Effectiveness and safety of the oxytocin antagonist(atosiban) versus beta-adrenergic agonists (salbutamol) in the treatment of preterm labor.

Yasamin H. Sharif Al-Shibany* ,Saba M. Swadi Al- Thuwainy *
*Obstetrics and Gynecology Department Medical college / Al-Qadisia University
,Email: yhsaso@yahoo.com , Email: saba.swadi1@yahoo.com

(Received 7 / 4 /2015 , Accepted 19 / 4 / 2015)

الخلاصة :
التأثيرات و الاعراض الجانبية لاستخدام عقار الاتوسيبان و هو عامل مضاد للاوكسيتوسين البشري عند مستقبلات الخلية بالمقارنة مع عقار السالبيوتامول وهو عامل محفز لمستقبلات البيتا في الخلية البشرية لعلاج حالات الولادة المبكرة.
الطريقة: أجريت الدراسة في مستشفى الولادة و الأطفال التعليمي في الديوانية-العراق ، للفترة من (شهر كانون الثاني/2014 و لغاية شهر كانون الثاني/2015) على 100 امرأة حامل بعمر (18-35 سنة) و ادخلن الى قسم الطوارئ مع اعراض للولادة المبكرة و كانت فترة الحمل من(24-34 أسبوع) مع وجود انقباضات للرحم تستغرق 30 ثانية بمعدل ≤ أربعة انقباضات خلال 60 دقيقة و كان اتساع عنق الرحم من (1الى 3 سم)و(0الى 3 سم)للسيدات عديمة الولادة وسرعة نبض الجنين طبيعية ، تم تقسيم المريضات الى مجموعتين: المجموعة الأولى و عددها 50 مريضة عولجت بعقار السالبيوتامول عن طريق محلول الحقن الوريدي و المجموعة الثانية 50 مريضة عولجت بعقار الاتوسيبان الوريدي مع مراقبة شدة الانقباضات و الاعراض الجانبية لكل عقار على الام و الجنين لغرض تأخير الولادة المبكرة و تقليل المضاعفات السريرية و الوفيات لدى المواليد الخدج حديثي الولادة.
النتائج: لم يكن هناك اختلاف في تأخير حالات الولادة المبكرة لمدة 48 ساعة(44% مقابل46%) و 7 أيام(20% مقابل 32%) بين المجموعة الأولى و الثانية على التوالي و لكن الاعراض الجانبية مثل تسارع نبضات قلب الام كانت اكثر عند المجموعة الأولى التي عولجت بعقار السالبيوتامول(22% مقابل 8%).لم تكن هناك اختلافات في النتائج الإحصائية للمضاعفات السريرية لدى المواليد الخدج حديثي الولادة بين المجموعتين.
الاستنتاج: استخدام عقار الاتوسيبان له نتائج مقاربة لاستخدام عقار السالبيوتامول في تأخير حدوث الولادة المبكرة و لكن له أهمية سريرية افضل من السالبيوتامول بسب قلة الاعراض الجانبية لدى الام و الجنين و ننصح باستخدامه كأول خط علاجي لحالات الولادة المبكرة لتقليل المضاعفات و نسب الوفيات لدى الخدج حديثي الولادة.

Abstract:
Background and Objectives: preterm labor complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide and 70-80% of perinatal deaths occur in preterm infants. The aim of this study is to compare the effectiveness, safety and adverse effects of the oxytocin antagonist medication(atosiban) with those of beta-adrenergic agonist (salbutamol) in the treatment of patients with preterm labor.
Patients and Methods: one hundred pregnant women with preterm labor were enrolled in this study from the period of(January 2014 – January 2015) at Al-Diwaniya Maternity and Pediatrics Teaching Hospital-Iraq with a gestational age of 24-34 weeks, they were randomly assigned to receive tocolytics either salbutamol (n=50) or atosiban (n=50).Salbutamol was given by(intravenous infusion 10-50 microgram)for up to 48 hour. Atosiban was given by (intravenous bolus dose of 6.75 mg then 300microgram/minute for 3 hour and 100microgram/minute for up to 48hour). Retreatment with the study drugs or alternative tocolytic agents was allowed. Main outcome measures included were tocolytic effectiveness, which was assessed in terms of number of women undelivered after 48hour and 7 days. Tocolytic safety was assessed in terms of maternal and fetal side effects and neonatal morbidity.
Results: there were no significant differences between the salbutamol and the atosiban group in prolongation of pregnancy for 48 hour (44% versus

46%;p=0841)and 7 days(20% versus 32%;p=0.171) ,respectively. Maternal adverse events , including tachycardia occurred more frequently in the salbutamol group(22% versus 8%;p=0.050).Neonatal outcomes and complications were comparable between the two study groups(42% versus 32%;p=0.30).

Conclusions: the oxytocin antagonist (atosiban) was as effective as beta-agonist(salbutamol) in delaying threatened preterm birth , and found to be better tolerated by both the mother and fetus than salbutamol , with a comparable neonatal safety profil.This study supports the clinical use of atosiban as a first line tocolytic in the treatment of preterm labor.

Key words: preterm labor ,tocolytics, salbutamol , atosiban ,pregnancy outcome ,neonatal outcome.

Introduction:

Preterm labor refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of the cervix with a gestational age between 24 weeks and less than 37 weeks of gestation , before 24 weeks the correct term is miscarriage rather than preterm labor (1).Preterm labor complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide ,and 70-80% of perinatal deaths occur in preterm infants (2).It is a major public health problem in terms of loss of life from respiratory distress syndrome(RDS) and intraventricular hemorrhage(IVH) ,long term disability (cerebral palsy ,blindness ,deafness ,chronic lung disease and health care cost) both in developing and developed world(1,2).Preterm labor precedes about 50% of preterm birth , but approximately 30% of preterm labor spontaneously resolves, less than 10% of women presenting with preterm contractions give birth within seven days and 50% of patients hospitalized for preterm labor give birth at term (3,4).For patients with true preterm labor ,tocolytic therapy often abolishes contractions temporarily , but does not remove the underlying stimulus that initiated the process of parturitions or reverse parturition changes in the uterus , and the net result is that a single course of tocolytics may delay delivery by hours or days ,but not weeks or months(5).

Tocolytics (also called anticontraction medications) are pharmacological agents used to suppress premature labor, and they are given when delivery would result in premature birth(6).These pharmacological agents act through a variety of mechanisms to decrease the availability of intracellular calcium ions leading to inhibition of actin-myosin interaction(7).Their effectiveness in suppression of preterm labor has been controversial and many of these agents are associated with serious side effects to both mother and her fetus(7).However, tocolytics should be considered if the few days gained would be put to good use such as completing a course of corticosteroids which greatly accelerate fetal lung maturity and reduce the risk of respiratory distress syndrome and its sequelae as well as intraventricular hemorrhage ,but it takes one to two days to work ,and also give time for in-utero transfer of the fetus to a tertiary center equipped for high risk pregnancies with neonatal intensive care unit(8).

Beta-adrenergic agonist drugs such as salbutamol are the commonly used tocolytic drugs (9).It acts through c-GMP to inhibit uterine contractions by inhibiting the entry of calcium ions into the smooth muscle of the uterus and produce uterine relaxation in most instance, but the onset is variable and depends on the dosage. (9).Salbutamol is known to cross the placental barrier as evidenced by the increase in fetal heart rate (10). It has been shown that these agents postpone the delivery for 24,48hours and even 7 days, however ,such a delay has not been associated with a significant reduction in either perinatal mortality or morbidity(9,10).They are associated with serious maternal side effects such pulmonary edema ,myocardial ischemia, arrhythmia ,chest pain and death(9).Although hyperglycemia and hypokalemia are

recognized complications ,so the drug used cautiously in patients with diabetes mellitus or who require surgery(9,10).

Atosiban is a new class of tocolytics, it is an oxytocin antagonist licensed for the management of preterm labor (11).Oxytocin is believed to initiate uterine contractility by increasing the intracellular calcium concentration of myometrium cells through a direct effect on membrane bound oxytocin receptors. Oxytocin further stimulates uterine contractility and initiates cervical ripening by stimulating the release of prostaglandins in the decidual and fetal membranes (12).Atosiban is a synthetic peptide which is a competitive antagonist of human oxytocin at receptor level in the uterus and potentially also in the decidual and fetal membranes and administration result in a dose dependent inhibition of uterine contractility with a reduction in oxytocin mediated prostaglandin release (13).As an antagonist of oxytocin , atosiban may facilitate uterine relaxation and postpartum bleeding ,therefore blood loss after delivery should be monitored(13).

This study aimed to compare the effectiveness, safety and adverse effects of two tocolytic drugs, oxytocin antagonist (atosiban) with those of beta-adrenergic agonist (salbutamol) in prolongation of pregnancy until and beyond 48hours and 7 day in patients with preterm labor to improve neonatal outcome and reduce perinatal morbidity and mortality rates.

Patients and methods:

This randomized clinical trial was performed at the emergency obstetric ward at Al-Diwaniya Maternity and Pediatrics Teaching Hospital-Iraq, in connection with neonatal intensive care unit at the same hospital.

One hundred pregnant women with preterm labor were enrolled in this study from the period of (January 2014-January 2015). The study was approved by Iraqi Ethical Committee and its protocol , benefits and complications were explained to all participants, all recruited patients completed and signed the" informed consent form", the dose, and regimen was identical to its license specification. Inclusion criteria: all women ranging in age from 18 to 35 years who presented to the labor ward between 24 and 34 weeks of pregnancy (determined by the date of the last menstrual period when known or by early ultrasound)with preterm labor which is defined as the persistence of ≥4 symptomatic uterine contractions of at least 30 second period during the 60-minutes after admission and despite bed rest, in the presence of cervical dilatation between (0 and 3 cm) for primigravida and between(1 and 3 cm) for multigravida , with cervical effacement of more than 50% with a normal fetal heart rate. Exclusion criteria: gestational age below 24 weeks or over 34 weeks ,cervical dilatation greater than 3 cm ,premature rupture of membranes ,intrauterine growth retardation abnormal fetal heart rate, antepartum uterine bleeding, eclampsia and sever pre-eclampsia requiring delivery, intrauterine fetal death suspected intrauterine infection multiple pregnancy ,fetal anomaly, maternal diabetes mellitus, maternal thyrotoxicosis ,oligohydramnious, polyhydramnios ,and known hypersensitivity to active substance of the drugs used in the study . After performing biochemical and hematological tests and electrocardiogram, women were randomly assigned to two study groups.

Women in the first group (n=50) received intravenous infusion beta-agonist drug salbutamol sulfate (Glaxowellcome S.P.A. ,Parma ,Italy) (ventolin obstetric injection) (5mg/5ml)diluted in 500 ml of either 0.9% sodium chloride solution or 5% dextrose solution or sodium chloride and dextrose solution in infusion pump initially (10 microgram/minute) increased by (5 microgram/minute)every 10 minutes to maximum(50 microgram/minute) until there is evidence of patient response shown by diminution in strength frequency or duration of contraction. The maternal pulse rate and fetal heart rate should be monitored and the infusion rate adjusted to avoid maternal heart rates in excess of 120 beat per minute, and once uterine contractions have ceased, the infusion rate should be maintained at the same level for one hour and then reduced by 50% decrements at 6 hourly intervals for up to 48 hours. The infusion should be stopped if labor progress despite treatment.

Second group(n=50) received oxytocin antagonist atosiban (Tractocile, Ferring SA, Germany) 7.5 mg/ml concentrate for solution for infusion, each vial contain 37.5mg atosiban diluted in one of the following solutions: 0.9% sodium chloride ,or ringer's lactate solution ,or5%dextrose solution. Withdrawal of 10 ml solution from a 100ml infusion bag and discarded and replaced by 10 ml atosiban 7.5 mg/ml concentrate for solution for infusion from two 5 ml vial to obtain a concentration of 75 mg atosiban in 100 ml..Atosiban is administered IV in 3 successive stages : an initial bolus dose 0.9 ml intravenous infusion (6.75mg) over 1 minute with atosiban 7.5mg/ml solution for injection ,followed by continuous high dose infusion of(300microgram/minute) of atosiban injection with infusion rate of 24ml/hour (atosibane dose 18mg/hour) over 3 hours period followed by a lower dose of atosiban (subsequent infusion 100microgram/minute) with infusion rate of 8ml/hour (atosibane dose 6mg/hour) for up to 48 hours.

Fetal heart rate and uterine contractions as well as maternal blood pressure and pulse rate were assessed every 12 hours for all participant patients ,if maternal pulse rate > 120 beat/minute , fetal heart rate >160 beat/minute ,maternal dyspnea or chest pain developed the treatment discontinued . Prolongation of pregnancy for a period of 48 hours was the primary outcome in this study. The interventions were considered a failure in participants who delivered during the period or still had contractions after 48hours or develop maternal or fetal complications, and it is considered a success in participants whose contractions stopped for the full 48 hours. Patients whose contractions discontinued after 48 hours were discharged from the hospital. If uterine contractions reappeared, relapse was diagnosed and treatment was repeated as indicated above. The secondary outcomes of the study were the prolongation of pregnancy until 7 days and the drug's safety, which was assessed in terms of maternal and fetal side effects of each medication with neonatal complications of the patients who delivered preterm after starting treatment such as respiratory distress syndrome, intraventricular hemorrhage, and sepsis.

Statistical analysis

Data were analyzed using SPSS version 16 and Microsoft Office Excel 2007. Numeric variables were expressed as mean±SD, while nominal variables were expressed as number and percent. Student t-test was used to compare mean between two groups. Ch-square test was used to compare frequencies. P-value less than or equal to 0.05 was regarded significant.

Results:

A total of 100 pregnant patients with preterm labor were enrolled and randomized into two study groups. Group 1 (n=50) treated with beta-agonist (salbutamol) and group 2 (n=50) treated with oxytocin antagonist (atosiban).None of the baseline parameters differed significantly between the two groups (table 1). A 48 hour prolongation of pregnancy was achieved in 22 (44%) patients receiving salbutamol and 23(46%) patients receiving atosiban which was not statistically significant(p=0.841)(table 2).There were no statistical differences between both groups in delaying delivery for 7 days(p=0.171)(table 2).The patients in the salbutamol group experienced more complications including maternal tachycardia and palpitations (22% versus 8%) (p=0.050)(table 3). No statistical differences in neonatal outcome were observed with either study medication in patients with preterm birth (42% versus 32%) (p= 0.30)(table 4).

Table 1: Baseline characteristics of the two study groups comparing the patients age(years) ,parity, gestational age(weeks), cervical dilatation(cm), number of uterine contraction and intensity of contraction(seconds).

Characteristic	Group 1 (Salbutamol) N = 50	Group 2 (Atosiban) N = 50	P-value
Age (years)	26.46±5.26	25.54±5.15	0.379
Parity	1 (0-3)	1(0-4)	0.624
Gestational age (weeks)	30.50±1.98	30.32±1.82	0.638
Cervical dilatation (cm)	2.44±0.64	2.32±0.71	0.379
Number of uterine contraction	2.76±0.59	2.94±0.62	0.140
Intensity of uterine contraction(seconds)	30.50±3.07	30.20±3.49	0.649

Table 2: Outcome of pregnancy in the two study groups comparing the time of delivery.

	Group 1 (Salbutamol) N = 50		Group 2 (Atosiban) N = 50		
Delivery time	**No.**	**%**	**No.**	**%**	**P-value**
Delivery within 48 hours	18	36	11	22	0.123
Delivery after 48 hours	22	44	23	46	0.841
Delivery after 7 days	10	20	16	32	0.171
Total	50	100	50	100	

Table 3: Maternal and fetal complications in the two study groups.

	Group 1 (Salbutamol) N = 50		Group 2 (Atosiban) N = 50		
	No.	**%**	**No.**	**%**	**P-value**
Maternal tachycardia	11	22	4	8	0.050
Fetal tachycardia	4	8	2	4	0.867
Maternal chest pain	6	12	1	2	0.112

Maternal dyspnea	3	6	1	2	0.617

Table 4: Neonatal complications in women with preterm labor in the two study groups.

	Group 1 (Salbutamol) N = 50		Group 2 (Atosiban) N = 50		
	No.	**%**	**No.**	**%**	**P-value**
Respiratory distress	9	18	8	16	0.790
Syndrome(RDS)					
Intra cranial hemorrhage	6	12	5	10	0.749
Sepsis	6	12	3	6	0.487
Total	21	42	16	32	0.300

Discussion:

In this study we compared the clinical effectiveness and adverse effects of salbutamol (beta-agonist drug) with those of atosiban (oxytocin antagonist drug) in suppression of preterm labor and maintaining a prolongation of pregnancy for few days, and these few days gained would be put to good use such as completing a course of corticosteroid or in utero-transfer to a tertiary center with neonatal intensive care unit to decrease the perinatal mortality and morbidity from prematurity.

Our findings in the study were consistent with Edwin Chandraharan , et al (2005) study which showed that atosiban was comparable in clinical effectiveness to beta-agonist salbutamol therapy in prolongation of pregnancy of 48 hours , and 7 days , but was associated with fewer maternal cardiovascular side effects as maternal tachycardia and palpitation if compared to salbutamol therapy(13).

Phuong , et al (2004) studied the effect of salbutamol on prolongation of pregnancy in those patients with preterm labor. Of the 132 pregnancies with preterm labor studied, 81.1% were prolonged for more than 24 hour, 59.8% for more than 48 hour, and 32.6% for more than 7 days (14). Maternal tachycardia was the more common side effects, which was experienced by 85.6% of patients. Neonatal complications occurred in 28% of the babies, and RDS occurred in 22.7% of babies (14).

These findings were consistent with our study as salbutamol group had 36% prolongation of pregnancy for more than 24 hour, 44% prolongation for 48 hour, and 20% prolongation for 7 days. Maternal tachycardia occurred in 22% of cases, and neonatal complications in 42% and RDS occurred in 18% of babies.

In an Italian observational study by Merenda A. , et al (2006) showed that 30% of patients with preterm labor treated with beta-agonist stopped treatment due to occurrence of

maternal and fetal side effects compared to 0% in the atosiban treated patients(15).The study showed the following side effects were reported for beta-agonist versus atosiban therapy : nausea and vomiting (20% versus 20%) , maternal tachycardia (60% versus 0%) , fetal tachycardia (50% versus 0%), headache (20% versus 10) , tremor (10% versus 0%) , hypotension (10% versus 0%) and palpitation (10% versus 0%) (15).

R. Lamont, et al (2002) study showed that beta-agonist drugs (e.g.) (salbutamol, ritodrine or isoxuprine) have been widely used for the last 30 years , but were being gradually phased out since the early 1990s due to maternal and fetal safety concerns(16).The occurrence of side effects were associated with the mechanism of action of beta-agonist drug , affecting multiple functions via ubiquitous beta-adrenergic receptors(16).

Furthermore, Di Renzo , et al (2006) study showed that beta-agonist drugs were contraindicated or should be used with caution in hyperthyroidism, cardiovascular diseases, arrhythmias, hypertension and diabetes due to increased risk of pulmonary edema and hypokalemia (17).

With similar efficacy , the clinical advantages of atosiban results from its superior safety profile with a significantly lower rate of fetal and maternal side-effects and a significantly lower rate of treatment discontinuation as showed by a recent study from the Netherlands and Belgium by R.de Hens , B.W.Mol , et al (2009) ,the study showed that the use of beta-agonist drugs were associated with higher incidence of mild and severe side effects compared with atosiban(oxytocin antagonist) with a relative risk of (R.R=24.5%)(18).They concluded that beta-agonist should no longer be used and the use of atosiban (oxytocin antagonist) should be considered especially in cases of preterm labor with multiple gestation, diabetes and maternal cardiovascular problems (18).

A World wide Atosiban versus Beta-agonists Study Group (2003) ,showed that there were no significant differences between atosiban and beta-agonists in delaying delivery for 48 hour (88.1% versus 88.9% ;p=0.99) or seven days (79.7% versus 77.6% ;p=0.28). Maternal side effects particularly cardiovascular adverse events (8.3% versus 81.2% ;p<0.001) were reported more frequently in women given beta- agonists , resulting in more treatment discontinuations due to side effects. No statistical differences in neonatal outcome (19).

Our study showed that there were no statistical differences between atosiban and salbutamol group in delaying delivery for 48 hours (46% versus 44% ;p=0.841) and 7 days (32% versus 20% ;p=0.171) , and maternal side effects particularly maternal tachycardia was more common in salbutamol group compared to atosiban treated group (22% versus 8% ;p=0.050) , although other maternal complication as chest pain and dyspnea and fetal tachycardia were more common in the salbutamol group but were statistically not significant , but lead to more treatment discontinuation. No statistical differences in neonatal outcome between the two study groups.

French/Australian Atosiban Investigators Group Study (2001) , showed that 241 women with preterm labor received either atosiban (n=119) or salbutamol (n=122) ,tocolytic effectiveness at 48 hour was(93.3% versus 95.0% ;p=0.67) and after 7 days (89.9% versus 90.1% ;p=0.93) in the atosiban and salbutamol group , respectively(20). Maternal adverse events as tachycardia occurred more frequently in the salbutamol group and neonatal outcomes were comparable between the study groups (20).

Our study was consistent with that study findings which showed that oxytocin antagonist (atosiban) was found to be better tolerated by the mother than beta-agonists (salbutamol) , and atosiban was as effective as salbutamol in delaying threatened preterm birth with less treatment discontinuation because of the side effects.

Taking into account safety of tocolytics treatment the UK's Royal College of Obstetricians and Gynecologists (RCOG) (2002) , recommended that oxytocin receptor antagonists (atosiban) be used as one of the first lines of treatment in preterm labor(7).

Conclusion:

Prevention and treatment of preterm labor is essential for survival and improves the quality of life such an approach will have a great impact on social and long term public health care cost and many developing countries are unable to cope with the health care cost associated with managing neonates that are born preterm , resulting in higher and often unacceptable neonatal morbidity and mortality. From our study we concluded that atosiban had a clinical advantages over current tocolytic therapy with salbutamol and we advise to consider this medication as a first line in the management of preterm labor. Further researches is needed on drugs with more utero-selectivity and fewer side effects with better efficacy.

References:

1-Slattery M.M , Morrison J.J .Preterm Delivery. Lancet 2002;360:1489-1497.

2-Kaltreider D.F ,Kohl S. Epidemiology of Preterm Labor.Clin Obstet Gynecol .1980;23:17-30.

3-King J.F,Grant A. ,Keirse M.J .Beta-mimetic in preterm labor: an overview of the randomized controlled trials. BrJ Obstet Gynecol 1988;95:211.

4-McPheeters M.L, Miller W.C ,Hartmann K.E, et al.The epidemiology of threatened preterm labor: a prospective cohort study . AmJ Obstet Gynecol.2005; 192:1325.

5-Haas D.M, Imperial T.F. , Kirk Patrick P.R , et al . Tocolytic therapy: a Meta – analysis and decision analysis. Obstet Gynecol 2009; 113:585.

6-Tan T.C. Devendra K. , Tan L. K. , et al.Tocolytic treatment for the management of preterm labor : a systemic review.Singapore Med J (may) 2006;47(5):361-366.

7-RCOG. Tocolytic drugs for women in preterm labor. Clinical Guideline NO.1 (B).October 2002. RCOG press.

8-Althuisius S.M. , Dekker G.A. , Hummel P. , et al .Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone . Am J Obest Gynecol .2003; 189:907-910.

9-Chua S., Razvik K., Wong M.T, et al. Is there a need to treat hypokalemia associated with intravenous salbutamol infusion? J Obeste Gynecol.1997; 23:381-387.

10-Treatment of preterm labor with the beta-adrenergic antagonist ritodrine:The Canadian Preterm Labor Investigators Group.N Eng J Med.1992;327:308-312.

11-Steer P. and Flint. Preterm labor and premature rupture of membranes. BMJ 1999; 318:1059-1062.

12-Tractocile (atosiban).Formulary pack. Summary of product characteristics. Ferring Pharmaceuticals Ltd. January 2000.

13-Edwin Chandraharan , Sabaratnam ,et al .Recent advances in management of preterm labor. Obestet Gynecol India. (March) 2005; 55:118-124.

14-Phupong V. ,Charalcorn C. , Charoenvidhya D.Oral salbutamol for treatment of preterm labor.J Med Assoc Thai.2004;87:1012-1016.

15- Merenda A.,Stile A. , nazzaro G. , et al. Isossisprinacloridrato vs atosiban in pazientia affetle da PROM. Congresso SIGO; 2006.

16-R. Lamount , J. vanEyck . Tocolysis with nifidepine or beta-adrenergic agonists: a meta-analysis. Obstet Gynecol.2002;99(march):518-519.

17-G.C.DiRenzo, L.C.Roura. Guidelines for the management of spontaneous preterm labor. Jperinat Med.2006; 34(5):359-366.

18-R.de Heus ,B.W.Mol , J.J.Erwich , et al. Adverse drug reactions to tocolytic treatment for preterm labor: prospective cohort study.BMJ.2009;338.

19-Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonists atosiban versus beta-adrenergic agonists in the treatment of preterm labor. BJOG. 2003 Jan;110(1):289.

20-French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double blind randomized controlled comparison with salbutamol. Eur J Obestet Gynecol Reprod Biol.2001;98 February(2):177-185.