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Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour (Review)

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Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

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ABSTRACT

Background

In some women, an episode of preterm labour settles and does not result in immediate preterm birth. Subsequent treatment with tocolytic agents such as oxytocin receptor antagonists may then have the potential to prevent the recurrence of preterm labour, prolonging gestation, and preventing the adverse consequences of prematurity for the infant.

Objectives

To assess the effects of maintenance therapy with oxytocin antagonists administered by any route after an episode of preterm labour in order to delay or prevent preterm birth.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2013), sought ongoing and unpublished trials by contacting experts in the field and searched the reference lists of relevant articles.

Selection criteria

Randomised controlled trials comparing oxytocin antagonists with any alternative tocolytic agent, placebo or no treatment, used for maintenance therapy after an episode of preterm labour.

Data collection and analysis

We used the standard methods of The Cochrane Collaboration and the Cochrane Pregnancy and Childbirth Group. Two review authors independently undertook evaluation of methodological quality and extracted trial data.

Main results

This review includes one trial of 513 women. When compared with placebo, atosiban did not reduce preterm birth before 37 weeks (risk ratio (RR) 0.89; 95% confidence intervals (CI) 0.71 to 1.12), 32 weeks (RR 0.85; 95% CI 0.47 to 1.55), or 28 weeks (RR 0.75; 95% CI 0.28 to 2.01). No difference was shown in neonatal morbidity, or perinatal mortality.

Authors' conclusions

There is insufficient evidence to support the use of oxytocin receptor antagonists to inhibit preterm birth after a period of threatened or actual preterm labour. Any future trials using oxytocin antagonists or other drugs as maintenance therapy for preventing preterm birth should examine a variety of important infant outcome measures, including reduction of neonatal morbidity and mortality, and long-term infant follow-up. Future research should also focus on the pathophysiological pathways that precede preterm labour.

PLAIN LANGUAGE SUMMARY

Oxytocin Antagonists for suppressing preterm birth after an episode of preterm labour

Preterm labour is indicated by regular contractions of the uterus and changes in the cervix (the opening of the womb) before 37 weeks of pregnancy. Preterm labour and birth may be associated with illness or death of the baby, and often place a substantial emotional burden on families. Preterm birth may also result in childhood disability. Even a short-term prolongation of pregnancy after the onset of threatened or actual preterm labour can allow the administration of corticosteroids to the mother to hasten fetal lung maturation and transfer of the mother to a centre with neonatal intensive care facilities. A range of drugs (tocolytic) are used to suppress labour. The oxytocin antagonist atosiban is one of these. Once the episode of threatened preterm labour settles, maintenance treatment with a tocolytic can then be used to try to prevent any reoccurrence. This has to be balanced against potential adverse outcomes such as intrauterine infection, fetal death, an increase in severe disability for survivors, and side-effects of the drugs.

This review identified only one good quality multicentre controlled trial which showed that subcutaneously administered atosiban as maintenance therapy did not reduce the incidence of preterm birth or improve neonatal outcomes when compared with placebo treatment. The trial randomised 513 women in whom preterm labour (with intact membranes and limited cervical dilatation) ceased following intravenous treatment with atosiban. The mean gestation at enrolment was around 31 weeks and the proportion of multiple births was similar in the two groups. Atosiban infused at 6 mL/hr (30 μg/min) did not reduce preterm birth before 28, 32, or 37 weeks. Women on maintenance therapy were discharged home with a continuous subcutaneous infusion pump and daily nursing contact. There was an increase in injection site reaction for the atosiban group. There is insufficient evidence of benefit to justify this intervention.

BACKGROUND

In developed countries, preterm birth, defined as birth before 37 completed weeks (WHO 2012), is the most important cause of perinatal morbidity and mortality after congenital anomalies (Goldenberg 2008).

Preterm birth occurring between 20 and 36 completed weeks is a major contributor to perinatal mortality and morbidity. More than one in 10 babies born worldwide in 2010 was born premature, with an annual estimation of 15 million preterm births (Blencowe 2012; WHO 2012). Preterm birth accounts for approximately 75% of perinatal mortality and more than 50% of long-term morbidity (Hack 1999).

Preterm birth is associated not only with high immediate costs attributable to neonatal intensive care, but also with substantial long-term costs, including costs for special education (Petrou 2011), and other services for infants and children with intellectual and physical disability (Petrou 2011). In addition to the lengthy neonatal intensive care treatment required for many preterm infants, preterm birth often constitutes a major crisis in the lives of parents, and places a substantial emotional burden on families (McCain 1993).

The exact causes of preterm birth are not known. Preterm labour can be the final clinical endpoint of several distinct but converging pathophysiological pathways, including: inflammation/infection causing maternal/fetal cytokine and prostaglandin production; maternal/fetal stress leading to endocrine changes; mechanical stress due to abnormal uterine distention; or abruption (placenta/decidual haemorrhage). Because there are several mechanisms, which can occur independently or in combination, it is difficult to identify universal management strategies to prevent preterm birth. To reduce the incidence of preterm birth, a better understanding of the complex triggers of the final common pathway is needed.

The incidence of preterm birth is increasing in developed and developing countries affecting, on average, 11.8% of births in low-income countries and 9.3% to 9.4% in upper-middle- and high-income countries (WHO 2012).

In developed countries, the incidence of preterm birth varies within a narrow range from 6% to 10% (Lumley 2003). This incidence has not declined over the past two decades despite intensive antenatal care programs aimed at identifying high-risk groups for preterm birth, the widespread use of tocolytic agents, and other preventive and therapeutic interventions.

The incidence of preterm birth is probably much higher in low-income than high-income countries, but precise data are lacking because of inaccurate estimation of gestation (Kramer 2003) and registration of births (Kramer 2003; Lumley 2003). Nevertheless, preterm delivery is one of the major direct causes of neonatal death in low-income countries, and is estimated to account for more than 1.1 million neonatal deaths worldwide annually (WHO 2012).

Although the incidence in preterm birth has not declined, even short-term prolongation of pregnancy is beneficial if it enables the administration of corticosteroids to the mother to hasten fetal lung maturation (Roberts 2006) and/or transfer to a centre with neonatal intensive care facilities (Powell 1995). Perinatal mortality and morbidity is significantly reduced after administration of a full course of corticosteroids (Roberts 2006).

A range of drugs (tocolytic) have been used to inhibit preterm labour to allow time for such co-interventions. These drugs are the topics of Cochrane systematic reviews including nitric oxide donors (glyceryl trinitrate) (Duckitt 2002), calcium channel blockers (such as nifedipine) (King 2003), betamimetics (Anotayanonth 2004), magnesium sulphate (Crowther 2002), cyclo-oxygenase (COX) inhibitors (Khanprakob 2012) and oxytocin receptor antagonists (Papatsonis 2005).

For those women with preterm labour who are treated with tocolytics and remain undelivered after 48 hours, maintenance treatment with a tocolytic is sometimes used to further delay delivery and to prolong pregnancy. Maintenance treatment regimens of differing duration, and using a number of different tocolytic, have been proposed. These include betamimetics (Dodd 2012; Nanda 2002), magnesium sulphate (Han 2013), and calcium channel blockers (Gaunekar 2004).

The potential advantages of prolonging pregnancy should be balanced against potential adverse outcomes such as intrauterine infection, fetal demise, and side-effects of the drugs. Prolonging pregnancy at the border of viability could increase the short-term survival rate, but without improving overall survival and/or at the cost of an increase in severe disability for survivors. Therefore, the assessment of effects of interventions to improve outcomes should be based not only on mortality rates but also on major morbidity including long-term outcomes.

Oxytocin antagonists (commonly atosiban) are used for tocolysis in several countries and atosiban has been registered in Europe as a tocolytic agent. This review will determine if there is sufficient evidence to support the use of maintenance therapy with oxytocin antagonists after an episode of threatened or actual preterm labour.

OBJECTIVES

To assess the efficacy and safety of maintenance treatment with oxytocin antagonists after an episode of threatened or actual preterm labour, in preventing preterm birth and other adverse outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised trials with data from women and infants in which oxytocin receptor antagonists, given for maintenance treatment after an episode of preterm labour (threatened or actual), were compared with an alternative tocolytic agent, placebo, or no treatment. Trials that employed quasi-random methods of treatment allocation were not eligible for inclusion.

Types of participants

Pregnant women who had at least one episode of preterm labour between 20 and 36 completed weeks that was suppressed or settled spontaneously without resulting in immediate preterm birth.
For the purposes of this review, preterm labour was defined as the presence of uterine contractions with intact or ruptured membranes, with or without cervical dilation.

Types of interventions

Oxytocin antagonists administered as maintenance therapy by any route and dose compared with either placebo, no treatment, or alternative tocolytic therapy. Trials of women where oxytocin antagonists are combined with any other tocolytic agent were not eligible for inclusion.

Types of outcome measures

Primary outcome measures

(1) Very preterm birth less than 32 weeks gestation.
(2) Perinatal or infant mortality or any neurological disability at long-term paediatric follow-up at two years of age (vision impairment, sensorineural deafness requiring hearing aids, cerebral palsy or developmental delay/intellectual impairment).

Secondary outcome measures

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

Maternal

(1) Serious maternal outcomes (defined as death, coma, cardiac arrest, respiratory arrest, use of a mechanical ventilator, admission to intensive care unit).
(2) Mild maternal side-effects (defined as not necessitating discontinuation of therapy).
(3) Serious maternal side-effects necessitating discontinuation of therapy.
(4) Antepartum haemorrhage.
(5) Postpartum haemorrhage.
(6) Prelabour rupture of the membranes before 34 weeks.
(7) Duration of antenatal and postnatal maternal hospital stay.
(8) Maternal satisfaction with treatment.
(9) Maternal quality of life after the birth (measured by validated instruments).

Infant/child

(1) Mortality
  - Perinatal mortality.
  - Fetal death.
  - Neonatal death.
  - Infant death (death of liveborn infants up to 12 months of age).

(2) Time to delivery
  - Preterm birth within 24, 48 and 72 hours and one week of commencing maintenance therapy.
  - Randomisation to birth interval.

(3) Neonatal morbidity
  - Birth less than 37 completed weeks.
  - Birth less than 28 completed weeks.
  - Apgar score less than seven at five minutes.
  - Neonatal hypoglycaemia.
  - Neonatal encephalopathy or seizures.
  - Respiratory distress syndrome.

- Use of mechanical ventilation.
- Duration of mechanical ventilation.
- Persistent pulmonary hypertension of the neonate.
- Intraventricular haemorrhage.
- Periventricular leukomalacia.
- Chronic lung disease.
- Necrotising enterocolitis.
- Retinopathy of prematurity.
- Neonatal jaundice requiring phototherapy.
- Neonatal early or late onset sepsis.
- Birthweight.
- Birthweight for gestation.
- Gestation at birth.

(3) Use of health service
  - Admission to a neonatal intensive care unit.
  - Neonatal length of hospital stay.
  - Maternal admission to intensive care unit.
  - Costs associated with maintenance therapy versus no maintenance therapy.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 July 2013).

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. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We sought ongoing and unpublished trials by contacting experts in the field and searched the reference lists of relevant articles. We did not apply any language restrictions.

Data collection and analysis

Selection of studies

We used the standard methods of The Cochrane Collaboration as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (Vicki Flenady (VF), Dimitri Papatsonis (DP)) considered trials for inclusion independently. We resolved discrepancies by discussion including the third review author (Helen Liley).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (VF, DP) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third author. We entered data into Review Manager software (RevMan 2012), and checked for accuracy.
We contacted the authors of the published abstracts for additional information or data (Valenzuela 2000); however, no additional information was forthcoming.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for the included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion, or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

For the included study, we describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For the included study, we describe the method used to conceal allocation at the point of randomisation, and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For the included study, we describe the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results.
We assessed the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For the included study, we describe the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received.
We assessed methods used to blind outcome assessment as low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For the included study, we describe the completeness of data including attrition and exclusions from the analysis. We looked at whether attrition and exclusions were reported, and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or supplied by the trial authors, we planned to re-include missing data in the analyses.
We assessed methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with

substantial departure of intervention received from that assigned at randomisation);

- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For the included study, we describe how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; or study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We describe any important concerns we have about other possible sources of bias such as baseline imbalance between groups.
We examined whether the study was free of other problems that could put it at risk of bias and assessed methods as:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We have made explicit judgements about whether the study is at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses, but as only one study was included we did not carry out this additional analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we present the mean difference with 95% confidence intervals. In this version of the review we have not pooled any findings as we included only one trial, but in updates we will use the mean difference to combine findings from trials provided outcomes are measured in the same way between trials. If appropriate, we will use the standardised mean difference to combine trials that report the same outcome, measured in different ways.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials in this version of the review. In future updates, if such trials are identified, we will include them in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* (Higgins 2011), using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information provided there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over studies were not included; this is not a suitable design for this type of intervention.

Other unit of analysis issues

If any multi-armed trials are identified when we update the review, where appropriate, we will combine arms (using methods described in the *Handbook* (Higgins 2011)) to create a single pairwise comparison. If it is not appropriate to combine experimental arms we will present results separately for each arm, sharing results for the control arm between each to avoid double counting (for dichotomous outcomes we will divide the number of events and total sample by two, for continuous outcomes we will assume the same mean and standard deviation but halve the control sample size for each comparison).

Dealing with missing data

For the included study, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis; in this version of the review we did not carry out any meta-analysis so we did not carry out this planned sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants are analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

If we had combined trials in meta-analysis, we planned to assess statistical heterogeneity using the T², I² and Chi² statistics. If we carry out meta-analysis in updates we will regard heterogeneity as substantial if an I² is greater than 30% and either the T² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

If in future updates there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2012). If in future updates we carry out any meta-analysis, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary where an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects, and we will discuss the clinical implications of treatment effects differing between trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T² and I².

Subgroup analysis and investigation of heterogeneity

In future updates, if sufficient data are available, we will carry out subgroup analysis as follows:

- all women with preterm labour before 32 completed weeks at randomisation compared with women at or beyond 32 weeks;
- dosage of oxytocin receptor antagonists;
- type of oxytocin receptor antagonists;
- duration of tocolytic therapy;
- type of tocolytic therapy comparisons.

We will examine only our primary outcomes in subgroup analysis. We will assess subgroup differences by interaction tests available in RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the χ2 statistic and P value, and the interaction test I² value.

Sensitivity analysis

If we had included cluster-randomised trials in the review, we planned to carry out sensitivity analysis. We also planned sensitivity analysis according to trial quality; temporarily excluding trials at high risk of bias to explore whether this has any impact on the direction or size of the effect estimate. In this version of the review we did not carry out any sensitivity analysis as we did not carry out any meta-analysis. If more data are included in updates, we will carry out planned sensitivity analysis using our primary outcomes only.

R E S U L T S

Description of studies

Three publications were identified as potentially eligible for inclusion in this review. Two of the three publications (Gagnon 1998; Sanchez-Ramos 1997) were abstracts reporting data from the only available identified study (Valenzuela 2000).

Included studies

One study including a total of 513 women that compared maintenance therapy using atosiban versus placebo to prevent recurrence of preterm labour (Valenzuela 2000) was included in this review.

Excluded studies

There were no excluded studies.

Participants

Gestation at inclusion ranged from 20 to 33 6/7 weeks. The mean gestation at inclusion was 31.0 (standard deviation (SD) 2.62) weeks for the placebo group and 30.6 (SD 2.78) weeks for the atosiban group. Women were eligible for the study when there was preterm labour in a pregnancy, with intact membranes and ≤ 3 cm cervical dilatation, with a live fetus, after uterine quiescence was achieved with intravenous atosiban (not placebo) in a multicentre trial comparing placebo or atosiban for the treatment of preterm labour. Exclusion criteria were: fetal or placental abnormalities by ultrasonography, maternal indications for delivery, urinary tract infection, and overt clinical manifestations of substance abuse.

Tocolysis

The trial (Valenzuela 2000) compared atosiban with placebo, both administered subcutaneously to women in whom preterm labour had ceased following treatment with atosiban. Atosiban and placebo were administered at the same volume and rate.

Atosiban group: atosiban for maintenance was administered by a subcutaneous infusion pump to provide a continuous atosiban infusion of 6 mL/hour (30 μg/min).

Placebo group: placebo for maintenance was administered by a subcutaneous infusion pump to provide a continuous placebo infusion of 6 mL/hour.

Both active drug and placebo were administered until the end of week 36 of gestation, delivery, or progression of labour requiring an alternative tocolytic agent. All women on maintenance therapy were discharged home with daily nursing contact for all, compliance was checked by diaries kept by women and records of drugs used.

Rescue therapy with intravenous atosiban could be given for any additional episode of preterm labour, followed by subcutaneous maintenance therapy with the assigned study treatment when uterine quiescence was again achieved.

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

Risk of bias in included studies

Maintenance therapy atosiban versus placebo

The included trial (Valenzuela 2000) was considered of good quality with a low risk of bias for each of the bias domains assessed with the exception of reporting bias, which had an unclear risk of bias.. The trial employed a blinded method of randomisation according to a computer-generated schedule using pre-numbered envelopes containing the allocation to study group provided to the pharmacist at each centre for use in sequential order. The randomisation schedule was developed using permuted blocks of four and was stratified by centre but not gestation. Blinding of the intervention

was undertaken with the use of a placebo which was identical in appearance and administration to the atosiban arm of the trial. One woman in the placebo group, who did not receive treatment, was excluded post-randomisation. Eight participants in the placebo group received some atosiban in error but were analysed by intention-to-treat for the purposes of assessing efficacy.

The primary outcome variable, on which the sample size calculation was based, was the number of days from the start of maintenance therapy until the recurrence of preterm labour.

Although all mothers appear accounted for in the reported outcomes of the study, the numbers of infants referred to in the text and tables amount to 568, 563 (272 placebo, 291 atosiban) and 558 infants (269 placebo, 289 atosiban), without further explanation of the discrepancies. One of these discrepant infants is possibly the single fetal death (in the atosiban group).

Further information on outcomes has been sought from the trial investigator and will be included in future updates when available. To date, no information has been forthcoming.

For further details see table of Characteristics of included studies.

Effects of interventions

This review included data from one study with a total of 513 women .

Compared with placebo, the use of atosiban as maintenance therapy for prevention of recurrent preterm labour did not reduce the incidence of preterm birth before 37 weeks (risk ratio (RR) 0.89; 95% confidence interval (CI) 0.71 to 1.12), 32 weeks (RR 0.85; 95% CI 0.47 to 1.55), or 28 weeks (RR 0.75; 95% CI 0.28 to 2.01). While not defined as an a priori outcome measure of this review, the median interval from the start of maintenance therapy to the first recurrence of labour was prolonged (32.6 days in the atosiban group versus 27.6 days in the placebo group, P = 0.02), as was the time to recurrence of preterm labour (36.2 versus 28.2 days, P = 0.03). The number of women who received 'rescue' tocolytic treatment was not significantly reduced.

Please *see* table 0f Characteristics of included studies for further details.

Maternal outcomes

There were no maternal deaths reported. While the data on maternal outcomes are not reported within the total adverse events for the study, Valenzuela 2000 state that the adverse event profiles were comparable, and there was an increase in injection site reaction for the atosiban group (RR 1.55; 95% CI 1.33 to 1.81).

Neonatal outcomes

Among the 558 infants, neonatal outcomes were similar for both groups with respect to birthweight (mean difference (MD) 0.10; 95% CI -131.78 to 131.98) respiratory distress syndrome (RR

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1.06; 95% CI 0.66 to 1.70), patent ductus arteriosus (RR 1.17; 95% CI 0.47 to 2.91) and necrotising enterocolitis (RR 2.34; CI 95% 0.46 to 11.93). The outcomes were also reported to be similar for intraventricular haemorrhage; however, these data were not able to be included until further clarification about the denominators is received from the authors. Neonatal intensive care unit admissions (RR 0.84; 95% CI 0.62 to 1.14) and fetal and neonatal deaths were similar for both groups (five in each). No long-term infant outcomes were reported.

DISCUSSION

The results of this review do not support the use of atosiban as maintenance therapy after an episode of preterm labour. When atosiban was compared with placebo, there was no reduction of the incidence of preterm birth and no improvement of any reported neonatal outcome. The treatment involved at least maternal inconvenience (continuous subcutaneous infusion pump for days to weeks) and although there was no excess of severe maternal side-effects, the incidence of maternal injection site reactions was significantly higher among women treated with atosiban maintenance than among those receiving placebo.

Any more than minor risk or burden to the pregnant mother of treatment for the sake of her fetus can only be justified if infant outcomes improve. Atosiban maintenance therapy when compared with placebo prolonged the interval until first recurrence of preterm labour. Although this was statistically significant, clinical relevance is dubious because the neonatal outcomes were very similar in the two groups. Although the trial size was calculated with the intention of demonstrating a difference in interval until labour recurred, not a difference in neonatal outcomes, the absence of even a trend towards improved infant outcomes leads the review authors to conclude that there is insufficient evidence to support the use of atosiban for this indication.

Outcomes of the infants born during the trial whose outcomes are not reported could affect the results. However, their outcomes would need to be markedly skewed between treatment groups to affect the overall conclusions. A further minor caution is that gestation at delivery is reported by infants, not by mothers. Since progeny of multiple births inevitably deliver in very quick succession, logic suggests that multiple births should not be considered independently when comparing gestation at delivery. However, the proportion of multiple births in the two groups was similar (25 of 251 in the placebo group and 20 of 261 in the atosiban group), and the distribution of gestation at delivery was sufficiently similar that it is unlikely that re-analysis would markedly affect interpretation of the study results.

The mean gestation at enrolment in the trial was approximately 31 weeks. A pharmaco-economic analysis mentioned by the authors but published only in abstract form suggests that benefits of treatment may be greater at earlier gestations (Gagnon 1998). Indeed, after mid-third trimester preterm birth, neonatal outcomes are sufficiently good that benefits to the infant of prolonging the pregnancy after corticosteroid treatment and transfer to a tertiary centre are relatively small. However, in the absence of data showing greater benefits, no recommendation for atosiban maintenance treatment can be made at any gestation.

The intention of this review was to consider maintenance treatment after threatened or actual preterm labour. Entry criteria for the sole trial included a definition of preterm labour that included regular contractions and documented cervical changes. It is conceivable that treatment of women with less advanced changes in the lower uterine segment and cervix would be more effective. However, such women may also be less likely to progress to very preterm delivery regardless of treatment. Furthermore, the number of women who delivered very prematurely in this study was small, despite the rigour of the entry criteria.

Several systematic reviews have reported that various tocolytic agents can postpone progression of preterm labour and delay preterm birth for at least 48 hours, although the incidence of neonatal morbidity and mortality was not reduced (Anotayanonth 2004; Gyetvai 1999; King 1988). However, after preterm labour has been suppressed, the review authors have concluded that maintenance therapy using a variety of agents does not reduce the incidence of preterm birth or improve neonatal outcomes (Dodd 2012; Gaunekar 2004; Han 2013; Khanprakob 2012; Nanda 2002; Sanchez-Ramos 1997). The triggering factors and mechanisms of preterm birth are likely to vary between pregnancies and preterm birth is the final common outcome of several discrete but converging pathophysiological pathways, including ascending infection, (utero) placental insufficiency, uterine distension and fetal stress. Tocolytic agents are thought to act where these pathways merge, when pathological influences may already be well established. Therefore, to have a substantial influence on neonatal outcomes, management strategies to prevent preterm birth may need a greater focus on the underlying causes and earlier steps in the development of preterm labour.

In this review, atosiban subcutaneously administered as maintenance therapy after a period of preterm labour was not shown to be associated with a reduction of the incidence of preterm birth, or any improvement of neonatal outcome.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence does not support the use of oxytocin receptor antagonists for maintenance therapy after a period of preterm labour.

Implications for research

A single large, high-quality trial of atosiban administered by continuous subcutaneous infusion as maintenance therapy after a period of preterm labour has not shown clinically significant benefits. To justify the risks and burdens of treatment for pregnant women, any future trials using oxytocin antagonists or other drugs as maintenance therapy for preventing preterm birth should examine a variety of important infant outcome measures, including not only reduction of neonatal morbidity and mortality, but also long-term infant follow-up. Future research should also focus on the pathophysiological pathways that precede preterm labour.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Valenzuela 2000

Methods	Placebo-controlled, randomised trial.
Participants	513 women in a multicentre trial who had preterm labour and intact membranes, with pregnancies between 20 and 33 6/7 weeks, less than or equal to 3 cm cervical dilatation, and a live fetus, who after uterine quiescence was achieved using IV atosiban (not placebo) were randomised to either placebo or atosiban maintenance therapy Exclusion criteria: fetal or placental abnormalities by ultrasonography, maternal indications for delivery, urinary tract infection, and overt clinical manifestations of substance abuse
Interventions	Active drug and placebo were administered at the same volume and rate. Atosiban group: Atosiban for maintenance was administered by a subcutaneous infusion pump to provide a continuous atosiban infusion of 6 mL/hr (30 μg/min). Placebo group: Placebo for maintenance was administered by a subcutaneous infusion pump to provide a continuous placebo infusion of 6 mL/hr. If subsequent IV treatment with atosiban was given for any additional episode of preterm labour, subcutaneous maintenance therapy using the assigned study treatment was recommenced if uterine quiescence was achieved. Both active drug and placebo were administered until the end of week 36 of gestation, delivery, or progression of labour requiring a tocolytic agent other than atosiban. All women on maintenance therapy were discharged home with daily nursing contact for all. Compliance was checked by diaries kept by women and drugs used
Outcomes	The objective of the study was to determine the safety and efficacy of maintenance therapy with the oxytocin receptor antagonist atosiban. The primary end point was the number of days from the start of maintenance therapy until the first recurrence of labour
Notes	A sample size of 250 women in each group was estimated to be required to provide 80% power to detect an atosiban/placebo ratio of 1.3 for the mean numbers of days from the start of maintenance therapy to the first recurrence of labour. Corticosteroids were administered for standard clinical indications. GBS protocol was unspecified Antibiotic therapy was allowed for standard clinical conditions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation stratified by centre, in permuted blocks of 4

Valenzuela 2000 (*Continued*)

Allocation concealment (selection bias)	Low risk	Active drug and placebo were prepared by the R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ: supplied to pharmacist in each centre in sequential pre-numbered envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, study personnel and monitors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation exclusion of one woman (placebo group) who did not receive treatment
Selective reporting (reporting bias)	Unclear risk	Assessment from published reports. Further information was sought from authors but was not forthcoming
Other bias	Low risk	Not apparent.

hr: hour
IV: intravenous
min: minute
mL: millilitre
µg: microgram
GBS: Group B Streptococcus

DATA AND ANALYSES

Comparison 1. Atosiban versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	512	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Birth before 28 weeks	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.01]
3 Birth before 32 weeks	1	285	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.47, 1.55]
4 Birth before 37 weeks	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.12]
5 Respiratory Distress Syndrome	1	557	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.66, 1.70]
6 Infant death (up to 12 months)	1	558	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.20, 2.74]
7 Necrotising enterocolitis	1	557	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [0.46, 11.93]
8 Patent ductus arteriosius	1	557	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.47, 2.91]
9 Neonatal Intensive Care Unit admission	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.62, 1.14]
10 Fetal death	1	512	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [0.12, 70.50]
11 Neonatal death	1	512	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.39]
12 Perinatal death	1	512	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.21, 2.83]
13 Birth weight (grams)	1	558	Mean Difference (IV, Fixed, 95% CI)	0.10 [-131.78, 131.98]

Analysis 1.1. Comparison 1 Atosiban versus placebo, Outcome 1 Maternal death.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 1 Maternal death

Study or subgroup	Atosiban n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	0/261	0/251			Not estimable
Total (95% CI)	**261**	**251**			**Not estimable**

Total events: 0 (Atosiban), 0 (placebo)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.2. Comparison 1 Atosiban versus placebo, Outcome 2 Birth before 28 weeks.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 2 Birth before 28 weeks

Study or subgroup	Atosiban n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	7/45	6/29		100.0 %	0.75 [0.28, 2.01]
Total (95% CI)	**45**	**29**		**100.0 %**	**0.75 [0.28, 2.01]**
Total events: 7 (Atosiban), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.3. Comparison 1 Atosiban versus placebo, Outcome 3 Birth before 32 weeks.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 3 Birth before 32 weeks

Study or subgroup	Atosiban n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	19/158	18/127		100.0 %	0.85 [0.47, 1.55]
Total (95% CI)	**158**	**127**		**100.0 %**	**0.85 [0.47, 1.55]**
Total events: 19 (Atosiban), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.4. Comparison 1 Atosiban versus placebo, Outcome 4 Birth before 37 weeks.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 4 Birth before 37 weeks

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	90/267	92/243	■	100.0 %	0.89 [0.71, 1.12]
Total (95% CI)	**267**	**243**	◆	**100.0 %**	**0.89 [0.71, 1.12]**
Total events: 90 (Atosiban), 92 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.5. Comparison 1 Atosiban versus placebo, Outcome 5 Respiratory Distress Syndrome.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 5 Respiratory Distress Syndrome

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	33/288	29/269	■	100.0 %	1.06 [0.66, 1.70]
Total (95% CI)	**288**	**269**	◆	**100.0 %**	**1.06 [0.66, 1.70]**
Total events: 33 (Atosiban), 29 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.6. Comparison 1 Atosiban versus placebo, Outcome 6 Infant death (up to 12 months).

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 6 Infant death (up to 12 months)

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	4/289	5/269		100.0 %	0.74 [0.20, 2.74]
Total (95% CI)	**289**	**269**		**100.0 %**	**0.74 [0.20, 2.74]**
Total events: 4 (Atosiban), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours Maintenance   Favours Placebo

Analysis 1.7. Comparison 1 Atosiban versus placebo, Outcome 7 Necrotising enterocolitis.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 7 Necrotising enterocolitis

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	5/288	2/269		100.0 %	2.34 [0.46, 11.93]
Total (95% CI)	**288**	**269**		**100.0 %**	**2.34 [0.46, 11.93]**
Total events: 5 (Atosiban), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

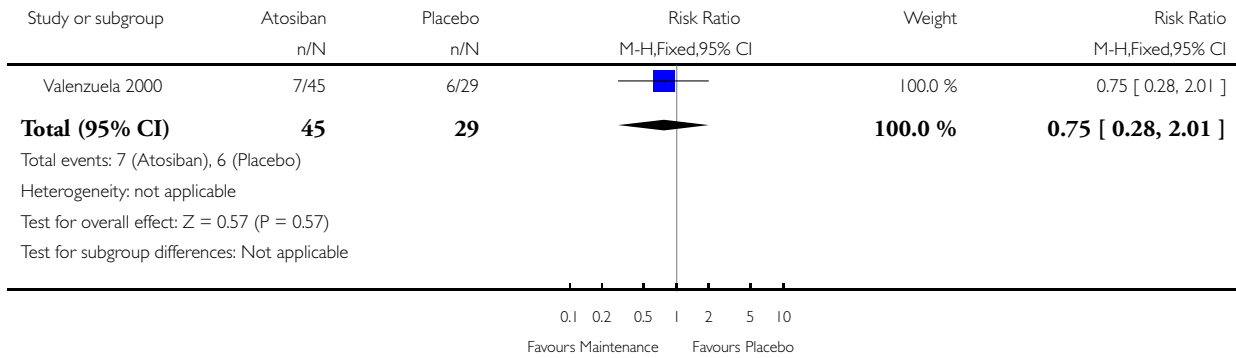Favours Maintenance   Favours Placebo

Analysis 1.8.   Comparison 1 Atosiban versus placebo, Outcome 8 Patent ductus arteriosius.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 8 Patent ductus arteriosius

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	10/288	8/269		100.0 %	1.17 [0.47, 2.91]
Total (95% CI)	**288**	**269**		**100.0 %**	**1.17 [0.47, 2.91]**

Total events: 10 (Atosiban), 8 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.33 (P = 0.74)

Test for subgroup differences: Not applicable

```
        0.1  0.2  0.5   1    2    5   10
     Favours Maintenance    Favours Placebo
```

Analysis 1.9.   Comparison 1 Atosiban versus placebo, Outcome 9 Neonatal Intensive Care Unit admission.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour
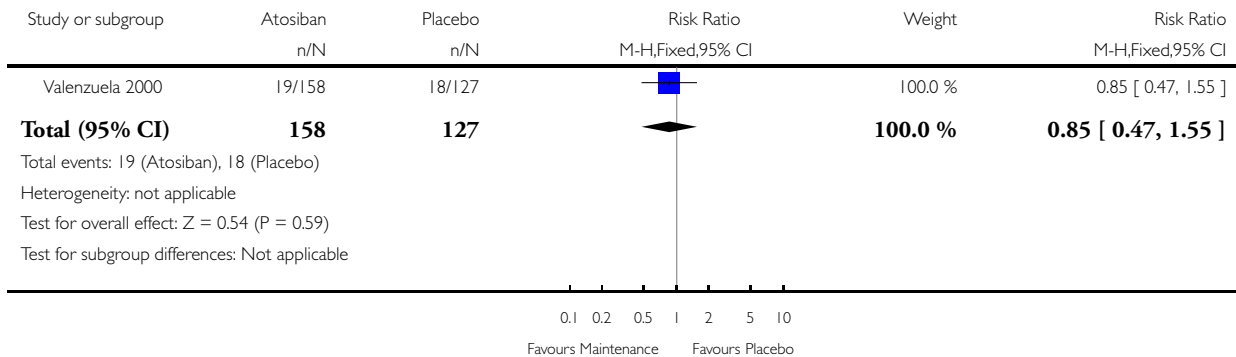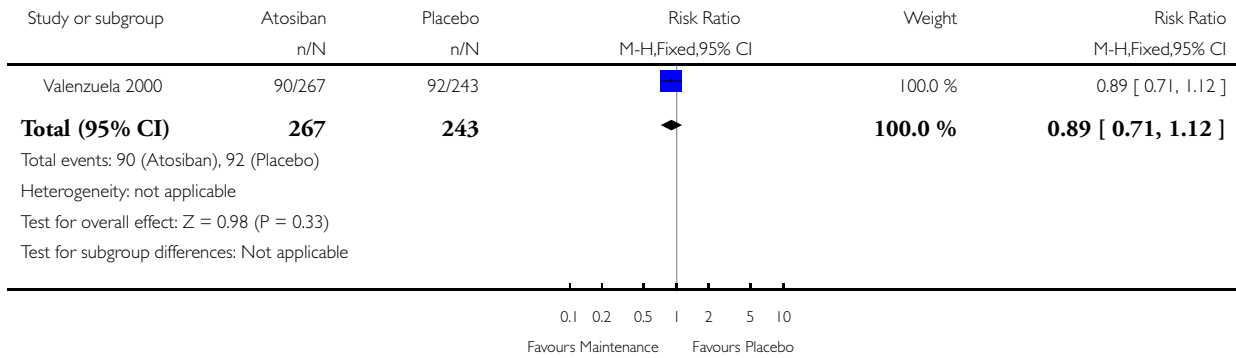
Comparison: 1 Atosiban versus placebo

Outcome: 9 Neonatal Intensive Care Unit admission

Study or subgroup	Atosiban	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Valenzuela 2000	61/284	68/266		100.0 %	0.84 [0.62, 1.14]
Total (95% CI)	**284**	**266**		**100.0 %**	**0.84 [0.62, 1.14]**

Total events: 61 (Atosiban), 68 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

```
        0.1  0.2  0.5   1    2    5   10
     Favours Maintenance    Favours Placebo
```

Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour (Review)   **18**

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Analysis 1.10. Comparison 1 Atosiban versus placebo, Outcome 10 Fetal death.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 10 Fetal death

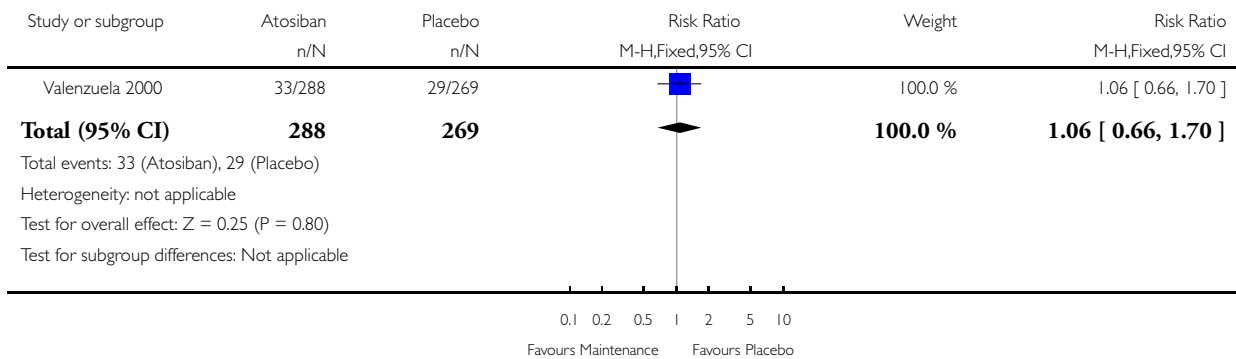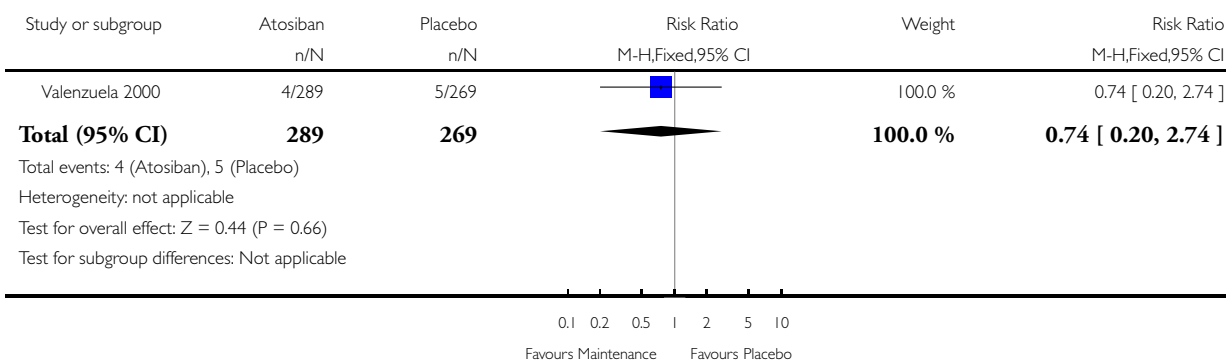| Study or subgroup	Atosiban n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	1/261	0/251		100.0 %	2.89 [0.12, 70.50]
Total (95% CI)	**261**	**251**		**100.0 %**	**2.89 [0.12, 70.50]**
Total events: 1 (Atosiban), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Not applicable					

```
       0.1  0.2  0.5   1    2    5   10
    Favours Maintenance   Favours Placebo
```

Analysis 1.11. Comparison 1 Atosiban versus placebo, Outcome 11 Neonatal death.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

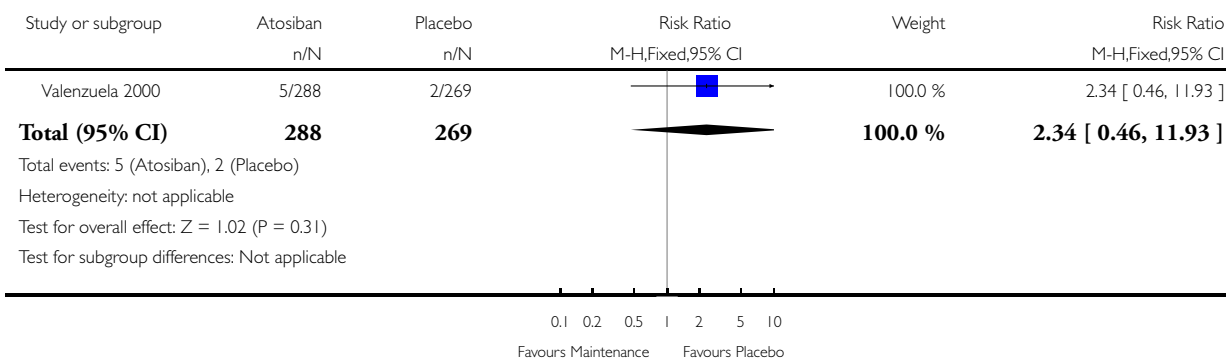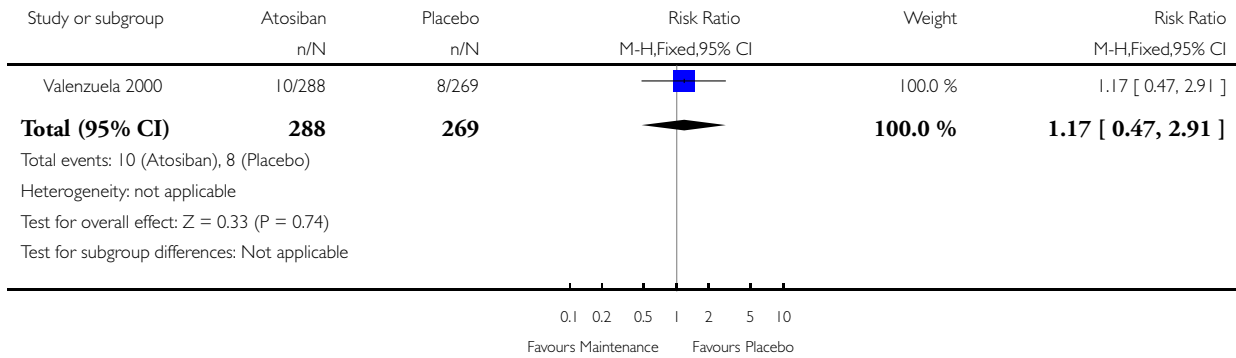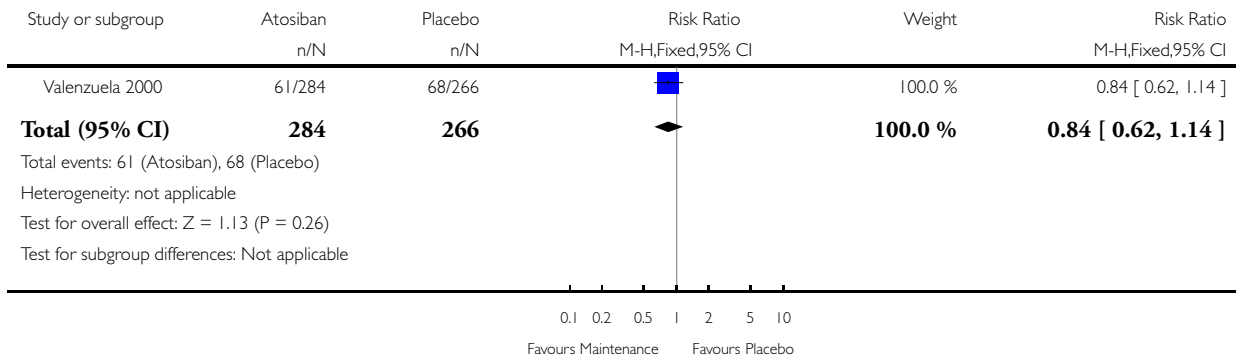Comparison: 1 Atosiban versus placebo

Outcome: 11 Neonatal death

Study or subgroup	Atosiban n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	3/261	5/251		100.0 %	0.58 [0.14, 2.39]
Total (95% CI)	**261**	**251**		**100.0 %**	**0.58 [0.14, 2.39]**
Total events: 3 (Atosiban), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Not applicable					

```
       0.1  0.2  0.5   1    2    5   10
    Favours Maintenance   Favours Treatment
```

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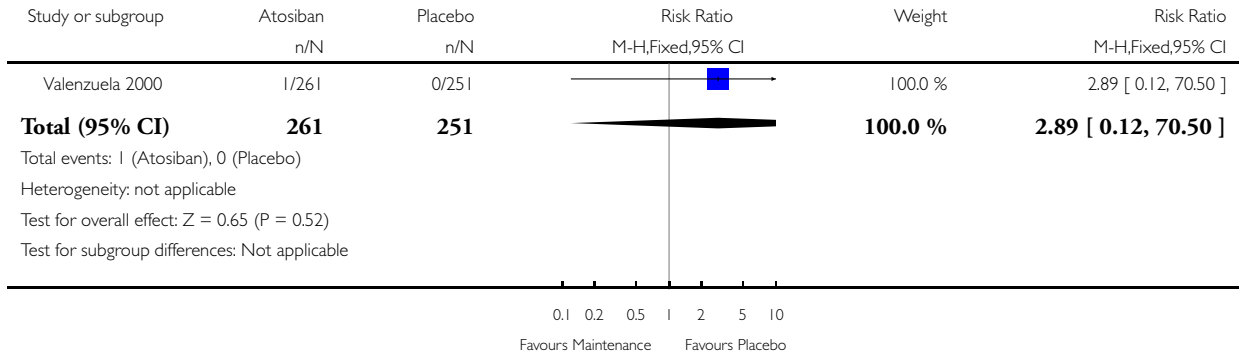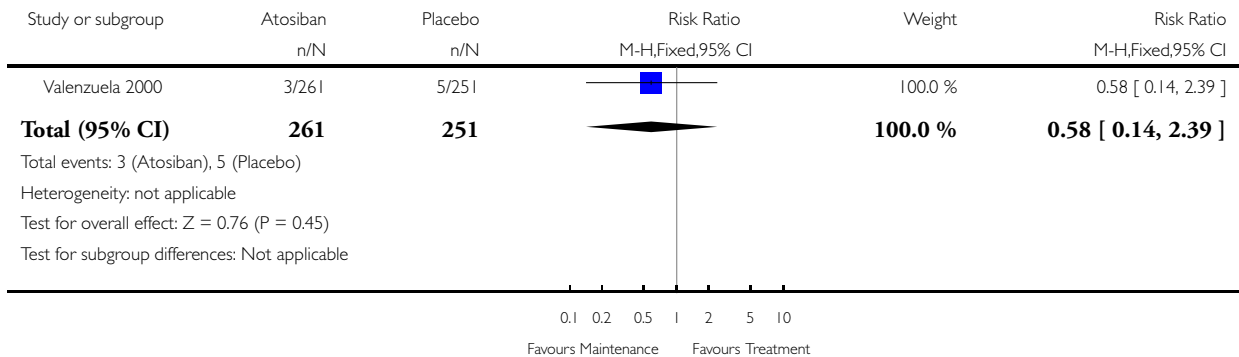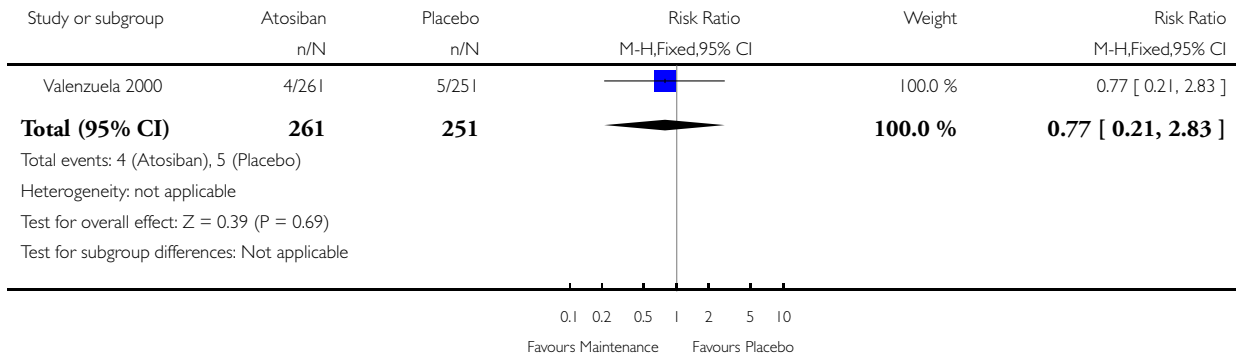
Analysis 1.12. Comparison 1 Atosiban versus placebo, Outcome 12 Perinatal death.

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo
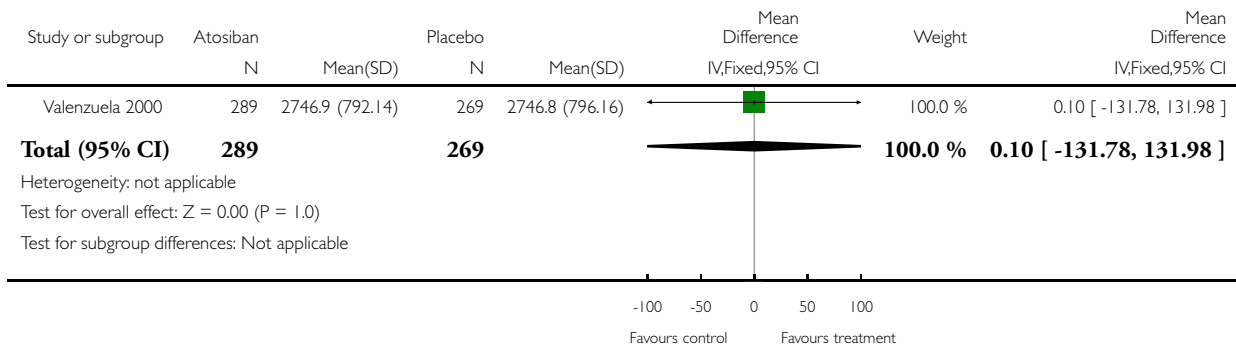
Outcome: 12 Perinatal death

Study or subgroup	Atosiban n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Valenzuela 2000	4/261	5/251		100.0 %	0.77 [0.21, 2.83]
Total (95% CI)	**261**	**251**		**100.0 %**	**0.77 [0.21, 2.83]**

Total events: 4 (Atosiban), 5 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.39 (P = 0.69)

Test for subgroup differences: Not applicable

```
        0.1  0.2   0.5   1   2   5   10
     Favours Maintenance    Favours Placebo
```

Analysis 1.13. Comparison 1 Atosiban versus placebo, Outcome 13 Birth weight (grams).

Review: Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour

Comparison: 1 Atosiban versus placebo

Outcome: 13 Birth weight (grams)

Study or subgroup	Atosiban N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Valenzuela 2000	289	2746.9 (792.14)	269	2746.8 (796.16)		100.0 %	0.10 [-131.78, 131.98]
Total (95% CI)	**289**		**269**			**100.0 %**	**0.10 [-131.78, 131.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.00 (P = 1.0)

Test for subgroup differences: Not applicable

```
     -100   -50    0    50   100
     Favours control    Favours treatment
```

WHAT'S NEW

Last assessed as up-to-date: 28 August 2013.

Date	Event	Description
25 October 2013	Amended	Contact details edited.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 1, 2009

Date	Event	Description
28 August 2013	New search has been performed	Review updated.
28 August 2013	New citation required but conclusions have not changed	Search updated. No new trials identified.
11 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dimitri Papatsonis and Vicki Flenady identified trials for inclusion, and extracted data. Three authors worked collaboratively in compiling the review. Dimitri Papatsonis is guarantor for the review.

All authors approved the 2013 update.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Amphia Hospital Breda, Breda, Netherlands.
- Centre for Clinical Studies - Women's and Children's Health, Mater Hospital, South Brisbane, Queensland, Australia.

External sources

- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), the Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Obstetric Labor, Premature [prevention & control]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Receptors, Oxytocin [*antagonists & inhibitors]; Tocolytic Agents [*therapeutic use]; Vasotocin [*analogs & derivatives; therapeutic use]

MeSH check words

Female; Humans; Pregnancy

Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour (Review) 22

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