, the occurrences of specific adverse reactions in the pregnant women and the fetuses were not significantly different between the two groups ($p>0.05$) (Table II).

Comparison of Neonatal Outcomes in the Atosiban and Ritodrine Groups

Perinatal mortality and neonatal asphyxia were significantly less frequent in the atosiban group compared with the ritodrine group ($p<0.05$) (Table III). Furthermore, considering only the subjects for whom the medication was initiated at a gestational age of fewer than 28 weeks, the perinatal mortality rate was also significantly lower in the atosiban group than in the ritodrine group ($p<0.05$). There were 29 newborns in the group treated with atosiban prior to 28 weeks of gestation, of which 21 survived and 8 died: five died after abandoning treatment, and three died during the treatment (two due to respiratory failure and one due to respiratory failure plus sepsis). There were 26 newborns in the group treated with ritodrine before 28 weeks of gestation, of which 11 survived and 15 died: seven died after abandoning treatment, and eight died during the treatment (three due to respiratory failure and five due to respiratory failure plus sepsis). Neonatal pneumonia was also significantly lower in the atosiban group relative to the ritodrine group ($p<0.05$). There were no significant differences in the rates of neonatal asphyxia, the need for pediatric treatment of a newborn, neonatal ARDS, neonatal brain injury, or neonatal sepsis ($p>0.05$) (Table IV).

Considering only the subjects for whom the medication was initiated at a gestational age of greater than or equal to 28 weeks, the need for pediatric treatment of a newborn was significantly lower in the atosiban group compared with the ritodrine group, but there were no significant differences in the occurrences of perinatal mortality, neonatal asphyxia, ARDS, neonatal brain injury,

Table II. Medication safety of atosiban and ritodrine in pregnant women who had undergone ART.

	Atosiban group (cases)	Ritodrine group (cases)
Number of pregnant women	35	35
Total number of cases in which adverse reactions occurred*	9	17
Tachycardia	1	3
Constipation	2	1
Nausea	2	3
Headache	1	1
Tremor	0	1
Hypotension	0	1
Anxiety	1	2
Difficulty breathing	0	1
Fetus		
Tachycardia	0	2
Abnormal FHR	0	2

*p=0.048<0.05

neonatal pneumonia, or neonatal sepsis (p>0.05) (Table V).

Discussion

Reasons for Threatened Preterm Labor in Pregnant Women Who Underwent ART and Current Treatment Status

Factors related to preterm birth include the following: patients with a history of late-term abortion and/or preterm birth, pregnant women whose transvaginal ultrasound examination in the second trimester revealed a cervical canal length of less than 25 mm, patients with a history of cervical surgery, extremely young or old maternal age, multiple pregnancies, patients who underwent ART to promote gestation, and patients with pregnancy complications or other complications[1]. Studies[5-7] inside and outside of China have indicated that the high rate of preterm birth in women who underwent ART might be related to the rate of multiple pregnancies and/or advanced maternal age. Studies have suggested that due to the long duration of infertility and more advanced age in women who undergo ART treatment, there is an increase in egg aneuploidy and reduced DNA content in endometrial stromal cells. Furthermore, lower levels of estrogen and progesterone receptors in such patients can elevate the miscarriage rate compared with natural pregnancy (15% to 20%)[8]. Preventing and treating threatened preterm birth in women who became pregnant through ART is thus an effective way to reduce perinatal mortality rates. The treatment for patients with signs of preterm birth includes 1) application of tocolytic agents; 2) routine application of magnesium sulfate as a fetal central nervous system protective agent in those with threatened preterm birth prior to 32 weeks of gestation; and 3) glucocorticoids to promote fetal lung maturity. Tocolytic agents play a very important role in treating preterm birth. Different tocolytic agents exert inhibitory effects on uterine contraction at different positions and levels of the common pathogenic pathway for preterm birth. The efficacy of β-receptor agonists has been clearly demonstrated: they can effectively inhibit uterine contractions and

Table III. Newborn outcomes in the atosiban and ritodrine groups with ART.

	Atosiban group (n=58 cases)	Ritodrine group (n=55 cases)	p
Number of perinatal deaths (cases)	9	18	0.032
Neonatal asphyxia (cases)	8	19	0.01

Table IV. Comparison of the subsets of the atosiban and ritodrine groups that were first medicated at a gestational age of less than 28 weeks.

	Atosiban group first medicated at <28 weeks	Ritodrine group first medicated at <28 weeks	p
Number of cases (cases)	29	26	
Perinatal death [cases (%)]	8 (27.6%)	15 (57.7%)	0.024
Neonatal asphyxia [cases (%)]	7 (24.1%)	17 (65.4%)	0.002
Number of cases in need of pediatric treatment [cases (%)]	19 (65.5%)	21 (80.8%)	0.205
Neonatal ARDS [cases (%)]	21 (72.4%)	20 (76.9%)	0.702
Neonatal brain injury [cases (%)]	21 (72.4%)	20 (76.9%)	0.702
Neonatal pneumonia [cases (%)]	10 (34.5%)	16 (61.5%)	0.045
Neonatal sepsis [cases (%)]	4 (13.8%)	6 (23.1%)	0.373

have broad clinical applications. However, they do not specifically affect the uterus, so there are clinical differences in individual sensitivity to these drugs, and an increase in adverse cardiovascular reactions in the mother or fetus may develop after long-term usage[9]. Atosiban is the only uterus-specific tocolytic agent approved by the European Medicines Agency for the treatment of preterm birth. Atosiban functions by competing with oxytocin for oxytocin receptors on the myometrium, decidua, and fetal membrane, reducing the effect of oxytocin and calcium levels in muscle cells and, thereby, inhibiting uterine contractions.

Results of Atosiban and Ritodrine Application in Pregnant Women with Threatened Preterm Birth Who had Undergone ART

There were more twins pregnancies than singleton pregnancies in the ritodrine and atosiban groups in this study, with comparable twins pregnancy rates between the two groups. The average age of the pregnant women in both groups was approximately 31 years old; therefore, the age factor should have had minimal influence on the results. There were no significant differences between the two groups in the rate of premature rupture of the fetal membrane or the average length of the cervical canal. Romero et al[10] showed that the protective effect of atosiban on the fetus was better than that of a placebo, with similar adverse reactions in the mothers. Nisell et al[11] indicated that atosiban had higher efficacy and tolerability within 48 hours and seven days of treatment. We studied the protective effect on the fetus in patients with ART-related threatened preterm birth and found that the 48-hour efficacy of atosiban was significantly better than that of ritodrine. However, the seven-day efficacies of atosiban and ritodrine were comparable and not significantly different. There was no significant difference in the average gestational age extension between the atosiban and ritodrine groups. We surmise that the short-term effects of atosiban are better than those of ritodrine for treating pregnant women with threatened preterm birth who had undergone ART, but the long-term efficacies of the two drugs are comparable.

Table V. Comparison of the subsets of the atosiban and ritodrine groups that were first medicated at a gestational age of greater than or equal to 28 weeks. than 28 weeks.

	Atosiban group first medicated at <28 weeks	Ritodrine group first medicated at <28 weeks	p
Number of cases (cases)	29	29	
Perinatal death [cases (%)]	1 (3.4%)	3 (10.3%)	0.604
Neonatal asphyxia [cases (%)]	1 (3.4%)	2 (6.9%)	1.000
Number of cases that turned into pediatric cases [cases (%)]	12 (41.4%)	22 (75.9%)	0.008
Neonatal ARDS [cases (%)]	17 (58.6%)	15 (51.7%)	0.0597
Neonatal brain injury [cases (%)]	7 (24.1%)	14 (48.3%)	0.056
Neonatal pneumonia [cases (%)]	5 (17.2%)	5 (17.2%)	1.000
Neonatal sepsis [cases (%)]	1 (3.4%)	3 (10.3%)	0.300

Safety of Atosiban and Ritodrine Application in Pregnant Women who Underwent ART

Driul et al[12] demonstrated that adverse reactions were more commonly associated with ritodrine than atosiban, with one case of pulmonary edema. The present study showed different levels of adverse reactions to atosiban and ritodrine. The total prevalence of adverse reactions was lower for atosiban than for ritodrine. However, there were no significant differences in the occurrences of specific types of adverse reaction between the two groups, perhaps due to the small number of included cases. The data indicated that adverse reactions to atosiban were mainly gastrointestinal. Adverse reactions to ritodrine mainly manifested as adverse cardiovascular reactions, e.g., increased heart rate and hypotension, adverse gastrointestinal reactions, and increased FHR or abnormal FHR monitoring. These effects might be related to the differences in the protective mechanisms of the two types of tocolytic agents. Ritodrine is a β-receptor antagonist that could potentially affect every system of the body, leading to diverse adverse reactions. Atosiban, by contrast, is a uterus-specific oxytocin receptor antagonist. Wex et al[13] compared atosiban and β-receptor antagonists from an economic perspective. The authors showed that to achieve similar clinical results, atosiban was more economical than β-receptor antagonists. The authors attributed this difference to atosiban's superior safety profile. However, because atosiban is expensive in China, further evaluation from an economic perspective is still needed.

Perinatal Outcomes of Pregnant Women with Threatened Preterm Birth Who Had Undergone ART

According to the National Maternal and Child Health Surveillance, the neonatal mortality rate was 19.0‰ in China in 2005. The top three causes of neonatal death were preterm birth/low body weight, asphyxia, and pneumonia. Asphyxia was also the second most common cause of death in children who died before five years of age (20.5%)[14]. Koivurova et al[15] showed that the rates of preterm birth, low birth weight, very low birth weight, neonatal mortality and hospitalization were higher in an ART group compared with a natural pregnancy group. Our study compared the perinatal outcomes of atosiban and ritodrine and showed that atosiban reduced the rates of perinatal mortality and neonatal asphyxia more effectively. Finnström et al[16] determined that in pregnancies between 22 and 28 weeks, the newborn survival rate increased by 3% for each day that birth was delayed; if the pregnancy could be delayed to 30 weeks, the survival rate increased to 90%. Therefore, in this study, the superiority of atosiban relative to ritodrine in improving perinatal outcomes could be related to its superior ability to prolong gestational age. In a comparison of the subsets of pregnant women who were medicated at a gestational age of fewer than 28 weeks, atosiban was superior to ritodrine at reducing the perinatal mortality rate, the neonatal asphyxia rate, and the occurrence of neonatal pneumonia. There was no significant difference between the atosiban and ritodrine groups in the rate of neonatal cases turning into pediatric cases or in the occurrences of ARDS, neonatal brain injury, or neonatal sepsis. Among the cases which were first medicated with atosiban or ritodrine at a gestational age greater than or equal to 28 weeks, significantly fewer neonatal cases turned into pediatric cases in the atosiban group. There were no significant differences between the atosiban and ritodrine groups in the rates of perinatal mortality, neonatal asphyxia, neonatal pneumonia, ARDS, neonatal brain injury, or neonatal sepsis. The neonatal survival rates in cases where atosiban or ritodrine was first applied between 26 and 28 weeks of gestation were 72.4% and 42.3%, respectively. The neonatal survival rates in cases where atosiban or ritodrine was first administered at a gestational age of 28 weeks or greater were 96.6% and 93.1%, respectively. The perinatal prognosis was thus closely related to the gestational age at which the pregnant women were medicated for the first time. The application of tocolytic agents significantly extended gestational age and, in turn, improved the perinatal prognosis. Although the tocolytic agents had greater effects when initiated at a gestational age of fewer than 28 weeks, such treatment could make it more difficult for women who underwent ART to become pregnant again. These women bear greater economic and family pressures, so the pros and cons of protecting the fetus must be considered carefully.

The aforementioned studies inside and outside of China concluded that women who were impregnated using ART had a higher rate of preterm birth. The causes of preterm birth are complicated and can influence a treatment's protective effect on the fetus.

Conclusions

The results of this study showed that the use of atosiban to immediately stall preterm labor in pregnant women with threatened preterm birth who had undergone ART had better results than the use of ritodrine. This treatment would allow ample time to apply glucocorticoids and thus improve perinatal outcomes. Atosiban is very safe and more tolerable for pregnant women who have undergone ART. The better results achieved with this medication should make atosiban the preferred treatment for patients with threatened preterm birth at a gestational age of fewer than 28 weeks.

Acknowledgements

This study was supported by Science and Technology Bureau of Zhengzhou (CZSYJJ13022).

Conflicts of interest

The authors declare no conflicts of interest.

References

1) The Subspecialty Group of Obstetrics, Obstetrics & Gynecology Society, Chinese Medical Association. Clinical diagnosis and treatment guidelines for preterm labor. Chinese Journal of Obstetrics and Gynecology 2014; 2014: 481-485.
2) Blickstein I. Does assisted reproduction technology, per se, increase the risk of preterm birth? BJOG 2006; 113 Suppl 3: 68-71.
3) Bai HW, Ren CE, Han HY, Qao PY, Jiang JY. Premature delivery of newborns after assisted reproductive technology: a meta-analysis of cohort studies. Journal of Weifang Medical College 2013; 246-249.
4) Yu YH, Gong SP, Su GD. Study on factors related to premature delivery and perinatal management. Journal of First Military Medical University 2004; 24: 59-61.
5) Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. Br Med J 2004; 328: 261.
6) McIntyre SH, Newburn-Cook CV, O'Brien B, Demianczuk NN. Effect of older maternal age on the risk of spontaneous preterm labor: a population-based study. Health Care Women Int 2009; 30: 670-689.
7) Waldenström U, Aasheim V, Nilsen AB, Rasmussen S, Pettersson HJ, Schytt E. Adverse pregnancy outcomes related to advanced maternal age compared with smoking and being overweight. Obstet Gynecol 2014; 123: 104-112.
8) Wang SZ. Practical Obstetrics and Gynecology. Beijing: People's Medical Publishing House, 1994; p. 172.
9) Shim JY, Park YW, Yoon BH, Cho YK, Yang JH, Lee Y, Kim A. Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women. BJOG 2006; 113: 1228-1234.
10) Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, Perry KG, Varner M, Goodwin TM, Lane R, Smith J, Shangold G, Creasy GW. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol 2000; 182: 1173-1183.
11) Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. BJOG 2001; 108: 133-142.
12) Driul L, Londero AP, Adorati-Menegato A, Vogrig E, Bertozzi S, Fachechi G, Forzano L, Cacciaguerra G, Perin E, Miceli A, Marchesoni D. Therapy side-effects and predictive factors for preterm delivery in patients undergoing tocolysis with atosiban or ritodrine for threatened preterm labour. J Obstet Gynaecol 2014; 34: 684-689.
13) Wex J, Abou-Setta AM, Clerici G, Di Renzo GC. Atosiban versus betamimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects. Eur J Obstet Gynecol Reprod Biol 2011; 157: 128-135.
14) Ye HM. Efforts in reducing China's neonatal asphyxia mortality and disability rates. Chinese Journal of Perinatal Medicine 2007; 10: 217-218.
15) Sari K, Anna-Liisa H, Mika G,Elina H,Ulla S, Marjo-Riitta J. Neonatal outcome and congenital malformations in children born after in-vitro fertilization. Obstet Gynecol Survey 2002; 57: 742-743.
16) Finnström O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K, Tunell R, Wennergren M, Wesström G. The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. Acta Paediatr 1997; 86: 503-511.