Oxytocin receptor antagonists for inhibiting preterm labour (Review)

Papatsonis D, Flenady V, Cole S, Liley H

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Oxytocin receptor antagonists for inhibiting preterm labour (Review)

Papatsonis D, Flenady V, Cole S, Liley H

Status: *Commented*

This record should be cited as:
Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub2.

This version first published online: 20 July 2005 in Issue 3, 2005.
Date of most recent substantive amendment: 18 May 2005

ABSTRACT

Background
Preterm birth, defined as birth before 37 completed weeks, is the single most important cause of perinatal mortality and morbidity in high-income countries. Oxytocin receptor antagonists have been proposed as effective tocolytic agents for women in preterm labour to postpone the birth, with fewer side-effects than other tocolytic agents.

Objectives
To assess the effects on maternal, fetal and neonatal outcomes of tocolysis with oxytocin receptor antagonists for women with preterm labour compared with placebo or no intervention and compared with any other tocolytic agent.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (September 2004), CENTRAL (*The Cochrane Library*, Issue 3, 2004), MEDLINE (1965 to June 2004), EMBASE (1988 to June 2004).

Selection criteria
Randomised trials of oxytocin receptor antagonists for tocolysis in the management of women in labour between 20 and 36 weeks' gestation.

Data collection and analysis
Two authors independently evaluated methodological quality and extracted trial data. We sought additional information from trial authors.

Main results
Six trials (1695 women) were included. Compared with placebo, atosiban did not reduce incidence of preterm birth or improve neonatal outcome. In one trial (583 infants), atosiban was associated with an increase in infant deaths at 12 months of age compared with placebo (relative risk (RR) 6.15; 95% confidence intervals (CI) 1.39 to 27.22). However, this trial randomised significantly more women to atosiban before 26 weeks' gestation. Use of atosiban resulted in lower infant birthweight (weighted mean difference -138.31 gm; 95% CI -248.76 to -27.86) and more maternal adverse drug reactions (RR 4.02; 95% CI 2.05 to 7.85, 2 trials, 613 women).

Compared with betamimetics, atosiban increased the numbers of infants born under 1500 gm (RR 1.96; 95% CI 1.15 to 3.35, 2 trials, 575 infants). Atosiban was associated with fewer maternal drug reactions requiring treatment cessation (RR 0.04; 95% CI 0.02 to 0.11, number needed to treat 6; 95% CI 5 to 7, 4 trials, 1035 women).

Authors' conclusions
This review failed to demonstrate the superiority of atosiban over betamimetics or placebo in terms of tocolytic efficacy or infant outcomes. The finding of an increase in infant deaths in one placebo controlled trial warrants caution. A recent Cochrane review suggests that calcium channel blockers (mainly nifedipine) are associated with better neonatal outcome and fewer maternal side-effects

than betamimetics. However, a randomised comparison of nifedipine with placebo is not available. Further well-designed randomised controlled trials of tocolytic therapy are needed. Such trials should incorporate a placebo arm.

PLAIN LANGUAGE SUMMARY

Atosiban, an oxytocin receptor antagonist, is no better than other drugs in delaying or preventing preterm birth but has fewer maternal side-effects

Tocolytic agents may postpone preterm delivery long enough to improve neonatal outcome, allow corticosteroids to be given to help the baby's lungs and other organs to mature and, if necessary, to allow transfer of the mother to a hospital that has facilities to provide neonatal intensive care. Tocolytic drugs called oxytocin receptor antagonists work by inhibiting the hormone oxytocin that stimulates labour. This review found that, although the oxytocin receptor antagonist atosiban resulted in fewer maternal side-effects than other tocolytic drugs (betamimetics), no benefit was shown in delaying or preventing preterm birth, and atosiban was associated with more infant deaths in one placebo controlled trial. Further well-designed trials are needed.

BACKGROUND

Preterm birth, defined as birth before 37 completed weeks, is the single most important cause of perinatal mortality and morbidity in high-income countries (Berkowitz 1993; Lumley 1993). The birth of a preterm infant who requires intensive care for its survival is a crisis, not only for the infant, but also for the parents (McCain 1993).

About two-thirds of preterm births result from spontaneous preterm labour or preterm premature rupture of the membranes, with the remainder due to medical interventions for maternal or fetal indications (Mercer 1996). The annual worldwide incidence is estimated at 13 million (Hall 1997). In high-income countries the incidence of preterm birth is estimated at 6% to 10% of all births (Lumley 2003) and has remained unchanged over the last four decades despite intensive antenatal care programs aimed at high-risk groups, the widespread use of pharmacological agents to inhibit preterm birth (tocolytics) and a series of other preventive and therapeutic interventions. The incidence of preterm birth in low-income countries is likely to be much higher, but accurate estimates are hampered by problems with valid estimation of gestational age (Kramer 2003a) and with registration of births (Kramer 2003a; Lumley 2003). Adverse outcomes for infants are far more frequent in low-income countries. More than nine million neonatal deaths occur each year, 98% of them in low-income countries. Preterm delivery is one of the major direct causes of neonatal death in developing countries (De L Costello 2003).

Preterm birth is responsible for between 75% to 90% of all the neonatal deaths that are not due to congenital anomalies, and 50% of childhood neurological disabilities (Hack 1999). The risk of adverse outcome associated with preterm birth increases with decreasing gestational age. The majority of severe adverse outcomes occur in infants born before 34 weeks who constitute 33% of all preterm births and account for 83% of the total preterm perinatal mortality. Births under 28 weeks account for 10% of preterm births and for 57% of preterm perinatal mortality while births under 26 weeks account for approximately 7% of preterm births and 46% of all perinatal mortality (Lumley 1993). The EPICure study (Costeloe 2000; Wood 2000) reported outcomes for the very high-risk group of infants born before 25 completed gestational weeks. The percentage of singleton infants who survived and were discharged from the neonatal intensive care unit increased from 23% at 23 weeks to 38% at 24 weeks, and 54% at 25 weeks. The incidence of disability for infants born before 25 completed weeks was 48%, 23% of the infants had severe disability. Birth beyond 32 weeks is considered to contribute less to the overall preterm mortality and morbidity (Lemons 2001). However, although the risk of mortality and morbidity is low, infants born between 32 and 36 weeks account for approximately 80% of all preterm births and because of their sheer numbers make a substantial contribution to the total perinatal mortality (Lumley 2003) and the public health burden of preterm birth (Kramer 2003b).

The costs of preterm birth and its associated neonatal intensive care unit admission are high and include immediate and long-term costs. The weekly cost of approximately $US 10,000 per baby gave an estimated annual total cost in the United States of more than $5 billion in 1990 (Morrison 1990). The mean cost to provide care for a premature infant from admission to discharge from the newborn intensive care unit was between $20,000 and $100,000 per infant, rising to $140,000 for those weighing less than 1000 gm. Infants with severe disability can have long-term care costs estimated to be more than $100,000 and lifetime custodial care as much as $450,000 (Morrison 1990).

Preterm labour and birth are the endpoints of a final common pathway. There may be diverse methods of activating this pathway, including impaired placentation, infection and polyhydramnios. Highly effective interventions to prevent preterm labour and birth may await better understanding at an epidemiological, cellular

and molecular level of the diverse triggers of the final common pathway.

Although little progress has been made over the last two decades in reducing the incidence of preterm labour, short-term prolongation of pregnancy allows maternal corticosteroid administration to promote maturation of fetal lungs and other organs (Crowley 1996) and maternal transfer before birth to a centre that can provide appropriate neonatal special or intensive care (Powell 1995). Short-term tocolytic therapy is commonly used to inhibit preterm labour and postpone preterm birth. Maintenance tocolytic therapy, used to prevent recurrence of preterm labour after an initial course of successful treatment, has not been shown to improve perinatal outcomes or effectively prolong pregnancy and is not widely used (Sanchez-Ramos 1999). The role of maintenance therapy for women following threatened preterm labour is not addressed in this review.

A range of tocolytic agents have been used to inhibit preterm labour and postpone preterm birth (and are the topics of Cochrane systematic reviews) including, nitric oxide donors (glyceryl trinitrate) (Duckitt 2002), calcium channel blockers (commonly nifedipine) (King 2003), betamimetics (Anotayanonth 2004), magnesium sulphate (Crowther 2002), cyclo-oxygenase (COX) inhibitors (King 2005) and oxytocin receptor antagonists.

Magnesium sulphate as a tocolytic agent is ineffective in delaying or preventing preterm birth and is associated with increased infant mortality (Crowther 2002). The tocolytic agents that have been most thoroughly evaluated are the betamimetics (ritodrine, salbutamol and terbutaline). These are effective in delaying delivery for up to 48 hours (Anotayanonth 2004), although no impact has been shown on perinatal mortality or morbidity (Anotayanonth 2004; Gyetvai 1999; King 1988). Betamimetic drugs may cause unpleasant, sometimes severe maternal side-effects including tachycardia, hypotension, tremor, anxiety and a range of biochemical disturbances. Betamimetic treatment has been reported to have caused maternal death from pulmonary edema (Keirse 1989). There is therefore a need for an effective tocolytic agent with fewer maternal side-effects than the betamimetic agents and good fetal safety profile and that allows prolongation of pregnancy sufficient to allow important reduction in perinatal morbidity and mortality. In a recent Cochrane review, calcium channel blockers have been suggested as safe and marginally more effective when compared to betamimetics with a lower incidence of maternal adverse side-effects and lower neonatal morbidity (King 2003).

Cyclo-oxygenase (COX)inhibitors as a tocolytic agent are easily administered (orally or rectally) and have fewer maternal side-effects compared with betamimetics. Some observational studies have raised concerns about increased adverse fetal/neonatal effects including oligohydramnios, renal failure, and premature closure of the ductus arteriosus, neonatal persistent patent ductus arteriosus, necrotising enterocolitis, and intraventricular haemorrhage, but a recent Cochrane review concluded that there is not enough information to substantiate or refute these findings (King 2005).

Unlike other tocolytic agents, oxytocin receptor antagonists have been developed specifically as tocolytics. Oxytocin receptor antagonists block oxytocin receptors in the myometrium, preventing a rise in intracellular calcium and thereby relaxing the myometrium (Melin 1994). Atosiban is an oxytocin receptor antagonist specifically developed for the treatment of preterm labour (Melin 1994). Early reports of the use of atosiban as a tocolytic agent, both in vitro and in animal studies were promising, and preliminary studies in pregnant and non-pregnant humans have suggested a very low incidence of maternal side-effects (Goodwin 1996a; Goodwin 1998). Potential maternal side-effects are relatively moderate: adverse injection side reaction, nausea, vomiting, headache, chest pain and hypotension (Moutquin 2000).

A recent review suggested that oxytocin antagonists could be effective and safe in preterm labour (Coomarasamy 2002). This systematic review examines the role of oxytocin receptor antagonists in the management of women in preterm labour to assist clinicians and women in informed decision making.

OBJECTIVES

Primary objectives of the review

(1) To assess the effects on maternal, fetal and neonatal outcomes of any oxytocin receptor antagonist administered as a tocolytic agent to women in preterm labour when compared with either placebo or no intervention.

(2) To assess the effects on maternal, fetal and neonatal outcomes of any oxytocin receptor antagonist administered as a tocolytic agent to women in preterm labour when compared with any other tocolytic agent.

Secondary objective

A secondary objective of the review is to determine whether the effects of oxytocin receptor antagonists, when compared with no tocolytic or any other tocolytic agent, are influenced by different population characteristics and duration of tocolytic therapy as follows:

(i) women randomised before 28 weeks' gestation versus those randomised at 28 weeks or after;

(ii) women with ruptured membranes at randomisation versus women with intact membranes;

(iii) women with a singleton pregnancy versus women with a multiple pregnancy;

(iv) women who received maintenance therapy* versus women who did not

(*use of continued tocolytic agents after successful suppression of threatened preterm labour).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All published and unpublished randomised trials in which oxytocin receptor antagonists were used for tocolysis in the management of women in preterm labour. Trials which employed quasi-random methods of treatment allocation were excluded.

Types of participants

Women assessed as being in preterm labour (between 20 and 36 weeks) and considered suitable for tocolysis.

For the purposes of the review, preterm labour was defined as the presence of regular uterine contractions (with intact or ruptured membranes) with or without cervical dilatation.

Types of intervention

Oxytocin receptor antagonists administered as a tocolytic by any route, compared with either placebo, no treatment or alternative tocolytic therapy.

Types of outcome measures

Predefined clinical outcome measures relating to the prolongation of pregnancy, infant morbidity and mortality and maternal side-effects.

Primary outcome
Short-term and long-term serious infant outcome determined by the presence of any of the following: death or chronic lung disease (need for supplemental oxygen therapy at 36 weeks' postmenstrual age); grade three or four intraventricular haemorrhage or periventricular leukomalacia; major sensorineural disability at two years of age defined as any one or more of the following: severe or profound vision impairment, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy or developmental delay/intellectual impairment (defined as developmental quotient or intelligence quotient more than two standard deviations below the mean).

Secondary outcomes
These include other measures of effectiveness, complications and health service use.

Maternal
Serious maternal outcomes (defined as death, cardiac arrest, respiratory arrest, admission to intensive care unit)
Adverse drug reaction
Discontinuation of therapy because of maternal side-effects
Caesarean section birth
Antepartum haemorrhage
Postpartum haemorrhage
Length of hospital stay
Satisfaction with treatment
Quality of life at 12 to 24 months after the birth (measured by validated instruments)

Infant/child
Birth before 28 completed weeks (28 + 0 days; 196 days)
Birth before 34 completed weeks (34 + 0 days; 238 days)
Birth before 37 completed weeks (37 + 0 days; 259 days)
Preterm neonate delivered with full course of antenatal steroids completed at least 12 hours before birth
Birth less than 48 hours after trial entry
Pregnancy prolongation (interval between randomisation and birth)
Gestation at birth
Birthweight
Apgar score less than seven at five minutes
Respiratory distress syndrome
Use of mechanical ventilation
Duration of mechanical ventilation
Persistent pulmonary hypertension of the neonate
Intraventricular haemorrhage
Intraventricular haemorrhage - grade three or four
Periventricular leukomalacia
Chronic lung disease
Necrotising enterocolitis
Retinopathy of prematurity
Neonatal jaundice
Neonatal sepsis
Fetal death
Neonatal death
Perinatal mortality
Infant death

Health service use
Admission to neonatal intensive care unit
Neonatal length of hospital stay

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (September 2004).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. hand searches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we conducted a search of the following electronic databases: CENTRAL (Issue 3, 2004) and MEDLINE (1966 to June 2004) using the MeSH term: oxytocin receptors; and EMBASE (1988 to June 2004) using the keywords: oxytocin antagonists, oxytocin receptors, and atosiban. We used text terms: atosiban, oxytocin antagonists, oxytocin receptor antagonists, oxytocin inhibitors, oxytocin receptor blockade, and antocin in conjunction with the above terms for each database.

We sought ongoing and unpublished trials by contacting experts in the field.

METHODS OF THE REVIEW

We used the standard methods of the Cochrane Collaboration as described in the Cochrane Reviewers' Handbook (Alderson 2004a). Two review authors (Vicki Flenady, Dimitri Papatsonis) considered trials for inclusion, evaluated methodological quality and extracted trial data independently. We resolved differences in interpretation by discussion. Where necessary, we contacted investigators of identified trials for additional information or data. We contacted the authors of seven trials for additional outcome data (Al-Omari 2004; Anonymous 2004; European 2001; French/ Austr. 2001; Goodwin 1994; Renzo 2003; Romero 2000), and at the time of this review we received additional data for two trials (European 2001; Goodwin 1994). When there was consensus about the additional data received from the original authors, we included these data in the analysis; when there was no consensus among the review authors or the data were incomplete, we asked the original authors again for additional data or comments.

Quality assessment

We conducted quality assessment according to the methods described in Section six of the Cochrane Reviewers' Handbook (Alderson 2004b). We considered four major sources of potential bias and methods of avoidance of these biases when assessing trial quality: (1) selection bias - blinding of randomisation; (2) performance bias - blinding of intervention; (3) attrition bias - complete follow up; (4) detection bias - blinding of outcome assessment. We assigned a quality rating to each trial for the criterion of blinding of randomisation as follows: (A) adequate, (B) unclear, (C) inadequate, or (D) not used. We assigned a quality rating of (A) yes, (B) cannot tell, or (C) no, to the other quality components (blinding of intervention, completeness of follow up and blinding of outcome assessment). High-quality trials were defined as those receiving an A rating for blinding of randomisation (central computerised randomisation service or sealed opaque envelopes) and for blinding of the intervention (use of a placebo). The quality assessment rating included in the table of 'Characteristics of Included Studies' refers to blinding of randomisation in the studies.

Data collection and analysis

We conducted data management and analysis using the Review Manager software (RevMan 2003) (method of data extraction is described above). For individual trials mean differences (and 95% confidence intervals), where possible, were reported for continuous variables. For continuous variables we have, where possible, reported mean differences (and 95% confidence intervals) for individual trials. For categorical outcomes, we reported the relative risk and risk difference (and 95% confidence intervals).

One trial (Goodwin 1996a) randomised women to one of five groups: four atosiban groups of different dosing regimens and one ritodrine group. For the meta-analysis we combined the four atosiban treatment arms.

Where more than 20% of outcomes for participants were missing, data were not included in the review. This applied to the only trial which reported longer term infant outcomes (Romero 2000), where data on neurodevelopmental outcome at one and two years were excluded due to a 35% and 45% loss to follow up respectively. However, data on infant death (to 12 months of age) reported in this trial were included in the review, as the follow up appeared to be complete.

We conducted meta-analysis using the fixed-effect model. We assessed heterogeneity by visual inspection of the outcomes tables and by using two statistics (H and I^2 test) of heterogeneity (Higgins 2002).

Using a fixed-effect model, statistical heterogeneity was evident for three non-statistically significant outcomes in the comparison of atosiban versus betamimetics. These were birthweight, respiratory distress syndrome and admission to neonatal intensive care unit. Use of a random-effects model for these outcomes did not alter our interpretation of the results. On visual inspection of the graphs and through sensitivity analyses, we identified one trial (Moutquin 2000) as an outlier for all of these outcomes. A possible explanation could be, as the authors of the trial stated themselves, that more women with a multiple pregnancy were randomised to the atosiban group. Although, there was no difference in the mean gestational age at entry into the trial or the mean gestational age at delivery between the two groups in this trial or when compared to the other trials, multiple gestation could have independently affected these outcomes. It is unclear why there was an imbalance in randomisation for multiple gestations in this study.

Due to insufficient data, planned subgroup analyses by population characteristics, tocolytic regimens that include use of maintenance therapy, and oxytocin receptor antagonist compared with calcium channel blockers were not undertaken.

DESCRIPTION OF STUDIES

Twenty-three publications of trials were identified as potentially eligible for inclusion in this review. Three trials with four reports (one duplicate publication) were excluded (Gagnon 1998; Valenzuela 1997; Valenzuela 2000). Two trials were excluded as they addressed only maintenance tocolytic therapy (Gagnon 1998; Valenzuela 2000), and the third trial was excluded as the purpose of the trial was to measure estradiol levels before and after treatment with atosiban and not tocolytic effectiveness (Valenzuela 1997). Three trials are awaiting classification, pending further information from the authors (Al-Omari 2004; Anonymous 2004; Renzo 2003). Therefore, this review includes six trials (with a total of 16 publications) testing the effects of oxytocin receptor antagonists for tocolysis in preterm labour. All six trials used the oxytocin receptor antagonist atosiban.

Included studies

A total of 1695 women participated in the six included trials comparing oxytocin antagonists with placebo or betamimetic agents for preterm labour (European 2001; French/Austr. 2001; Goodwin 1994; Goodwin 1996a; Moutquin 2000; Romero 2000). There were two studies including 651 women comparing oxytocin antagonists with placebo (Goodwin 1994; Romero 2000). There were four studies, including 1044 women, comparing oxytocin antagonist with betamimetic agents (European 2001; French/Austr. 2001; Goodwin 1996a; Moutquin 2000). Long-term follow-up data for one trial (Romero 2000) were reported in another publication (Goodwin 1998a).

Participants

The participants in these trials were reasonably homogenous. In the placebo controlled trials the minimal gestational age at inclusion was 20 weeks, and the maximum ranged from 33 to 35 weeks. In the trials comparing atosiban with betamimetic agents the minimum gestational age at study entry ranged from 20 to 23 weeks, and the maximum from 33 to 35 weeks. The presence of ruptured membranes was an exclusion criterion in all trials. Exclusion of women with ruptured membranes reflects the clinical uncertainty about the role of tocolytic agents in this situation because infection is more likely to be present and delay in delivery may harm the mother and baby. In all studies, standard maternal and fetal contraindications to tocolysis were reported, i.e., pre-eclampsia, and gestational hypertension. Exclusion criteria also included the use of non-steroidal anti-inflammatory agents 12 hours prior to randomisation in three studies (European 2001; French/Austr. 2001; Moutquin 2000), and prior tocolytic therapy within 72 hours in one study (Goodwin 1996a). High order multiple gestations (triplets or more) were excluded in three studies (European 2001; French/Austr. 2001; Moutquin 2000) and all multiple pregnancies were excluded in one study (Goodwin 1996a).

Tocolysis

Two trials compared atosiban with placebo (Goodwin 1994; Romero 2000) and four trials compared atosiban with betamimetics (salbutamol, terbutaline, ritodrine) (European 2001; French/Austr. 2001; Goodwin 1996a; Moutquin 2000). In one placebo controlled trial (Romero 2000), initial tocolytic therapy with atosiban was started with a bolus of 6.75 mg intravenously (i.v.) followed by an infusion ranging from 100 to 300 μg/min to a maximum duration of 48 hours. The other placebo controlled trial (Goodwin 1994) gave an i.v. infusion of atosiban 300 μg/min for two hours.

Both placebo controlled trials included rescue tocolysis as a part of the study protocol. In the Goodwin trial (Goodwin 1994) the primary aim was to determine the effect of atosiban on uterine activity during an infusion limited to two hours. In the atosiban group 19.6% of the participants required an additional rescue tocolytic agent versus 32% in the placebo group. In this trial (Goodwin 1994) maintenance therapy after the two hour infusion was not instituted. In the Goodwin trial (Goodwin 1994), of the 120 women enrolled, twenty-nine (11 atosiban and 18 placebo) required additional tocolysis with magnesium sulfate (n = 23) or subcutaneous terbutaline (n = 6). There is, however, no description of the doses or duration of this additional tocolysis. In the Romero study (Romero 2000) rescue therapy was given in 42% of the atosiban group and in 51% of the placebo group. Participants received rescue tocolytic therapy with an alternate tocolytic of the investigator's choice after discontinuation of the study drug. Rescue tocolysis was considered in this study when preterm labour has progressed after at least one hour of observation and either of the following occurred: (1) cervical effacement of $\geq$ 75% ($\leq$ 0.5 cm) with no decrease in the frequency or intensity of contractions and continued cervical change (at least a 1 cm change in dilatation or effacement); or (2) cervical dilatation of $\geq$ 4 cm with a 1 cm increase since the last cervical examination. Maintenance therapy was started with either atosiban or placebo in women who achieved uterine quiescence with a subcutaneous infusion of 0.004 ml (30 μg/min for atosiban) and was ceased at the end of the 36th week of gestation, at delivery, or if progression of labour necessitated an alternate tocolytic agent.

In the betamimetic controlled trials (European 2001; French/Austr. 2001; Goodwin 1996a; Moutquin 2000) an initial bolus of i.v. atosiban ranging from 0.6 to 6.75 mg was given, followed by a continuous infusion ranging from 30 to 300 μg/min for up to a maximum of 12 to 48 hours. One trial (Goodwin 1996a) randomised women to one of five groups: four atosiban groups of different dosing regimens and one ritodrine group. Betamimetic therapy in all of these studies was administered intravenously for a maximum of 48 hours. Rescue tocolytic therapy was reported as a part of the trial protocol for all trials in this comparison. In the European trial (European 2001) administration of an alternative tocolytic agent was dependent on both efficacy and tolerability of study medication and could be administered when there was recurrence or progression of preterm labour. In the French/Australian

trial (French/Austr. 2001) if labour was progressing or women experienced intolerable adverse effects of study drug administration, an alternative tocolytic agent could be given. There were 58% (n = 69) in the atosiban group versus 63.1% (n = 77) in the salbutamol group who needed an alternate tocolytic agent. The Goodwin trial (Goodwin 1996a) included an alternate tocolytic agent to be used when: (1) the cervix dilated 1 cm or more during therapy, (2) uterine contraction persisted at a same or higher rate, or (3) to the judgement of the investigator. In the Moutquin trial (Moutquin 2000) an alternative tocolytic agent could be given after the study treatment was stopped if labour was progressing, or if any woman had an intolerable adverse event. Maintenance therapy was used in at least one trial in this comparison (Goodwin 1996a); however, the details of the regimen were not provided. One trial reported that maintenance therapy was not a part of the study protocol (French/Austr. 2001). Whether maintenance therapy was used in the remaining two trials is not known.

Please *see* table of 'Characteristics of Included Studies' for further details.

Outcomes

All included trials reported on the important clinical outcomes of respiratory distress syndrome and maternal adverse drug reaction. The outcome of birth within 48 hours of initiation of treatment was reported in five of the six included studies and perinatal mortality in four trials. Other important outcomes were inconsistently reported including preterm birth, which was reported in only two trials and also major neonatal morbidity, which was largely not well reported across the trials. Long-term outcomes up to two years of age were reported for infants enrolled in one placebo controlled trial (Romero 2000). In this follow up, the following outcomes were assessed: (1) illness, accidents, and physical abnormalities; (2) measurements of infant weight, length, and head circumference; (3) neurological examinations; (4) Bayley II assessment of mental and motor development; and (5) infant deaths. Although the report stated all infants were followed up and infant death up to 12 months was reported, only 55% of the infants who were originally included in the study were assessed for Bayley II Mental and Motor Development Index (Mean ± SD) and neurological examination at two years.

In the Romero trial (Romero 2000) data for the outcomes of delivery within 48 hours, and 7 days were reported only for women who did not receive alternative tocolytics and therefore these data were not included in the review.

Please *see* table of 'Characteristics of included studies' for further details.

METHODOLOGICAL QUALITY

Atosiban versus placebo

The two multicentred placebo controlled trials included in this comparison (Goodwin 1994; Romero 2000) are considered to be high quality according to the review criteria. Both trials employed a blinded method of randomisation according to a computer-generated randomisation schedule using pre-numbered envelopes containing the allocation to study group provided to the pharmacist at each centre for use in a sequential order. The randomisation schedule was developed using permuted blocks. The Romero trial used blocks of six stratified by centre but not gestational age, while the Goodwin trial used permuted blocks of four (stratification was not reported). In both trials, loss to follow up was minimal (below 10%) for outcomes to the time of hospital discharge, however, due to missing data, denominators differ for some outcomes. One trial (Romero 2000), reported infant outcomes to two years of age; however, due to a high loss to follow up these data were not included in the meta-analysis.

Although the Romero trial (Romero 2000) met the review criteria for a high-quality trial there are some methodological concerns. Firstly, as mentioned previously, the trial reported outcomes for infants up to 24 months of age; however, due to the high loss to follow up of 45%, these outcome data were not included in the review. The trial also reported the outcome of infant death up to 12 months of age and, as the follow up appeared complete, these data were included. Secondly, there was an imbalance in the randomisation of women before 26 weeks' gestation at study entry between atosiban and placebo groups (24/246 (10%) versus 13/255 (5%) respectively) with fewer women in the atosiban group above 32 weeks' gestation compared with placebo (96/246 versus 116/255). The increase in fetal-neonatal deaths shown for infants in the atosiban group may be explained by this imbalance. As the method of random allocation was undertaken in a blinded fashion, the risk of bias introduced at the time of randomisation is considered to be low. It is possible that this imbalance occurred by chance alone due to the fact that randomisation was not stratified by gestational age.

In both trials rescue tocolysis was included in the protocol. The high level of rescue tocolysis used in both arms of both trials may have confounded the estimation of the true effects of atosiban when compared with placebo (please *see* 'Description of studies' for further details).

Atosiban versus betamimetics

Three of the four trials in this comparison were considered to be of high quality (European 2001; French/Austr. 2001; Moutquin 2000). One trial (Goodwin 1996a) was not considered high quality as blinding of the intervention was not undertaken. In the Goodwin trial (Goodwin 1996a) there were five treatment arms: four different intravenous atosiban treatments which were blinded for the dose of atosiban, and one ritodrine arm which was not blinded.

All trials employed a blinded method of randomisation according to computer-generated random numbers table stratified by centre

alone in one trial (Goodwin 1996a) and by centre and gestational age in the remaining three trials (European 2001; French/Austr. 2001; Moutquin 2000). In two studies, randomisation was carried out with pre-randomised boxes labelled with country code and case number (European 2001; French/Austr. 2001). One study reported using sealed opaque envelopes (Goodwin 1996a). One study used computer-generated block randomisation (Moutquin 2000). Losses to follow up were minimal in all included trials (less than 10%).

For further details *see* table 'Characteristics of included studies'.

RESULTS

This review included six trials with a total of 1695 women. There were two trials including 651 women where atosiban was compared with placebo (Goodwin 1994; Romero 2000) and four trials including 1044 women where atosiban was compared with betamimetics (European 2001; French/Austr. 2001; Goodwin 1996a; Moutquin 2000).

Atosiban compared with placebo

When compared with placebo, atosiban resulted in lower birthweight (weighted mean difference -138.31 gm 95% confidence interval (CI) -248.76 to -27.86, two trials 692 infants); an increase in infant deaths at 12 months of age (relative risk (RR) 6.15; 95% CI 1.39 to 27.22, one trial of 583 infants); and an increase in maternal adverse drug reaction (RR 4.02; 95% CI 2.05 to 7.85, two trials of 613 women). As mentioned in the 'Methodological quality', it is likely that some of these differences can be attributed to an imbalance in randomisation which resulted in more women under 26 weeks' gestation and fewer over 32 weeks assigned to the atosiban group. Women in the atosiban group had more preterm births under 37 weeks (58% versus 51%), and under 28 weeks (27% versus 12%) but this increase was not statistically significant. No other differences were shown in any other reported maternal or neonatal outcomes.

Long-term follow-up data of infants from one trial (Romero 2000) were reported as an abstract in a poster presentation (Goodwin 1998a). The results demonstrated that, when compared with placebo, infants of mothers who received atosiban had similar outcomes at 6, 12, and 24 months as measured by the Bayley II Mental Development Index (SD). The reported results of the assessments at 12 and 24 months are as follows: Bayley II Mental Development Index mean (SD) for atosiban and placebo respectively: 12 months 95 (15) versus 97 (14) and at 24 months 84 (19) versus 89 (18); Motor Development Index: 12 months; 94 (18) versus 95 (16) and at 24 months 93 (17) versus 94 (16). However, the number of infants who were lost to follow up for the neurodevelopmental assessment increased over time from 35% at 12 months to 45% at 24 months. With such a high loss to follow up, these results should be interpreted with caution. No clear explanation was given for the losses. Two post-hospital discharge deaths within 12 months of age were also reported for the atosiban group (one from asphyxia at five months and one ascribed to sudden infant death syndrome at eight months).

Atosiban compared with betamimetics

More atosiban exposed infants had birthweights under 1500 gm than infants exposed to betamimetics (RR 1.96; 95% CI 1.15 to 3.35, 2 trials of 575 infants). However, neither neonatal mortality nor measures of neonatal morbidity differed. Atosiban was associated with a significant reduction in maternal drug reactions requiring cessation of treatment (RR 0.04; 95% CI 0.02 to 0.11, 4 trials and 1034 women). This result gives a number need to treat of 6; 95% CI 5 to 7. In other words, on average, one additional adverse drug reaction requiring cessation of treatment will be prevented for every six women who receive atosiban instead of betamimetics. No other differences were demonstrated for reported maternal, fetal or neonatal outcomes.

The planned subgroup analyses were not undertaken due to insufficient data .

DISCUSSION

In this review atosiban was shown to have similar tocolytic efficacy to betamimetics and placebo. Perinatal outcome for atosiban compared with placebo was similar except for mean birthweight and maternal side-effects requiring cessation of treatment which favoured the placebo. Compared with placebo, data from one trial (Romero 2000) showed more neonatal deaths. This increase reached statistical significance when deaths to 12 months were considered. Neurological follow-up data from this trial showed no difference between the atosiban and placebo group at the age of six months, one year, and two years of age. However, this result should be interpreted with caution due to the potential for bias resulting from high loss to follow up.

The most likely explanation for the increase in adverse infant outcome in the atosiban group could be the imbalance in allocation of women with threatened preterm labour in very early gestation (under 26 weeks) with significantly more women in this subgroup being allocated to the atosiban group. Another explanation, which was suggested by the US Food and Drug Administration (FDA), is that there could be a fetal vasopressin receptor blockade by atosiban which could give changes in maternal amniotic fluid volume, with resultant alterations to fetal renal development, and secondary alterations to fetal lung development (FDAa 1998). A similar increase in adverse events among infants exposed to atosiban was reported to the FDA for one trial of maintenance therapy (Valenzuela 2000) comparing placebo and atosiban (FDAb 1998).

There is a possibility that rescue treatment confounded the estimation of the true effects of atosiban when compared with placebo. In the trial by Romero et al (Romero 2000), rescue tocolysis was given in 43% of the atosiban group and in 51% of the placebo

group. In the other placebo controlled trial (Goodwin 1994), rescue tocolysis was used in 20% and 32% of the participants in the atosiban and placebo groups respectively after a short infusion of study medication (two hours).

When compared to betamimetics, atosiban did not prevent important perinatal outcomes such as delivery before 48 hours after initiation of treatment, respiratory distress syndrome, and admission to neonatal intensive care. However, atosiban caused fewer maternal adverse drugs reactions requiring cessation of treatment than betamimetics.

Atosiban's lack of tocolytic efficacy in these trials may relate to its mechanism of action (FDAa 1998). It interacts with oxytocic receptors in myometrial cells, the density of which is gestation dependent. It is possible that atosiban is more effective for women in preterm labour at higher gestations.

In a recent Cochrane review, calcium channel blockers have been shown to be superior to betamimetics for tocolytic efficacy and some neonatal morbidity (King 2003). To date, trials comparing atosiban with calcium channel blockers have not been undertaken. Coomarasamy et al (Coomarasamy 2003) reported an indirect comparison of randomised trials on atosiban and nifedipine and concluded that nifedipine was more effective than atosiban and lowered the incidence of respiratory distress syndrome. Nifedipine has the advantage of ease of oral administration and is very inexpensive compared with atosiban (Papatsonis 2004). However, more robust evidence from well-designed randomised trials with direct comparisons of nifedipine and atosiban are required before recommendations for clinical practice can be made. The role of COX inhibitors for preterm labour (mainly indomethacin) has also been the focus of a recent Cochrane review (King 2005) which concluded that, due to insufficient evidence, further well-designed placebo controlled trials are needed and should include comparisons with other agents and incorporate long-term follow up of infants.

In conclusion, although atosiban results in fewer and fewer maternal side-effects than betamimetics, there is no evidence of benefit for the infant when compared with betamimetics or placebo. Further well-designed trials are urgently needed. Future trials should incorporate adequate long-term infant follow up.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review do not support the superiority of atosiban over betamimetics or placebo in terms of tocolytic efficacy or infant outcomes, although atosiban has a clear advantage over betamimetics with respect to maternal side-effects profile. The higher incidence of infant deaths seen in one trial where atosiban was compared with placebo merits caution.

Implications for research

A recent Cochrane review (King 2003) showed that calcium channel blockers compared with any other tocolytic agent for the management of preterm labour have a similar tocolytic efficacy with better infant outcome and fewer maternal side-effects. There have been no controlled trials comparing placebo with calcium channel blockers.

Although both atosiban and calcium channel blockers have a better side-effect profile than betamimetics, there is no evidence that either of them are clinically superior to placebo when it comes to important perinatal outcome including long-term safety for babies. Future studies should address the possibility that different tocolytic strategies are needed at different gestational ages in order to optimise safety and efficacy. When tocolytic trials are performed in the future, adequate long-term follow up of all randomised infants is of utmost importance. A direct comparison between atosiban and calcium channel blockers is long overdue, but the current evidence makes a placebo arm in any such trial mandatory.

FEEDBACK

Goodwin, September 2005

Summary

I have a number of concerns about this review. First, the inclusion of two reports (Goodwin 1994 and Goodwin 1996a) is misleading, as neither study had delay in delivery or prolongation of pregnancy as endpoints. Information was collected on these endpoints, but the studies were not designed to demonstrate efficacy. In Goodwin 1994 the intervention was an intravenous infusion of atosiban for just 2 hours. This aim of this study was to describe the effect on uterine activity as measured by external tocodynamometry. Women were specifically chosen as having uterine activity, but unlikely to be in true preterm labor. Goodwin 1996a was a dose ranging study in which most women (3 of 4 arms) received doses far below what is currently recommended. Any effect of atosiban would therefore be underestimated. As these studies were not designed and executed as efficacy trials it seems inappropriate to use them in a discussion of efficacy.

Second, the excess perinatal mortality in Romero 2000 is overemphasized. This excess has not been seen in other trials, and had a plausible explanation based on study design. Although this is acknowledged in the review, the finding is given undo emphasis in the conclusions. The statement in the discussion that the excess mortality in Romero 2000 reachs statistical significance when the 2 infant deaths up to 12 months are included seems to rely on counting these 2 deaths between 28 days and 12 months twice.

Third, the concern about long term follow up of exposed infants, because of 45% being lost to follow up, is arbitrary. There are few precedents for attempting to follow up a cohort in which 90%

of the children are well. The only other study to attempt follow up on this scale (the Canadian Preterm Labor Investigators Trial) simply avoided the problem by selecting an available portion for follow up.

Finally, the exclusion of Romero 2000 from any discussion of efficacy (and the inappropriate inclusion of other trials - see above) is confusing. The pre-specified endpoint of delay without requirement for an alternate tocolytic (approved by the US FDA) remains the only way to describe a placebo trial in the US. To simply say that it is not included oversimplifies the complexity of studying and understanding tocolytics. It is true to say there is insufficient evidence of a tocolytic benefit, but it is an overstatement to say that there is no such evidence.

One of the main reasons I wish to comment on the review is that the acknowledgement of my assistance may give the impression that I concur with the conclusions. While I was happy to help with gathering of some information, I feel that this analysis is flawed and not up to the high standards of Cochrane Reviews.

(Summary of comment from Murphy Goodwin, September 2005)

Author's reply

To respond to these comments in the order in which they are made:

First, our pre-specified methods did not exclude studies based on either duration or dose of tocolysis. Both Goodwin 1994 and Goodwin 1996a where therefore eligible for inclusion. We disagree that trials should have been excluded if delay in delivery or prolongation of pregnancy were not primary endpoints. Also, both these studies enrolled women judged to be in preterm labour based on definitions that are consistent with those used in the other trials within the review, and that meet commonly used clinical criteria for tocolysis. Although Goodwin 1996a was a dose-finding study, three of the four treatment arms used doses that are now considered reasonable clinical regimens.

Second, we disagree that the excess in perinatal and infant mortality in Romero 2000 is overemphasized. The explanation given by the trial authors for the excess perinatal mortality is that it may have been due to an unexpected imbalance in randomization between the atosiban and placebo groups for women randomised before 26 weeks (13/255 versus 24/246). We are not aware they have published an analysis controlling for gestational age to support this explanation, however. Also, our attempts to obtain further information from the authors about possible reasons for this imbalance between the placebo and atosiban groups have been unsuccessful. In particular, it would be helpful to clarify whether this imbalance was likely to be due to chance alone, or whether there was any possibility of bias at trial entry, or an error in the randomization sequence. We do not think we have double counted any infant deaths. Romero 2000 reported 10 infant deaths in the treatment group versus 2 in the placebo group, a difference which achieves statistical significance (RR 5.12, 95% CI 1.13-23.17). Our understanding is that there were two additional deaths in the atosiban group. This is based on unpublished data in the document "Antocin Final Two-Year Infant Safety report" (issued 15 July 1999) which was initially supplied by Ferring UK to the Royal College of Obstetricians and Gynaecologist in the UK, and which Ferring later kindly agreed to share with us. This document describes 12 infant deaths plus 3 fetal deaths (total 15 deaths) in the atosiban group and 2 infant deaths plus 3 fetal deaths (total 5 deaths) in the placebo group. Thus, for infant deaths this 12 versus 2. If there is any dispute about these data it would be helpful if the results of this two-year follow-up study could be presented for public scrutiny in a peer reviewed journal.

Third, high attrition is a common problem in long-term follow. It is reassuring that the losses were similar between the groups and that the majority of children were neurologically normal. Nevertheless, in the absence of any explanation for the high loss to follow up, concerns remain about potential systematic differences between the groups amongst those who were not contacted and assessed. Once again, to help allay such concerns it would be helpful if this follow-up study could be published.

Finally, the outcome measures in our review were all prespecified. Romero 2000 did not report outcome for all women who remained undelivered after 24 hours, 48 hours or 7 days. Data are only available for women who remained undelivered and did not require an additional (rescue) tocolytic drug. Data for the outcomes in our review have been requested from the trial authors, but to date have not been received.

It was not our intention to imply that Professor Goodwin agreed with our conclusions. We remain grateful for his help in supplying additional data, and agree that such assistance in no way implies concurrence with our conclusions.

(Summary of response from Dimitri Papatsonis, January 2006)

Contributors

Murphy Goodwin

Åkerlund et al, December 2005

Summary

The authors conclude that the review failed to demonstrate the superiority of atosiban over placebo or betamimetics in terms of either tocolytic efficacy or infant outcomes. We disagree with this conclusion for the following reasons:

For the comparison of atosiban with placebo
In Goodwin 1994 the decrease in uterine contractions was significantly greater with atosiban than placebo. There was a complete cessation of contractions for 25% of women receiving atosiban and 5% of women receiving placebo. Romero 2000 and Valenzuela 2000 followed different study protocols with different primary end-points, and provide data for safety analyses only.

In Romero 2000 and Valenzuela 2000 women in the placebo group were treated with bed-rest and hydration. Hydration reduces oxytocin secretion, which may have contributed to the decrease in contractions in the placebo group. Atosiban is also a vasopressin V1a receptor- inhibiting compound, more potent than an oxytocin antagonist. Vasopressin may well be involved in the aetiology of preterm labour, and its secretion may also be reduced by hydration.

For the comparison of atosiban with betamimetics
The reviewers state that atosiban is no better than other classes of drug in delaying preterm birth. However, in European 2001 atosiban was significantly better, in terms of fewer women undelivered and not requiring alternative tocolysis after 7 days of treatment, than either ritodrine, salbutamol or pooled data for three betamimetics.

For infant outcomes
In European 2001 1.2% of the infants died in the atosiban group versus 2.3% for betamimetics. There were no differences in infant deaths between atosiban and placebo in Goodwin 1994, Romero 2000 or Valenzuela 2000. The only exception to this was for infants of women randomised before 26 weeks gestation in Romero 2000.

Our main criticism of the review is that the rationale underlying the selection of trials for inclusion is unclear. For example, the reviewers included Valenzuela 2000, even though it was excluded from other perspectives. Furthermore, the studies were not designed to have infant follow up and so these data were incomplete.

Romero 2000 is included as a high-quality trial, despite an imbalance between the atosiban and placebo groups for women randomised before 26 weeks gestation. To compare tocolytic efficacy and infant outcome of these data is not relevant. That was also the attitude of authorities when atosiban was registered in European countries.

Finally, the conclusions state that calcium channel blockers are superior to betamimetics, although this comparison is not part of the review. Meta-analysis is an efficient way of providing the basis for evidence-based medicine. However, the weaknesses of this method, such as selection bias and lack of quality weighting, are well recognized (1.). This Cochrane review exemplifies the drawbacks of meta-analysis, and its limitation in yielding valid conclusions.

References
1. Spector TD, Thompson SG. The potential and limitations of meta-analysis. J Epidemiol Commun Health 1991;45:89-92

(Summary of comments from Mats Åkerlund, Karel Marsl, and Ingemar Ingemarsson, December 2005)

Author's reply

First, to clarify any misunderstanding about whether there was a rationale for the selection of trials to include in our review. The criteria used for selecting trials were described a priori in the protocol, published on The Cochrane Database of Systematic Reviews. These methods adhere to the rigorous process defined by the Cochrane Collaboration, and followed by the Cochane Pregnancy and Childbirth Group. Therefore, the threat to the internal validity of our review from bias in selection of which studies to include was minimised.

Quality weighting in a meta-analysis has not be shown empirically to impact on reliability of the summary statistic, hence why it was not done within our review

For the comparison of atosiban with placebo
We agree that Goodwin 1994 reported a cessation of contractions for 25% of women receiving atosiban compared with 5% of those receiving placebo. As this was a small study, however, these data are based on just 14 women versus 5 women who ceased contractions. Also, a more clinically important measure of tocolytic efficacy is the proportion of women who delivered within 48 hours. This outcome was not statistically significant between the groups (relative risk 2.50, 95% CI 0.51 to 12.35).

Valenzuela 2000 was excluded from the review because it evaluated maintenance tocolysis, and so did not meet our inclusion criteria.

The impact of hydration in the placebo group on any decrease in contraction is likely to be limited. The effect of atosiban and hydration on vasopressin V1a receptors is known, although its impact, if any, on preterm labour is less clear. Our view is that the overall effect of hydration on the incidence of preterm labour is limited, although hydration could lead to some reduction in oxytocin release.

Atosiban is also a vasopressin receptor antagonist. The human placenta is permeable to atosiban and the fetus has functional vasopressin receptors in the third trimester. The exact effect of fetal vasopressin receptor blockade on the fetus, following administration of atosiban, is unclear. Also unclear is whether a decrease in vasopressin due to hydration has any effect on preterm labour. For Romero 2000 this is not an issue, however, as hydration seems to have been similar in both groups.

For the comparison of atosiban with betamimetics
The conclusion that atosiban is no better than betamimetics in delaying preterm birth is based on the lack of clear benefit for atosiban on the number of infants delivered after seven days of starting treatment, or any other prespecified outcome. We did not use the composite outcome "delay in delivery and no alternate tocolytic agent". This was because the decision to start an alternative tocolytic may have been biased by awareness of the study treatment allocation, due to maternal signs and symptoms such as palpitations, flushing and tachycardia associated with betamimetics. The potential benefit of atosiban on this composite outcome measure, reported by some trials in the review, is clearly questionable as this benefit did not translate into improved outcome for the infants.

For infant outcomes

The incidence of infant deaths was similar in the trials comparing atosiban and betamimetics.

Although Romero 2000 met the criteria for inclusion in the review, we agree there were methodological concerns and these are described under 'methodological quality of included studies'. There was an imbalance between the groups in women randomised before 26 weeks' gestation (24/246 [10%] atosiban versus 13/255 [5%] placebo), with fewer women randomised after 32 weeks allocated atosiban compared with placebo (96/246 [4%] versus 116/255 [5%]). The increase in fetal-neonatal deaths in the atosiban group may, therefore, be explained by this imbalance. However, we are not aware of an analysis of infant outcome controlling for this imbalance. As the randomisation sequence was adequately concealed at trial entry, the risk of this imbalance having been due to bias seems to be low. While the reason for the imbalance remains unclear, and has not been provided by the principal investigators nor the pharmaceutical company sponsoring the trial, it is possible that it occurred by chance alone due to the fact that randomization was not stratified by gestational age.

Although some of included trials were not designed for follow-up, this is not a reason to exclude them from the analysis of short term outcomes.

When a new tocolytic drug is being developed, the question most parents are likely to want answered is whether there is any beneficial effect for the child. Trials of tocolytic drugs should be designed to establish any such effect. It is therefore surprising that the authorities in Europe did not ask for any evidence of tocolytic efficacy or benefit for the fetus before approving atosiban for use in Europe, in contrast to similar authorities in the USA who did require such evidence.

Finally, we stand by the conclusions of our systematic review that the superiority of atosiban over placebo or betamimetics was not been demonstrated, in terms of either delay in delivery or any short or longer term neonatal morbidity or mortality.

(Summary by Dimitri Papatsonis, on behalf of the review authors, May 2006)

Contributors

Mats Åkerlund, Karel Marsl, and Ingemar Ingemarsson

Thornton S et al, July 2006

Summary

We are concerned about the conclusions and implications for clinical practice in this review. In particular, (i) the trial methodology may not allow reliable evaluation of outcome; (ii) there seems undue importance attached to the risk of infant deaths in one study (Romero 2000) with imbalance at baseline, and (iii) the conclusion that calcium channel blockers are associated with a better neonatal outcome is not qualified.

First, the review acknowledges that some women in the trials of oxytocin receptor antagonists required rescue tocolysis. In practice, this means that women are randomised to treatment or comparator/placebo, and those who progress in labour are given an alternative tocolytic. This means that any women could be given an effective drug for rescue, which prevents direct comparison of outcome. It is therefore not possible to categorically say that one of the agents administered initially is superior, or inferior, to the other. The most reasonable inferences that can be drawn, in studies where co-intervention is likely to have a substantial impact on outcome, concern the effects observed under treatment combinations. The effectiveness of initial tocolytic agents alone cannot be studied. What can be studied is the effect of initial plus rescue tocolysis allowed in the care protocol. Therefore it is acknowledged that in such trials direct comparison of many (including neonatal) outcomes is inappropriate (Romero 2000). For this reason the endpoint of delay in delivery without alternate tocolytic has been used in that study. Given that it is inappropriate to compare neonatal outcomes in such trials, it is disappointing that the outcomes are given such importance in the conclusion.

Second, it is also disappointing that the abstract states Atosiban is associated with an increase in infant deaths at 12 months of age compared with placebo. As'the trial randomised more women in the Atosiban arm at very early gestational ages, this would be expected to increase mortality. Randomisation (when methodologically sound) uses a chance procedure for group allocation, which may produce imbalances in important prognostic variables at baseline by chance alone. If such differences are observed, an appropriate analysis of the trial would include statistical corrections for baseline differences to have valid results. Moreover, it is not clear why it was felt that mortality at one year should be included in the analysis when outcomes up to two years were excluded. If Atosiban were associated with an increase in mortality risk for the child, it is likely that this would have been demonstrated in the numerous other large clinical trials. As there is no increase in mortality in other trials, it is a reasonable assumption that the excess mortality in the placebo controlled trial was due to the disproportionate allocation to Atosiban at early gestational ages.

Finally, the conclusion suggests that calcium channel blockers are associated with better neonatal outcome and fewer maternal side effects than betamimetics. Although it is stated that no trials have directly compared nifedipine with placebo, it is not acknowledged that the clinical studies on calcium channel blockers were not blinded, that comparison was often with an extremely high dose of ritodrine and that these studies also often included rescue tocolysis. The conclusions regarding the possible improvement in outcome with calcium channel blockers must therefore be taken in context.

(Summary of comments from Steve Thornton, Khalid S Khan, and Patrick FW Chien, July 2006)

Potential conflict of interest: Steve Thornton provides consultancy advice for the pharmaceutical industry. Khalid Khan has a UK

NHS HTA research grant on prevention of preterm birth.

Author's reply

Responding to the comments in the order in which they were made:

First, we do not agree that the use of rescue tocolysis means direct comparison of outcome is inappropriate. We used the standard methods as described in the Cochrane Reviewers Handbook (1). The inclusion criteria, outcome measures and comparisons, as with all methods of this review, were pre-specified on the basis of ensuring that a clinically relevant "real life" question was addressed. Rescue tocolysis is a real life situation and therefore was handled in a necessarily pragmatic approach in this review. Our pre-specified methods did not exclude studies based on having an alternative (rescue) tocolytic agent. Romero 2000 (2) did report that a substantial number of women received an alternate "rescue tocolytic agent" (42% in the atosiban arm versus 51% in the placebo). However, we remain convinced that this study, and its outcomes, should be included in our review as it fulfils the inclusion criteria. We remain convinced that the pre-specified clinically important outcomes of all women undelivered after 24 hours, 48 hours or 7 days should remain. The outcome used in Romero 2000, of women who were undelivered and did not require an alternate tocolytic agent, does not reflect real life and is more susceptible to bias. Despite repeated requests to the authors of Romero 2000 for data on the outcome of delay in delivery, in a format which would enable inclusion in this review, no such data have been forthcoming.

Secondly, as discussed in an earlier response to a comment on this Cochrane review, we disagree that the excess in perinatal and neonatal mortality in Romero 2000 is overemphasized. Our view is that the data on outcome for this trial are presented and discussed appropriately. Although the trial authors stated that the excess mortality may have been attributable to an imbalance between the groups in women randomized before 26 weeks gestation. Without an analysis controlling for gestation this remains a tentative explanation. We are not aware that any such analysis has been undertaken. We have attempted on numerous occasions to obtain further information from the trial authors, but to date have been unsuccessful. As central computer randomization was used, we concluded that the imbalance was most likely due to the lack of stratification by gestational age (random error) and not bias due to flaws in the allocation concealment, and have clearly stated this in the review.

Finally, whilst we agree with Prof Thornton that there were no placebo controlled trials in the Cochrane review on calcium channel blockers compared with betamimetics, we also agree with the conclusions of the relevant review about the superiority of calcium channel blockers in terms of safety and neonatal outcomes. Blinding of studies, when comparing calcium channel blockers with betamimetics, is almost impossible because of the cardiovascular side effects of betamimetics, such as palpitations and anxiety. In these studies the additional rescue tocolysis used was comparable for the different study arms.

We are aware that because there is only indirect comparison between atosiban and nifedipine as tocolytic agents (and therefore the evidence for which of two tocolytic agents is most effective and safe is inconclusive) both tocolytic agents are currently advocated by obstetricians across several countries. Cost and mode of administration are also important considerations in the choice of tocolytic agent. We therefore believe that a well designed trial comparing oxytocin receptor antagonists and calcium channel blockers for the management of preterm labour is important in the advancement of care for women in preterm labour.

(Reply from Dimitri Papatsonis, on behalf of the review authors, August 2007)

References

(1) Cochrane Reviewers' Handbook 4.2.3 (updated November 2004). In: Alderson P, Green S, Higgins J, editors. http:/www.cochrane.org/resources/handbook/hbook.htm (accessed 20th December 2004) 2004.
(2) Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. American Journal of Obstetrics and Gynecology 2000; VL:182(5):1173-1183.

Contributors

Steve Thornton, Khalid S Khan, and Patrick FW Chien

Thornton J, July 2006

Summary

I am concerned that there is unintentional bias in favour of the use of calcium channel blockers and against oxytocin antagonists in two recent Cochrane reviews, this one and the review of calcium channel blocker trials (1).

Objective judgement of trial quality

Four studies of oxytocin antagonists (European 2001, French/Austr. 2001, Moutquin 2000, and Romero 2000) are recorded as 'Blinding outcome assessment: unknown' despite their using a double dummy technique with no mention that the blinding was broken. Another, Goodwin 1994, is classified as 'Blinding outcome assessment: no' despite the review authors correctly noting that a double dummy technique was used. The relevant section of the published paper reads as follows: "the pharmacist would open the envelope to reveal the patient's treatment assignment for the purpose of preparing the study drug infusion solution. The treatment assignment was not revealed to other persons, and the individual preparing the drug was not involved in patient care." Surely all five trials should be classified as 'Blinding outcome assessment: yes'.

Subjective judgement of trial quality
In the text of the calcium channel review (1), the trials are classified as of reasonable quality and no statement is made about quality in the abstract.

In fact none were blinded; they were all relatively small (mean group size 43) and only four had performed a sample size calculation. The lack of blinding is particularly important since all the reported outcomes favouring calcium channel blockers are susceptible to biased ascertainment, and the only hard outcome, perinatal death, showed a trend against calcium channel blockers (see below).

In contrast the oxytocin antagonist reviewers classify Goodwin 1996a as 'not high quality' because it was unblinded.

Choice of outcomes to report in the abstract
The calcium channel review (1) abstract finds space to report seven beneficial effects of calcium channel blockers on surrogate outcomes, either prolongation of labour or surrogate fetal outcomes, but fails to mention perinatal deaths which had a relative risk 1.65 (95% CI 0.74-3.64) favouring other tocolytics. Nor are total pregnancy losses mentioned. These would include the four neonatal deaths reported by Koks 1993 in a ratio of 3:1 against calcium channel blockers.

In the oxytocin antagonist review abstract, five unfavourable conclusions against placebo are reported. Although all of them might be explained by the gestational age imbalance at trial entry in the relevant trial (Romero 2000), this qualification is only mentioned in relation to one, infant death, and is removed from the synopsis where the association is repeated. In the comparison with beta-mimetics, the first outcome reported is birth weight under 1,500g, an outcome which was not pre-specified in the review methods and which is the only statistically significant outcome out of 21 reported for this comparison. Only later is the reduction in adverse drug reactions compared to beta-mimetics reported.

Choice of language
In the review of calcium channel blockers (1), all of the seven sentences in the abstract conclusions and the plain language summary contain a favourable opinion of calcium channel blockers. The single exception is a call for research into the effect of different dosing regimes, with the implication that the primary effectiveness question has been answered.

The authors' conclude: "it is considered unlikely that [placebo controlled trials of calcium
channel blockers] will be conducted given the unequivocal impact that this method of tocolysis has on short term postponement of delivery" This statement is much too strong. It is based entirely on unblended trials against other tocolytics. Two of the five relevant outcomes (birth prior to 37 weeks, and birth within 48 hours) showed only a non-significant
effect, two (birth prior to 34 weeks and within seven days) just reached the 0.05 level, and the final outcome (pregnancy prolongation in days), while statistically significant, shows significant heterogeneity between trials.

In neither the abstract nor the conclusion section of the calcium channel blocker review is it mentioned that there have been no placebo-controlled trials of calcium channel blockers in preterm labour.

In contrast, instead of saying that oxytocin antagonists had shown equivalent efficacy to other tocolytics in four high quality trials, the authors phrase their summaries as either 'has failed to demonstrate superiority' or 'is no better than other drugs'. This seems gratuitous negativity.

Choice of outcomes to report
The outcomes selected for the oxytocin review differ significantly from those chosen for the calcium channel blocker review. The reason is not clear.

Finally, the oxytocin antagonist review claims to be going to look at predefined outcomes measured related to the prolongation of pregnancy. However the predefined outcomes for the two placebo-controlled trials, namely 'time to delivery' or 'therapeutic failure' were not reported.

Authorship of the reviews
I note that both these reviews share an author, Dimitri Papatsonis, who is the first author of the largest trial of calcium channel blockers, upon which many of the favourable calcium channel blocker meta analyses depend.

I recognise that it is probably impossible to always avoid using trial authors to write systematic reviews, and that Dr Papatsonis acknowledges his possible conflict of interest. Nor do I accuse him, or any of the review authors, of any intentional bias. Nevertheless, I am concerned about possible unintentional bias against commercially developed pharmacological agents. This risks harming the future development of drugs for use in pregnancy, something which I am sure everyone would support.

Conflict of Interest
I have acted as advisor to Ferring and when I was editor of BJOG the journal received sponsorship from Ferring to publish supplements.

Jim Thornton, July 2006

References
(1) King JF, Flenady VJ, Papatsonis DNM, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD002255. DOI: 10.1002/14651858.CD002255.

Author's reply

A response from the authors will be published as soon as it is available.

Contributors

Jim Thornton

POTENTIAL CONFLICT OF INTEREST

Dimitri Papatsonis is the first author on a completed multicentre trial of nifedipine tocolysis. Vicki Flenady and Dimitri Papatsonis are authors on a Cochrane review titled 'Calcium channel blockers for inhibiting preterm birth' (King 2003). Vicki Flenady and Stephen Cole are authors on a Cochrane review titled 'Cyclo-oxygenase (COX) inhibitors for treating preterm labour' (King 2005).

ACKNOWLEDGEMENTS

We would like to acknowledge Drs K Marsal, and TM Goodwin for providing additional data for this review. We thank James King for assistance with the development of the protocol and Katie Welsh for assistance with reference management.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

SOURCES OF SUPPORT

External sources of support

- Department of Health and Ageing, Commonwealth Government, Canberra AUSTRALIA

Internal sources of support

- Centre for Clinical Studies - Women's and Children's Health, Mater Hospital, South Brisbane, Queensland AUSTRALIA
- Division of Obstetrics and Gynaecology, John Hunter Hospital, New South Wales AUSTRALIA
- Department of Obstetrics and Gynaecology, Amphia Hospital Breda, Breda, Netherlands NETHERLANDS
- Department of Neonatology, Mater Mothers' Hospital, South Brisbane, Queensland AUSTRALIA

REFERENCES

References to studies included in this review

European 2001 *{published data only}*

* The European Atosiban Study Group. The oxytocin antagonist atosiban versus the ß-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstetricia et Gynecologica Scandinavica* 2001;**80**:413–22.

The Worldwide Atosiban versus Beta-antagonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *BJOG: an international journal of obstetrics and gynaecology* 2001;**108**:133–42.

French/Austr. 2001 *{published data only}*

* French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *European Journal Obstetrics, Gynecology and Reproductive Biology* 2001;**98**:177–85.

The Worldwide Atosiban versus Beta-antagonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *BJOG: an international journal of obstetrics and gynaecology* 2001;**108**:133–42.

Goodwin 1994 *{published data only}*

* Goodwin TM, Paul R, Silver H, Spellacy W, Parsons M, Chez R, et al. The effect of the oxytocin antagonist atosiban on preterm uterine activity in the human. *American Journal of Obstetrics and Gynecology* 1994;**170**:474–8.

Goodwin TM, Paul RH, Silver H, Parsons M, Chez R, Spellacy W, et al. Safety and efficacy of the oxytocin antagonist atosiban in threatened preterm labor: initial US trial. *American Journal of Obstetrics and Gynecology* 1992;**166**:359.

Goodwin 1996 *{published data only}*

Goodwin TM, Valenzuela GJ, Silver H, Creasy G, Atosiban Study Group. Dose ranging study of the oxytocin antagonist atosiban in the treatment of preterm labor. *Obstetrics & Gynecology* 1996;**88**:332–6.

Moutquin 2000 *{published data only}*

Moutquin J, Rabinovici J. Comparison of atosiban versus ritodrine in the treatment of pre-term labour. *Acta Obstetrica et Gynecologica Scandinavica* 1997;**76**(167):33.

* Moutquin JM, Sherman D, Cohen H, Mohide PT, Hochner-Celnikier D, Fejgin M, et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *American Journal of Obstetrics and Gynecology* 2000;**182**(5):1191–9.

Romero 2000 *{published data only}*

Goodwin TM. 1st International preterm labour congress. Strategies to prevent the morbidity and mortality associated with prematurity; 2002 June 27-30. Le Montreux Palace, Montreux Switzerland. 2002.

Goodwin TM. Long-term safety with oxytocin antagonists. 4th World Congress on Controversies in Obstetrics, Gynecology and Infertility; 2003 April 24-27; Berlin, Germany. 2003:291.

Goodwin TM, Randall H, Perry K, Menard MK, Bauer C, Shangold G, et al. A report on infant outcomes at 6 and 12 months after the use of atosiban in the management of preterm labor. 46th ACOG annual meeting; 1998 May 9-13; New Orleans, Louisiana. 1998.

Goodwin TM, Randall H, Perry K, Menard MK, Bauer C, Shangold G, et al. A report on infant outcomes up to 24 months after the use of atosiban in the management of preterm labor. 46th ACOG annual meeting; 1998 May 9-13; New Orleans, Louisiana. 1998.

* Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *American Journal of Obstetrics and Gynecology* 2000;**182**(5):1173–83.

Sibai B, Romero R, Sanchex-Ramos L, Valenzuela G, Veille J, Tabor B, et al. A double-blind placebo-controlled trial of an oxytocin-receptor antagonist (antocin) in the treatment of preterm labor. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S2.

Silver H, Valenzuela G, Sanchez-Ramos L, Romero R, Sibai B, Goodwin T, et al. Maternal side effects and safety of the oxytocin receptor antagonist antocin. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S45.

References to studies excluded from this review

Gagnon 1998

Gagnon D, Martens L, Creasy G, Henke C. An economic analysis of atosiban maintenance therapy in preterm labor. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S181.

Valenzuela 1997

Valenzuela G, Diaz A, Germain A, Foster T, Hayashi R, Seron-Ferre M. Estradiol levels are increased before and after preterm labor treatment with an oxytocin (OT) antagonist: evidence for chronic activation of the mechanism of labor. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):88.

Valenzuela 2000

Sanchez-Ramos L, Valenzuela G, Romero R, Silver H, Koltun W, Millar L, et al. A double-blind placebo-controlled trial of oxytocin receptor antagonist (antocin) maintenance therapy in patients with preterm labor. *American Journal of Obstetrics and Gynecology* 1997; **176**(1 Pt 2):S30.

* Valenzuela GJ, Sanchez-Ramos L, Romero R, Silver HM, Koltun WD, Millar L, et al. Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. The atosiban ptl-098 study group. *American Journal of Obstetrics and Gynecology* 2000;**182**(5):1184–90.

References to studies awaiting assessment

Al-Omari 2004

Al-Omari WR. Atosiban and nifedipine in acute tocolysis, comparative study [abstract]. XVIII European Congress of Obstetrics and Gynaecology; 2004 May 12-15; Athens, Greece. 2004:103.

Anonymous 2004

Anonymous. TREASURE (Tractocile efficacy assessment survey in Europe). Trial to commence in July. http://www.ferring.com/; (accessed 2004 May 24).

Renzo 2003

Renzo DGC, Mignosa MM, Rosati A, Burnelli L, Epicoco G, Luzi G. Can we effectively arrest premature labour in women with multiple gestations or other high-risk factors?. 4th World Congress on Controversies in Obstetrics, Gynecology & Infertility; 2003 April 24-27; Berlin, Germany. 2003:286–90.

Additional references

Alderson 2004a

Alderson P, Green S, Higgins J, editors. Cochrane Reviewers' Handbook 4.2.3 [Updated November 2004]. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 20th December 2004).

Alderson 2004b

Alderson P, Green S, Higgins J, editors. Assessment of study quality. In: Cochrane Reviewers' Handbook 4.2.3 [Updated November 2004]; Section 6. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 20th December 2004).

Anotayanonth 2004

Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD004352. DOI: 10.1002/14651858.CD004352.pub2.

Berkowitz 1993

Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiologic Reviews* 1993;**15**(2):414–43.

Coomarasamy 2002

Coomarasamy A, Knox EM, Gee H, Khan KS. Oxytocin antagonists for tocolysis in preterm labour. *Medical Science Monitor* 2002;**8(11)**: RA268–73.

Coomarasamy 2003

Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour: a meta-analysis with an indirect comparison of randomised trials. *BJOG: an international journal of obstetrics and gynaecology* 2003;**110**:1045–9.

Costeloe 2000

Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The Epicure study: outcomes to discharge from infants born at the threshold of viability. *Pediatrics* 2000;**106**:659–71.

Crowley 1996

Crowley P. Prophylactic corticosteroids for preterm birth. *Cochrane Database of Systematic Reviews* 1996, Issue 2. Art. No.: CD000065. DOI:10.1002/14651858.CD000065.pub2.

Crowther 2002

Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD001060. DOI: 10.1002/14651858.CD001060.

De L Costello 2003

De L Costello AM, Osrin D. Micronutrient status during pregnancy and outcomes for newborn infants in developing countries. *Journal of Nutrition* 2003;**133**:1757–64S.

Duckitt 2002

Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No.: CD002860. DOI:10.1002/14651858.CD002860.

FDAa 1998

Advisory Committee for Reproductive Health Drugs. Issue-NDA 20-797 Antocin, (atosiban injection) for use in the management of preterm labor. Centre for Drug Evaluation and Research, Food and Drug Administration. Gaithersburg, Maryland April 20 1998:83–5.

FDAb 1998
Advisory Committee for Reproductive Health Drugs. Issue-NDA 20-797 Antocin, (atosiban injection) for use in the management of preterm labor. Centre for Drug Evaluation and Research, Food and Drug Administration. Gaithersburg, Maryland April 20 1998:81.

Goodwin 1996a
Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban. *American Journal of Perinatology* 1996;**13**(3):143–6.

Goodwin 1998
Goodwin TM, Zograbyan A. Oxytocin receptor antagonists. Update. *Clinics in Perinatology* 1998;**25**(4):859–71.

Goodwin 1998a
Goodwin TM, Randall H, Perry K, Menard MK, Bauer C, Shangold G, et al. A report on infant outcomes up to 24 months of age after the use of atosiban in the management of preterm labour. 46th ACOG annual meeting; 1998 May 9-13; New Orleans, Louisiana. 1998.

Gyetvai 1999
Gyetvai K, Hannah M, Hodnett E, Ohlsson A. Tocolysis for preterm labor: a systematic review. *Obstetrics & Gynecology* 1999;**94**(5):869–77.

Hack 1999
Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. *Early Human Development* 1999;**53**(3):193–218.

Hall 1997
Hall M, Danielian P, Lamont RF. The importance of preterm birth. In: ElderMG, RomeroR, LamontRF editor(s). *Preterm labour*. Edinburgh: Churchill Livingstone, 1997:1–28.

Higgins 2002
Higgins J, Thompson S. Quantifying heterogeneity in meta-analysis. *Statistics in Medicine* 2002;**21**:1559–74.

Keirse 1989
Keirse MJNC, Grant A, King JF. Preterm labour. In: ChalmersI, EnkinM, KeirseMJNC editor(s). *Effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1989:694–745.

King 1988
King JF, Grant A, Keirse MJNC, Chalmers I. Beta-mimetics in preterm labour: an overview of the randomized controlled trials. *British Journal of Obstetrics and Gynaecology* 1988;**95**:211–22.

King 2003
King JF, Flenady V, Papatsonis DNM, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002255. DOI:10.1002/14651858.CD002255.

King 2005
King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD001992. DOI: 10.1002/14651858.CD001992.pub2.

Kramer 2003a
Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. *Journal of Nutrition* 2003;**133**:1592–6S.

Kramer 2003b
Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. *JAMA* 2003;**284**:843–9.

Lemons 2001
Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the national institute of child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics* 2001;**107**:E1.

Lumley 1993
Lumley J. Epidemiology of preterm birth. *Bailliere's Clinical Obstetrics and Gynaecology* 1993;**7**:477–98.

Lumley 2003
Lumley J. Defining the problem: the epidemiology of preterm birth. *BJOG: an international journal of obstetrics and gynaecology* 2003; **110**:3–7.

McCain 1993
McCain GC, Deatrick JA. The experience of high-risk pregnancy. *Journal of Obstetric, Gynecologic and Neonatal Nursing* 1993;**23**:421–7.

Melin 1994
Melin P. Development of an oxytocin antagonist atosiban. *Research Clinical Forums* 1994;**16**:155–68.

Mercer 1996
Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, et al. The preterm prediction study: a clinical risk assessment system. *American Journal of Obstetrics and Gynecology* 1996;**174**(6):1885-93; discussion 1893-5.

Morrison 1990
Morrison JC. Preterm birth: a puzzle worth solving. *Obstetrics & Gynecology* 1990;**76**:5–12S.

Papatsonis 2004
Papatsonis DNM, Decker GA. Nifedipine in the management of preterm labour: evidence from the literature. In: CritchleyH, BennettP, ThorntonS editor(s). *Preterm Birth*. London: RCOG Press, 2004:296–307.

Powell 1995
Powell SL, Holt VL, Hickok DE, Easterling T, Connell FA. Recent changes in delivery site of low-birth-weight infants in Washington: impact on birth weight-specific mortality. *American Journal of Obstetrics and Gynecology* 1995;**173**(5):1585–92.

RevMan 2003
The Cochrane Collaboration. Review Manager (RevMan). 4.2.3 for Windows. Oxford, England: The Cochrane Collaboration, 2003.

Sanchez-Ramos 1999
Sanchez-Ramos L, Kaunitz AM, Gaudier FL, Delke I. Efficacy of maintenance therapy after acute tocolysis: a meta-analysis. *American Journal of Obstetrics and Gynecology* 1999;**181**:484–90.

Wood 2000
Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. *New England Journal of Medicine* 2000;**343**:378–84.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	European 2001
Methods	Blinding of randomisation: yes. Prepared by Ferring Pharmaceuticals: computer-generated randomisation stratified by GA and centre, supplied to pharmacists at each centre in pre-randomised boxes labelled with country code and case number. Blinding of intervention: yes. Double-dummy technique. Blinding outcome assessment: unknown. Completeness of follow up: postrandomisation exclusions 4 in the terbutaline group, 1 in the atosiban group.
Participants	249 women with preterm labour in a multicentre trial with singleton pregnancies between 23-33 completed weeks' gestation. Exclusion criteria: high-order multiple pregnancy (triplets or greater), ruptured membranes, severe pre-eclampsia/ hypertension, use of non-steroidal anti-inflammatory agents 12 hrs prior to randomisation, standard maternal or fetal contraindications to tocolysis.
Interventions	Atosiban group: initial single 6.75 mg iv bolus followed by an infusion of 300 ug/min for the first 3 hrs followed by 100 ug/min for up to 18 hrs. A placebo iv infusion of 5% dextrose was given separately but simultaneously. Terbutaline group: terbutaline was given iv in 5% dextrose at 10-25 ug/min. A placebo was given as a single bolus (0.9 ml saline) injection followed by an iv infusion of 5% dextrose. Both infusions run up to 18 hours.
Outcomes	Primary goals were the safety and effectiveness of atosiban versus terbutaline as tocolytic agents. Additional data received for the following outcomes: days of pregnancy prolongation, fetal death, maternal death, delivery before 34 weeks and delivery before 37 weeks' gestation, NEC, ROP.
Notes	Sample size calculation: a sample size of 120 women per group was calculated to achieve a power of 80%. Antenatal corticosteroids: yes. GBS protocol: not reported.
Allocation concealment	A – Adequate

Study	French/Austr. 2001
Methods	Blinding of randomisation: yes. Prepared by Ferring Pharmaceuticals: computer-generated randomisation stratified by GA and centre, supplied to pharmacists at each centre in pre-randomised boxes labelled with country code and case number. Blinding of intervention: yes. Double-dummy technique. Blinding outcome assessment: unknown. Completeness of follow up: postrandomisation exclusion 1 in the salbutamol group.
Participants	241 women with preterm labour in a multicentre trial with a gestational age 23-33 wks and intact membranes. Exclusion criteria; higher order multiple pregnancy (triplets or greater), ruptured membranes, prior to randomisation use of tocolytic agents (NSAID's within 12 hrs, ß-agonists within 30 minutes, calcium channel blockers within 24 hrs), standard maternal or fetal contraindications to tocolysis, gestational hypertension or pre-eclampsia.
Interventions	Atosiban group: initial single 6.75 mg iv bolus followed by an infusion of 300 ug/min for the first 3 hrs, followed by 100 ug/min for up to 48 hrs. A placebo iv infusion of 5% dextrose was given separately but simultaneously.

	Salbutamol group: an initial single placebo bolus injection (0.9 ml normal saline) was administered followed by an intravenous 5% dextrose infusion. Separately but simultaneously salbutamol was given as an intravenous infusion in 5% dextrose at 5-25 ug/min (in France) or 2.5-45 ug/min (in Australia), Both infusions were continued for 48 hours.
Outcomes	The main objectives were to compare the effectiveness and safety of atosiban versus salbutamol as tocolytic agents.
Notes	Sample size calculation: a sample size of 120 women in each group was estimated to be sufficient to find a difference of 18% in terms of women delivering within 7 days having a 95% level of significance and a power of 80%. Antenatal corticosteroids: not reported. GBS protocol: not reported.
Allocation concealment	A – Adequate

Study	**Goodwin 1994**
Methods	Blinding of randomisation: yes. Prepared by the biostatistics department of the R.W. Johnson Pharmaceutical Research Institute: computer-generated randomisation in block size of four at each centre supplied to pharmacists at each centre in sequentially numbered, opaque, sealed envelopes. Blinding of intervention: yes. Double-dummy technique. Blinding outcome assessment: no. Completeness of follow up: postrandomisation exclusions 4 women in the atosiban group and 4 women in the placebo group.
Participants	120 women with preterm labour in a multicentre trial with different entering gestational ages; one centre 20-35 wks, one 20 - 34 wks, one 25-35 wks, one < 35 wks, one 28-37 wks. Exclusion criteria: prior study participant, ruptured membranes, amnionitis, standard contraindications to tocolysis.
Interventions	Atosiban group: atosiban 300 ug/min intravenous for 2 hours. Placebo group: intravenous for 2 hours.
Outcomes	Primary goal was effect on cessation of uterine contractions at two hours. Secondary goal was safety data of atosiban in pregnancy. Additional data received on maternal adverse drug reaction.
Notes	Sample size calculation: not reported. Antenatal corticosteroids: not reported. GBS protocol: not reported.
Allocation concealment	A – Adequate

Study	**Goodwin 1996**
Methods	Blinding of randomisation: yes. Prepared by the biostatistics department of the R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ: computer-generated randomisation to one of the five treatment arms stratified by centre, allocation distributed in and sealed, opaque envelopes. Blinding of intervention: no; dose of atosiban blinded only not the ritodrine arm. Blinding outcome assessment: unknown. Completeness of follow up: one woman did not meet the inclusion criteria after randomisation but was included in the analysis. 8 missing data in the neonatal outcome in the atosiban group and 2 in the ritodrine group.
Participants	302 women with preterm labour at 20-35 weeks' gestation. Exclusion criteria: ROM, prior enrolment in the study, cervix dilatation more than 3 cm, multiple gestation, gestational hypertension or pre-eclampsia, prior tocolytic therapy within 72 hours, maternal or fetal medical conditions.

Characteristics of included studies (*Continued*)

Interventions	Atosiban group: four dosing regimens; 1. atosiban bolus of 6.5 mg with 300 ug/min iv infusion; 2. atosiban placebo bolus with 300 ug/min iv infusion; 3. atosiban 2 mg bolus with 100 ug/min iv infusion; 4. atosiban 0.6 mg bolus with 30 ug/min iv infusion. Continuation of treatment was until 6 hours after the last contraction with a maximum of 12 hours. Ritodrine group: ritodrine infusion was started at 0.1 mg/minute and eventually increased until cessation of contractions with a maximum of 0.35 mg/minute. Treatment was stopped when the cervix dilatated 1 cm or more during therapy, uterine contractions continued for more than 6 hours, or adverse side-effects needed discontinuation of medication.
Outcomes	Primary goals were to establish the minimal effective dose regimen for atosiban in the initial treatment of preterm labour and to evaluate the effect of a bolus atosiban.
Notes	Sample size calculation: a sample size of 60 women per treatment arm was based to detect a 25% difference in cessation of contractions with a power of 80%. Antenatal corticosteroids: no. GBS protocol: no.
Allocation concealment	A – Adequate

Study	**Moutquin 2000**
Methods	Blinding of randomisation: yes. Prepared by Ferring Pharmaceuticals: computer-generated block randomisation stratified by GA and centre. Blinding of intervention: yes. Double-dummy technique. Blinding outcome assessment: unknown. Completeness of follow up: postrandomisation exclusions 5 women (2 atosiban and three in the ritodrine group) who did not receive treatment.
Participants	252 women with preterm labour between 23 and 33 weeks' gestation in a multicentre trial. Exclusion criteria: high order multiple (triplets or greater) pregnancy, ruptured membranes, use of NSAID's within 12 hrs prior to randomisation, severe pre-eclampsia or hypertension, fetal or placental abnormalities, standard maternal or fetal contraindications to tocolysis.
Interventions	Atosiban group: initial single 6.75 mg iv bolus followed by an infusion of 300 ug/min for the first 3 hrs followed by 100 ug/min for up to 18 hrs. A placebo iv infusion of 5% dextrose was given separately but simultaneously. Ritodrine group: an initial single placebo bolus injection was administered followed by an intravenous 5% dextrose infusion. Separately but simultaneously ritodrine was given as an intravenous infusion in 5% dextrose at 0.10 to 0.35 mg/min, by increments every 10 minutes as required until contractions ceased. Both infusions were continued for 18 hours.
Outcomes	The purpose of the study was to compare clinical effectiveness and safety profile of atosiban with that of ritodrine. Effectiveness was defined as no delivery within 48 hours and 7 days without additional tocolytics.
Notes	Sample size calculation: a sample size of 120 women in each group was estimated to be sufficient to show an increase of 18% in tocolytic efficacy from 38%, with a 95% level of significance and a power of 80%. Antenatal corticosteroids: yes. GBS protocol: not reported.
Allocation concealment	A – Adequate

Study	**Romero 2000**
Methods	Blinding of randomisation: yes. Prepared by the R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ: computer-generated randomisation stratified by centre but not by GA, in blocks of 6, supplied to pharmacists at each centre in sequential order prenumbered envelopes. Blinding of intervention: yes. Double-dummy technique. Blinding outcome assessment: unknown.

	Completeness of follow up: postrandomisation exclusions 30 women who did not receive the study drug (15 in the atosiban group and 15 in the placebo group). Neonatal data missing between 5 and 24. Loss to follow up in this trial was reported as 27% at six months, 35% at 12 months, and 45% at two years for neurodevelopmental assessments
Participants	531 women with preterm labour in a multicentre trial with a gestational age between 20-33 6/7 wks. Exclusion criteria: ruptured membranes, cervical dilatation > 3 cm, fetal or placental abnormalities, standard maternal or fetal contraindications to tocolysis.
Interventions	Active drug and placebo were administered at the same volume and rate. Atosiban group: initial bolus of 6.75 mg atosiban administered over 1 minute. Followed by an infusion of 300 ug/min for 3 hours followed by an infusion of 100 ug/min atosiban for 45 hours. When uterine quiescence was achieved maintenance therapy was continued subcutaneously with either atosiban or placebo until the end of the 36th week of gestation. Control: initial bolus or placebo administered over 1 minute. Followed by an infusion of placebo for 48 hours. Maintenance therapy with subcutaneous placebo until 36 wks.
Outcomes	The purpose of the study was to evaluate the efficacy and safety of atosiban in the treatment of preterm labour. Primary end point was the time (days) to delivery or therapeutic failure (progression of labour necessitating an alternate tocolytic agent). Secondary end points were the number of women who were successfully treated up to 24 hours, 48 hours, and 7 days after the start of intravenous therapy. Long-term neurodevelopmental outcome was reported in a subsequent publication.
Notes	Sample size calculation: a sample size of 250 women in each treatment group would be necessary to provide a 80% power to detect an atosiban to placebo ratio of 1:3 for the mean number of days from the start of the medication to delivery or therapeutic failure. Antenatal corticosteroids: yes; 45% in the atosiban arm versus 51% in the placebo arm. GBS protocol: unknown. Outside the protocol antibiotic therapy was allowed to be given for standard clinical conditions. Any antibiotics 52% in the atosiban arm versus 46% in the placebo arm.
Allocation concealment	A – Adequate

hrs: hours
GBS: Group B streptococci
iv: intravenous
min: minute
NEC: necrotising enterocolitis
NSAID: nonsteroidal anti-inflammatory drug
ROP: retinopathy of prematurity
wks: weeks

Characteristics of excluded studies

Study	Reason for exclusion
Gagnon 1998	Trial of maintenance tocolysis.
Valenzuela 1997	The purpose of the trial was to measure estradiol levels before and after treatment with Atosiban.
Valenzuela 2000	Trial of maintenance tocolysis.

ANALYSES

Comparison 01. Atosiban versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Perinatal death	1	583	Relative Risk (Fixed) 95% CI	2.25 [0.79, 6.40]
02 Fetal death	2	585	Relative Risk (Fixed) 95% CI	1.02 [0.21, 5.03]
03 Neonatal death (up to 28 days)	1	583	Relative Risk (Fixed) 95% CI	4.10 [0.88, 19.13]
04 Infant death (up to 12 months)	1	583	Relative Risk (Fixed) 95% CI	6.15 [1.39, 27.22]
05 Preterm birth less than 28 weeks' gestation	1	77	Relative Risk (Fixed) 95% CI	2.25 [0.80, 6.35]
06 Preterm birth less than 37 weeks' gestation	1	501	Relative Risk (Fixed) 95% CI	1.17 [0.99, 1.37]
07 Birth within 48 hours of initiation of treatment	1	112	Relative Risk (Fixed) 95% CI	2.50 [0.51, 12.35]
08 Gestational age at birth (weeks)	1	114	Weighted Mean Difference (Fixed) 95% CI	-0.50 [-1.56, 0.56]
09 Birthweight (grams)	2	692	Weighted Mean Difference (Fixed) 95% CI	-138.31 [-248.76, -27.86]
10 Respiratory distress syndrome	2	689	Relative Risk (Fixed) 95% CI	1.28 [0.93, 1.76]
11 Intraventricular haemorrhage	1	489	Relative Risk (Fixed) 95% CI	0.85 [0.45, 1.62]
12 Necrotising enterocolitis	1	575	Relative Risk (Fixed) 95% CI	0.21 [0.02, 1.76]
13 Hypoglycaemia	1	114	Relative Risk (Fixed) 95% CI	0.75 [0.18, 3.20]
14 Patent ductus arteriosus	2	689	Relative Risk (Fixed) 95% CI	1.28 [0.68, 2.40]
15 Admission neonatal intensive care	1	560	Relative Risk (Fixed) 95% CI	1.09 [0.89, 1.34]
16 Maternal drug reaction requiring cessation of treatment	2	613	Relative Risk (Fixed) 95% CI	4.02 [2.05, 7.85]
17 Maternal death	1	501	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 02. Atosiban versus betamimetics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Perinatal death	3	836	Relative Risk (Fixed) 95% CI	0.66 [0.24, 1.83]
02 Fetal death	3	836	Relative Risk (Fixed) 95% CI	0.55 [0.05, 6.04]
03 Neonatal death (up to 28 days)	4	1130	Relative Risk (Fixed) 95% CI	0.70 [0.27, 1.81]
04 Preterm birth less than 37 weeks' gestation	1	244	Relative Risk (Fixed) 95% CI	0.90 [0.71, 1.13]
05 Birth within 48 hours of initiation of treatment	4	1033	Relative Risk (Fixed) 95% CI	0.98 [0.68, 1.41]
06 Birth within 7 days of initiation of treatment	3	731	Relative Risk (Fixed) 95% CI	0.91 [0.69, 1.20]
08 Pregnancy prolongation (days)	1	244	Weighted Mean Difference (Fixed) 95% CI	4.60 [-2.95, 12.15]
09 Birthweight less than 1500 g	2	575	Relative Risk (Fixed) 95% CI	1.96 [1.15, 3.35]
10 Birthweight less than 2500 g	2	575	Relative Risk (Fixed) 95% CI	0.99 [0.81, 1.20]
11 Birthweight (grams)	3	836	Weighted Mean Difference (Fixed) 95% CI	26.28 [-82.22, 134.78]
12 Gestational age at birth (weeks)	3	836	Weighted Mean Difference (Fixed) 95% CI	0.27 [-0.25, 0.80]
13 Apgar score less than 7 at 5 minutes	3	807	Relative Risk (Fixed) 95% CI	0.64 [0.33, 1.23]
14 Respiratory distress syndrome	4	1129	Relative Risk (Fixed) 95% CI	0.99 [0.76, 1.29]

15 Necrotising enterocolitis	2	576	Relative Risk (Fixed) 95% CI	0.48 [0.12, 1.98]
16 Hypoglycaemia	3	837	Relative Risk (Fixed) 95% CI	1.07 [0.63, 1.82]
17 Patent ductus arteriosus	4	1129	Relative Risk (Fixed) 95% CI	1.02 [0.58, 1.79]
18 Neonatal sepsis	4	1129	Relative Risk (Fixed) 95% CI	0.91 [0.56, 1.46]
19 Admission to neonatal intensive care	3	836	Relative Risk (Fixed) 95% CI	1.03 [0.84, 1.26]
20 Maternal adverse drug reaction	2	486	Relative Risk (Fixed) 95% CI	0.86 [0.72, 1.03]
21 Maternal drug reaction requiring cessation of treatment	4	1034	Relative Risk (Fixed) 95% CI	0.04 [0.02, 0.11]
22 Maternal death	1	245	Relative Risk (Fixed) 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Albuterol [therapeutic use]; Obstetric Labor, Premature [*drug therapy]; Randomized Controlled Trials; Receptors, Oxytocin [*antagonists & inhibitors]; Ritodrine [therapeutic use]; Terbutaline [therapeutic use]; Tocolytic Agents [*therapeutic use]; Vasotocin [adverse effects; analogs & derivatives; therapeutic use]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Oxytocin receptor antagonists for inhibiting preterm labour
Authors	Papatsonis D, Flenady V, Cole S, Liley H
Contribution of author(s)	Dimitri Papatsonis and Vicki Flenady worked collaboratively in the development of the review. Steven Cole and Helen Liley provided assistance with resolving differences in data collection and provided advice in the development of the review, interpretation of the results of the review and final editing.
Issue protocol first published	2003/4
Review first published	2005/3
Date of most recent amendment	22 August 2007
Date of most recent SUBSTANTIVE amendment	18 May 2005
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 September 2004
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Dimitri Papatsonis Department of Obstetrics and Gynaecology

Amphia Hospital Breda
Langendijk 75
Breda
4819 EV
NETHERLANDS
E-mail: hoog.pap@wxs.nl
Tel: +31 76 5951000
Fax: +31 76 5952467

DOI 10.1002/14651858.CD004452.pub2

Cochrane Library number CD004452

Editorial group Cochrane Pregnancy and Childbirth Group

Editorial group code HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Atosiban versus placebo, Outcome 01 Perinatal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour
Comparison: 01 Atosiban versus placebo
Outcome: 01 Perinatal death

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	11/288	5/295		100.0	2.25 [0.79, 6.40]
Total (95% CI)	288	295		100.0	2.25 [0.79, 6.40]
Total events: 11 (Atosiban), 5 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					

Analysis 01.02. Comparison 01 Atosiban versus placebo, Outcome 02 Fetal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 02 Fetal death

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Goodwin 1994	0/1	0/1		0.0	Not estimable
Romero 2000	3/288	3/295		100.0	1.02 [0.21, 5.03]
Total (95% CI)	289	296		100.0	1.02 [0.21, 5.03]
Total events: 3 (Atosiban), 3 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.03 p=1					

Analysis 01.03. Comparison 01 Atosiban versus placebo, Outcome 03 Neonatal death (up to 28 days)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 03 Neonatal death (up to 28 days)

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	8/288	2/295		100.0	4.10 [0.88, 19.13]
Total (95% CI)	288	295		100.0	4.10 [0.88, 19.13]
Total events: 8 (Atosiban), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.79 p=0.07					

Analysis 01.04. Comparison 01 Atosiban versus placebo, Outcome 04 Infant death (up to 12 months)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 04 Infant death (up to 12 months)

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	12/288	2/295		100.0	6.15 [1.39, 27.22]
Total (95% CI)	288	295		100.0	6.15 [1.39, 27.22]
Total events: 12 (Atosiban), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.39 p=0.02					

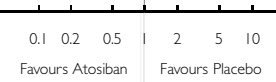
Analysis 01.05. Comparison 01 Atosiban versus placebo, Outcome 05 Preterm birth less than 28 weeks' gestation

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 05 Preterm birth less than 28 weeks' gestation

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	12/44	4/33		100.0	2.25 [0.80, 6.35]
Total (95% CI)	44	33		100.0	2.25 [0.80, 6.35]
Total events: 12 (Atosiban), 4 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.53 p=0.1					



Analysis 01.06. Comparison 01 Atosiban versus placebo, Outcome 06 Preterm birth less than 37 weeks' gestation

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 06 Preterm birth less than 37 weeks' gestation

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	144/246	128/255		100.0	1.17 [0.99, 1.37]
Total (95% CI)	246	255		100.0	1.17 [0.99, 1.37]
Total events: 144 (Atosiban), 128 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.87 p=0.06					

Analysis 01.07. Comparison 01 Atosiban versus placebo, Outcome 07 Birth within 48 hours of initiation of treatment

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 07 Birth within 48 hours of initiation of treatment

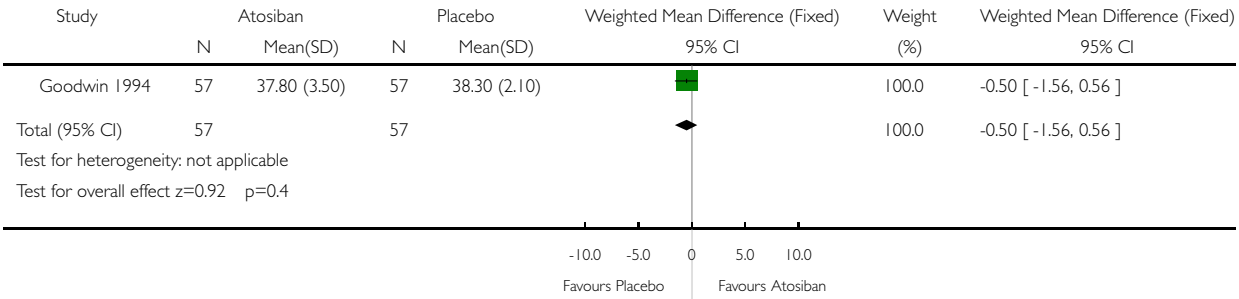
Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1994	5/56	2/56		100.0	2.50 [0.51, 12.35]
Total (95% CI)	56	56		100.0	2.50 [0.51, 12.35]
Total events: 5 (Atosiban), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.12 p=0.3					

Analysis 01.08. Comparison 01 Atosiban versus placebo, Outcome 08 Gestational age at birth (weeks)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 08 Gestational age at birth (weeks)

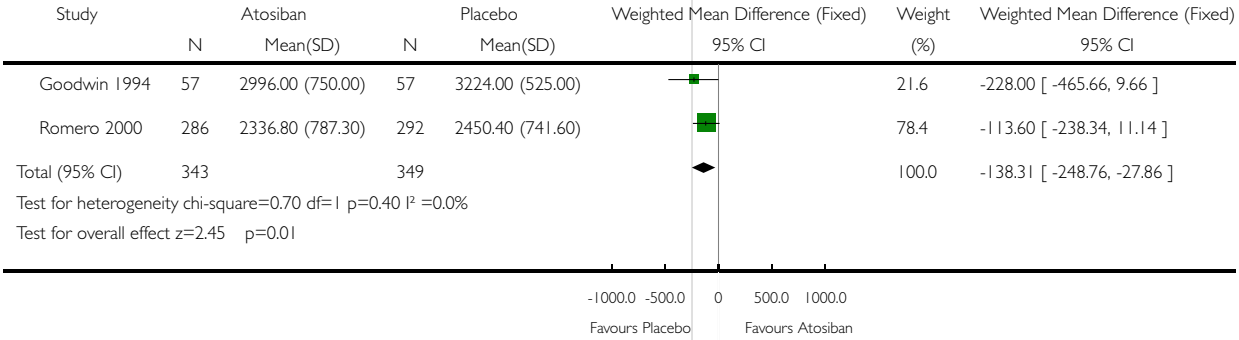


Analysis 01.09. Comparison 01 Atosiban versus placebo, Outcome 09 Birthweight (grams)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 09 Birthweight (grams)



Analysis 01.10. Comparison 01 Atosiban versus placebo, Outcome 10 Respiratory distress syndrome

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 10 Respiratory distress syndrome

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1994	3/57	0/57		0.9	7.00 [0.37, 132.51]
Romero 2000	64/283	54/292		99.1	1.22 [0.89, 1.69]
Total (95% CI)	340	349		100.0	1.28 [0.93, 1.76]
Total events: 67 (Atosiban), 54 (Placebo)					
Test for heterogeneity chi-square=1.35 df=1 p=0.24 I^2 =26.2%					
Test for overall effect z=1.50 p=0.1					

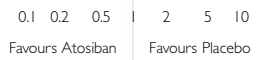
Analysis 01.11. Comparison 01 Atosiban versus placebo, Outcome 11 Intraventricular haemorrhage

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 11 Intraventricular haemorrhage

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	16/243	19/246		100.0	0.85 [0.45, 1.62]
Total (95% CI)	243	246		100.0	0.85 [0.45, 1.62]
Total events: 16 (Atosiban), 19 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.49 p=0.6					



Analysis 01.12. Comparison 01 Atosiban versus placebo, Outcome 12 Necrotising enterocolitis

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 12 Necrotising enterocolitis

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	1/283	5/292		100.0	0.21 [0.02, 1.76]
Total (95% CI)	283	292		100.0	0.21 [0.02, 1.76]
Total events: 1 (Atosiban), 5 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.44 p=0.1					

Analysis 01.13. Comparison 01 Atosiban versus placebo, Outcome 13 Hypoglycaemia

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 13 Hypoglycaemia

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1994	3/57	4/57		100.0	0.75 [0.18, 3.20]
Total (95% CI)	57	57		100.0	0.75 [0.18, 3.20]
Total events: 3 (Atosiban), 4 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.39 p=0.7					

Analysis 01.14. Comparison 01 Atosiban versus placebo, Outcome 14 Patent ductus arteriosus

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 14 Patent ductus arteriosus

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1994	2/57	0/57		3.1	5.00 [0.25, 101.89]
Romero 2000	18/283	16/292		96.9	1.16 [0.60, 2.23]
Total (95% CI)	340	349		100.0	1.28 [0.68, 2.40]
Total events: 20 (Atosiban), 16 (Placebo)					
Test for heterogeneity chi-square=0.87 df=1 p=0.35 I^2 =0.0%					
Test for overall effect z=0.76 p=0.4					

Analysis 01.15. Comparison 01 Atosiban versus placebo, Outcome 15 Admission neonatal intensive care

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 15 Admission neonatal intensive care

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Romero 2000	115/274	110/286		100.0	1.09 [0.89, 1.34]
Total (95% CI)	274	286		100.0	1.09 [0.89, 1.34]
Total events: 115 (Atosiban), 110 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.85 p=0.4					

Analysis 01.16. Comparison 01 Atosiban versus placebo, Outcome 16 Maternal drug reaction requiring cessation of treatment

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 16 Maternal drug reaction requiring cessation of treatment

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Goodwin 1994	0/56	0/56		0.0	Not estimable
Romero 2000	40/250	10/251		100.0	4.02 [2.05, 7.85]
Total (95% CI)	306	307		100.0	4.02 [2.05, 7.85]
Total events: 40 (Atosiban), 10 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.06 p=0.00005					

Analysis 01.17. Comparison 01 Atosiban versus placebo, Outcome 17 Maternal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 01 Atosiban versus placebo

Outcome: 17 Maternal death

Study	Atosiban n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Romero 2000	0/246	0/255		0.0	Not estimable
Total (95% CI)	246	255		0.0	Not estimable
Total events: 0 (Atosiban), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 02.01. Comparison 02 Atosiban versus betamimetics, Outcome 01 Perinatal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 01 Perinatal death

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	3/130	7/153		68.7	0.50 [0.13, 1.91]
French/Austr. 2001	1/129	2/143		20.3	0.55 [0.05, 6.04]
Moutquin 2000	2/146	1/135		11.1	1.85 [0.17, 20.16]
Total (95% CI)	405	431		100.0	0.66 [0.24, 1.83]

Total events: 6 (Atosiban), 10 (Betamimetics)

Test for heterogeneity chi-square=0.89 df=2 p=0.64 I^2 =0.0%

Test for overall effect z=0.79 p=0.4

Analysis 02.02. Comparison 02 Atosiban versus betamimetics, Outcome 02 Fetal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 02 Fetal death

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× European 2001	0/130	0/153		0.0	Not estimable
French/Austr. 2001	1/129	2/143		100.0	0.55 [0.05, 6.04]
× Moutquin 2000	0/146	0/135		0.0	Not estimable
Total (95% CI)	405	431		100.0	0.55 [0.05, 6.04]

Total events: 1 (Atosiban), 2 (Betamimetics)

Test for heterogeneity: not applicable

Test for overall effect z=0.48 p=0.6

Analysis 02.03. Comparison 02 Atosiban versus betamimetics, Outcome 03 Neonatal death (up to 28 days)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

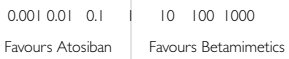
Outcome: 03 Neonatal death (up to 28 days)

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	3/130	7/153		60.4	0.50 [0.13, 1.91]
French/Austr. 2001	0/129	2/143		22.3	0.22 [0.01, 4.57]
Goodwin 1996	4/238	0/56		7.6	2.15 [0.12, 39.30]
Moutquin 2000	2/146	1/135		9.8	1.85 [0.17, 20.16]
Total (95% CI)	643	487		100.0	0.70 [0.27, 1.81]

Total events: 9 (Atosiban), 10 (Betamimetics)

Test for heterogeneity chi-square=1.99 df=3 p=0.57 I^2 =0.0%

Test for overall effect z=0.74 p=0.5



Analysis 02.04. Comparison 02 Atosiban versus betamimetics, Outcome 04 Preterm birth less than 37 weeks' gestation

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 04 Preterm birth less than 37 weeks' gestation

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	60/115	75/129		100.0	0.90 [0.71, 1.13]
Total (95% CI)	115	129		100.0	0.90 [0.71, 1.13]

Total events: 60 (Atosiban), 75 (Betamimetics)

Test for heterogeneity: not applicable

Test for overall effect z=0.93 p=0.4

Analysis 02.05. Comparison 02 Atosiban versus betamimetics, Outcome 05 Birth within 48 hours of initiation of treatment

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

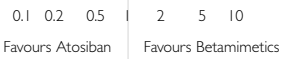
Outcome: 05 Birth within 48 hours of initiation of treatment

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	17/115	22/129		40.6	0.87 [0.48, 1.55]
French/Austr. 2001	8/119	6/121		11.6	1.36 [0.49, 3.79]
Goodwin 1996	14/244	5/58		15.8	0.67 [0.25, 1.77]
Moutquin 2000	19/126	16/121		32.0	1.14 [0.62, 2.11]
Total (95% CI)	604	429		100.0	0.98 [0.68, 1.41]

Total events: 58 (Atosiban), 49 (Betamimetics)

Test for heterogeneity chi-square=1.39 df=3 p=0.71 I^2 =0.0%

Test for overall effect z=0.11 p=0.9



Analysis 02.06. Comparison 02 Atosiban versus betamimetics, Outcome 06 Birth within 7 days of initiation of treatment

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 06 Birth within 7 days of initiation of treatment

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	27/115	42/129		48.8	0.72 [0.48, 1.09]
French/Austr. 2001	12/119	12/121		14.7	1.02 [0.48, 2.17]
Moutquin 2000	34/126	29/121		36.5	1.13 [0.73, 1.73]
Total (95% CI)	360	371		100.0	0.91 [0.69, 1.20]

Total events: 73 (Atosiban), 83 (Betamimetics)

Test for heterogeneity chi-square=2.25 df=2 p=0.32 I^2 =11.2%

Test for overall effect z=0.65 p=0.5

Analysis 02.08. Comparison 02 Atosiban versus betamimetics, Outcome 08 Pregnancy prolongation (days)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 08 Pregnancy prolongation (days)

Study	Atosiban N	Atosiban Mean(SD)	Betamimetics N	Betamimetics Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
European 2001	115	39.70 (30.00)	129	35.10 (30.10)		100.0	4.60 [-2.95, 12.15]
Total (95% CI)	115		129			100.0	4.60 [-2.95, 12.15]

Test for heterogeneity: not applicable

Test for overall effect z=1.19 p=0.2

Analysis 02.09. Comparison 02 Atosiban versus betamimetics, Outcome 09 Birthweight less than 1500 g

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 09 Birthweight less than 1500 g

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1996	14/238	3/56		26.4	1.10 [0.33, 3.69]
Moutquin 2000	32/146	13/135		73.6	2.28 [1.25, 4.15]
Total (95% CI)	384	191		100.0	1.96 [1.15, 3.35]

Total events: 46 (Atosiban), 16 (Betamimetics)

Test for heterogeneity chi-square=1.11 df=1 p=0.29 I^2 =10.3%

Test for overall effect z=2.49 p=0.01

Analysis 02.10. Comparison 02 Atosiban versus betamimetics, Outcome 10 Birthweight less than 2500 g

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

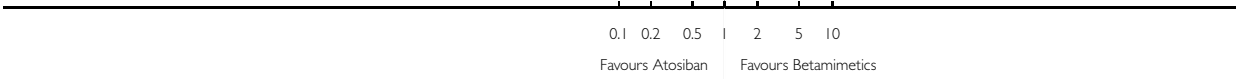
Outcome: 10 Birthweight less than 2500 g

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goodwin 1996	68/238	20/56		31.1	0.80 [0.53, 1.20]
Moutquin 2000	80/146	69/135		68.9	1.07 [0.86, 1.34]
Total (95% CI)	384	191		100.0	0.99 [0.81, 1.20]

Total events: 148 (Atosiban), 89 (Betamimetics)

Test for heterogeneity chi-square=1.57 df=1 p=0.21 I^2 =36.3%

Test for overall effect z=0.13 p=0.9



Analysis 02.11. Comparison 02 Atosiban versus betamimetics, Outcome 11 Birthweight (grams)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

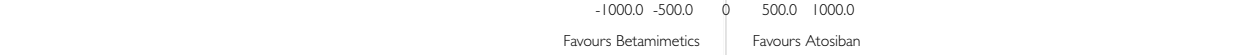
Comparison: 02 Atosiban versus betamimetics

Outcome: 11 Birthweight (grams)

Study	Atosiban N	Atosiban Mean(SD)	Betamimetics N	Betamimetics Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
European 2001	130	2473.00 (819.70)	153	2298.00 (939.00)		28.0	175.00 [-29.92, 379.92]
French/Austr. 2001	129	2708.00 (743.00)	143	2619.00 (743.00)		37.6	89.00 [-87.83, 265.83]
Moutquin 2000	146	2314.00 (825.00)	135	2478.00 (759.00)		34.3	-164.00 [-349.20, 21.20]
Total (95% CI)	405		431			100.0	26.28 [-82.22, 134.78]

Test for heterogeneity chi-square=6.56 df=2 p=0.04 I^2 =69.5%

Test for overall effect z=0.47 p=0.6



Analysis 02.12. Comparison 02 Atosiban versus betamimetics, Outcome 12 Gestational age at birth (weeks)

Review: Oxytocin receptor antagonists for inhibiting preterm labour

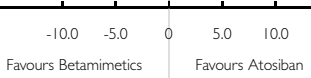
Comparison: 02 Atosiban versus betamimetics

Outcome: 12 Gestational age at birth (weeks)

Study	Atosiban N	Atosiban Mean(SD)	Betamimetics N	Betamimetics Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
European 2001	130	35.11 (4.20)	153	34.30 (4.50)		26.7	0.81 [-0.20, 1.82]
French/Austr. 2001	129	36.50 (3.00)	143	36.30 (3.70)		43.3	0.20 [-0.60, 1.00]
Moutquin 2000	146	35.10 (4.20)	135	35.20 (4.00)		29.9	-0.10 [-1.06, 0.86]
Total (95% CI)	405		431			100.0	0.27 [-0.25, 0.80]

Test for heterogeneity chi-square=1.69 df=2 p=0.43 I^2 =0.0%

Test for overall effect z=1.02 p=0.3



Analysis 02.13. Comparison 02 Atosiban versus betamimetics, Outcome 13 Apgar score less than 7 at 5 minutes

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 13 Apgar score less than 7 at 5 minutes

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	4/131	13/130		59.3	0.31 [0.10, 0.91]
French/Austr. 2001	5/129	5/138		22.0	1.07 [0.32, 3.61]
Moutquin 2000	5/144	4/135		18.8	1.17 [0.32, 4.27]
Total (95% CI)	404	403		100.0	0.64 [0.33, 1.23]

Total events: 14 (Atosiban), 22 (Betamimetics)

Test for heterogeneity chi-square=3.29 df=2 p=0.19 I^2 =39.2%

Test for overall effect z=1.35 p=0.2

Analysis 02.14. Comparison 02 Atosiban versus betamimetics, Outcome 14 Respiratory distress syndrome

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 14 Respiratory distress syndrome

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	27/131	47/153		48.6	0.67 [0.44, 1.01]
French/Austr. 2001	20/129	19/143		20.2	1.17 [0.65, 2.09]
Goodwin 1996	20/236	5/56		9.1	0.95 [0.37, 2.42]
Moutquin 2000	32/146	19/135		22.1	1.56 [0.93, 2.61]
Total (95% CI)	642	487		100.0	0.99 [0.76, 1.29]

Total events: 99 (Atosiban), 90 (Betamimetics)

Test for heterogeneity chi-square=6.69 df=3 p=0.08 I^2 =55.2%

Test for overall effect z=0.06 p=1

Analysis 02.15. Comparison 02 Atosiban versus betamimetics, Outcome 15 Necrotising enterocolitis

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 15 Necrotising enterocolitis

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	2/131	4/153		69.5	0.58 [0.11, 3.14]
Goodwin 1996	1/236	1/56		30.5	0.24 [0.02, 3.74]
Total (95% CI)	367	209		100.0	0.48 [0.12, 1.98]

Total events: 3 (Atosiban), 5 (Betamimetics)

Test for heterogeneity chi-square=0.30 df=1 p=0.58 I^2 =0.0%

Test for overall effect z=1.02 p=0.3

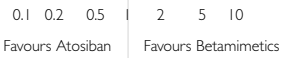
Analysis 02.16. Comparison 02 Atosiban versus betamimetics, Outcome 16 Hypoglycaemia

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 16 Hypoglycaemia

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	8/131	14/153		52.0	0.67 [0.29, 1.54]
French/Austr. 2001	8/129	6/143		22.9	1.48 [0.53, 4.15]
Moutquin 2000	10/146	6/135		25.1	1.54 [0.58, 4.13]
Total (95% CI)	406	431		100.0	1.07 [0.63, 1.82]
Total events: 26 (Atosiban), 26 (Betamimetics)					
Test for heterogeneity chi-square=2.13 df=2 p=0.35 I^2 =6.0%					
Test for overall effect z=0.26 p=0.8					



Analysis 02.17. Comparison 02 Atosiban versus betamimetics, Outcome 17 Patent ductus arteriosus

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 17 Patent ductus arteriosus

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	8/131	14/153		56.8	0.67 [0.29, 1.54]
French/Austr. 2001	1/129	1/143		4.2	1.11 [0.07, 17.54]
Goodwin 1996	3/236	1/56		7.1	0.71 [0.08, 6.72]
Moutquin 2000	13/146	7/135		32.0	1.72 [0.71, 4.18]
Total (95% CI)	642	487		100.0	1.02 [0.58, 1.79]
Total events: 25 (Atosiban), 23 (Betamimetics)					
Test for heterogeneity chi-square=2.41 df=3 p=0.49 I^2 =0.0%					
Test for overall effect z=0.08 p=0.9					

Analysis 02.18. Comparison 02 Atosiban versus betamimetics, Outcome 18 Neonatal sepsis

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 18 Neonatal sepsis

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	13/131	21/153		58.1	0.72 [0.38, 1.39]
French/Austr. 2001	1/129	1/143		2.8	1.11 [0.07, 17.54]
Goodwin 1996	12/236	1/56		4.8	2.85 [0.38, 21.45]
Moutquin 2000	11/146	11/135		34.3	0.92 [0.41, 2.06]
Total (95% CI)	642	487		100.0	0.91 [0.56, 1.46]

Total events: 37 (Atosiban), 34 (Betamimetics)

Test for heterogeneity chi-square=1.72 df=3 p=0.63 I^2 =0.0%

Test for overall effect z=0.40 p=0.7

Analysis 02.19. Comparison 02 Atosiban versus betamimetics, Outcome 19 Admission to neonatal intensive care

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 19 Admission to neonatal intensive care

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	44/130	64/153		46.4	0.81 [0.60, 1.10]
French/Austr. 2001	27/129	29/143		21.7	1.03 [0.65, 1.65]
Moutquin 2000	57/146	39/135		32.0	1.35 [0.97, 1.89]
Total (95% CI)	405	431		100.0	1.03 [0.84, 1.26]

Total events: 128 (Atosiban), 132 (Betamimetics)

Test for heterogeneity chi-square=4.97 df=2 p=0.08 I^2 =59.7%

Test for overall effect z=0.29 p=0.8

Analysis 02.20. Comparison 02 Atosiban versus betamimetics, Outcome 20 Maternal adverse drug reaction

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 20 Maternal adverse drug reaction

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	39/116	56/129		41.1	0.77 [0.56, 1.07]
French/Austr. 2001	69/119	77/122		58.9	0.92 [0.75, 1.13]
Total (95% CI)	235	251		100.0	0.86 [0.72, 1.03]
Total events: 108 (Atosiban), 133 (Betamimetics)					
Test for heterogeneity chi-square=0.81 df=1 p=0.37 I^2 =0.0%					
Test for overall effect z=1.68 p=0.09					

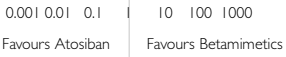
Analysis 02.21. Comparison 02 Atosiban versus betamimetics, Outcome 21 Maternal drug reaction requiring cessation of treatment

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 21 Maternal drug reaction requiring cessation of treatment

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
European 2001	1/115	11/129		12.3	0.10 [0.01, 0.78]
French/Austr. 2001	1/119	13/122		15.3	0.08 [0.01, 0.59]
Goodwin 1996	1/244	15/58		28.8	0.02 [0.00, 0.12]
Moutquin 2000	1/126	36/121		43.6	0.03 [0.00, 0.19]
Total (95% CI)	604	430		100.0	0.04 [0.02, 0.11]
Total events: 4 (Atosiban), 75 (Betamimetics)					
Test for heterogeneity chi-square=2.22 df=3 p=0.53 I^2 =0.0%					
Test for overall effect z=6.42 p<0.00001					



Analysis 02.22. Comparison 02 Atosiban versus betamimetics, Outcome 22 Maternal death

Review: Oxytocin receptor antagonists for inhibiting preterm labour

Comparison: 02 Atosiban versus betamimetics

Outcome: 22 Maternal death

Study	Atosiban n/N	Betamimetics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× European 2001	0/116	0/129		0.0	Not estimable
Total (95% CI)	116	129		0.0	Not estimable
Total events: 0 (Atosiban), 0 (Betamimetics)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable