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REVIEW ARTICLE

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ATOSIBAN EFFICACY AND SAFETY IN PREGNANT WOMEN WITH THREATENED PRETERM DELIVERY: SYSTEMATIC REVIEW OF THE LITERATURE WITH NETWORK META-ANALYSIS

Eficacia y seguridad de Atosiban en mujeres gestantes con diagnóstico de amenaza de parto pretérmino: revisión sistemática de la literatura con metaanálisis en red

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ABSTRACT

Objective: To assess the efficacy and safety of atosiban in pregnant women with risk of preterm delivery as compared to nifedipine, indomethacin, terbutaline, fenoterol and placebo.

Materials and methods: A systematic literature review was carried out in eight electronic databases, including Medline, Central, and Embase, using free and standardized search terms. Outcomes assessment included time delay until delivery, neonatal mortality, ratio of adverse maternal events, and ratio of neonatal complications. The quality of the evidence was evaluated per study and for the body of evidence and, whenever feasible, the information was synthesized into a meta-analysis. Alternatively, a narrative summary was presented.

Results: Eleven studies were included. Atosiban did not show any statistically significant differences in terms of delaying delivery versus other uterine contraction inhibitors. The neonatal mortality was lower compared to indomethacin (RR = 0.21; 95% CI: 0.05 to 0.92), and the percentage of total maternal adverse events was lower compared to fenoterol (RR = 0.16; 95% CI: 0.08 to 0.31), nifedipine (RR = 0.48; 95% CI: 0.3 to 0.78), and terbutaline (RR = 0.44; 95% CI: 0.28 to 0.71).

Conclusions: Atosiban has similar efficacy for delivery delay in patients with risk of preterm delivery as compared to other agents (moderate certainty), showing some advantages regarding neonatal mortality (low certainty) versus indomethacin, and compared to fenoterol, nifedipine and terbutaline in terms of maternal adverse events (moderate certainty).

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Keywords: preterm labor, meta-analysis, nifedipine, indomethacin, terbutaline, fenoterol, placebos, and medication-associated adverse reactions.

RESUMEN

Objetivo: evaluar la eficacia y seguridad de atosiban en gestantes con amenaza de parto pretérmino comparado con nifedipino, indometacina, terbutalina, fenoterol y placebo.

Materiales y métodos: se realizó una revisión sistemática de la literatura en ocho bases de datos electrónicas (Medline, Central, Embase, entre otras), mediante términos de búsqueda libres y estandarizados. Los desenlaces evaluados incluyeron tiempo de retardo del parto, mortalidad neonatal, proporción de eventos adversos maternos y proporción de complicaciones neonatales. Se evaluó la calidad de la evidencia por estudio y para el cuerpo de evidencia, y se sintetizó la información mediante metaanálisis, cuando fue posible; de lo contrario, se resumió de forma narrativa.

Resultados: se incluyeron once estudios. Atosiban no mostró diferencias estadísticamente significativas en retardo del parto contra otros uteroinhibidores. Mostró menor mortalidad neonatal que la indometacina (RR = 0,21; IC 95 %: 0,05 a 0,92), y menor proporción de eventos adversos maternos totales que el fenoterol (RR = 0,16; IC 95 %: 0,08 a 0,31), el nifedipino (RR = 0,48; IC 95 %: 0,3 a 0,78) y la terbutalina (RR = 0,44; IC 95 %: 0,28 a 0,71).

Conclusiones: atosiban tiene una eficacia similar para retardar el parto ante la amenaza de un parto pretérmino con otros comparadores (certeza moderada), con ventajas frente a indometacina en mortalidad neonatal (certeza baja) y frente a fenoterol, nifedipino y terbutalina en eventos adversos maternos (certeza moderada).

Palabras clave: trabajo de parto prematuro, metaanálisis, nifedipino, indometacina, terbutalina, fenoterol, placebos, reacciones adversas relacionadas con medicamentos.

INTRODUCTION

The risk of preterm delivery is defined as onset of labor generating changes in the cervix to allow for the descent and birth of the baby before week 38 (1). Preterm delivery, defined as childbirth between 20 and 37 weeks plus 6 days of pregnancy, is the major cause of neonatal morbidity and mortality (2). It is estimated that every year there are approximately 15 million preterm deliveries worldwide, which corresponds to 11.1% of all births (3). A study led by the World Health Organization (WHO) found that the percentage of preterm deliveries in South America/Latin America is 8.1 and 7.9%, respectively, versus the total number of deliveries recorded in each region (4). In Colombia, according to the figures of the National Statistics Department (Departamento Administrativo Nacional de Estadística - DANE), premature deliveries accounted for 20.1% of all births in 2016 (5).

Risk factors associated with preterm delivery include maternal risks such as age (under 18 or over 40 years), low socioeconomic bracket, smoking, use of psychoactive substances or alcohol, excess physical activity, stress and malnutrition, uterine disorders, infections, a history of preterm delivery, rupture of membranes, multiple gestation, first and second trimester bleeds, and fetal causes, such abnormal placentation (1, 6).

It has been estimated that 28% of the fetal deaths that occur annually are due to preterm deliveries (7). Neonatal morbidity and mortality are inversely proportional to gestational age at birth: 99% of preterm delivery-associated morbidity and mortality occur before 34 weeks (2). Of babies born at 24 weeks, 80% will die, whilst 90% of the babies born during week 30 of gestation will survive. It has been shown that babies born at 22, 24 and 26 weeks of gestation show mortality rates of 54, 21 and 2% respectively, with higher disease-free one-year survival rates greater than 0.02, 14.1 and 45.9% (8). This means that prolonging pregnancy increases the probability of survival for the newborn.

Premature neonates have higher rates of neurodevelopmental disorders (5), respiratory complications such as asthma and bronchitis (9), and potential physical, psychological and economic consequences (10). Long term impact on premature birth survivors include: visual impairment (blindness, myopia, retinopathy, hyperopia) in 25% of cases, hearing impairment in 5-10%, prematurity-related chronic pulmonary disease requiring oxygen supplementation at home (40%), cardiovascular disease including high blood pressure, reduced pulmonary function, higher asthma rates, growth failure and accelerated weight gain during adolescence. Neurodevelopmental problems include gait disorders, overall developmental delay, and psychiatric and behavioral sequelae (attention deficit/hyperactivity disorder, increased anxiety and depression disorder) (10).

The diagnosis of preterm labor is based on the presence of regular uterine contractions causing cervical changes (11). According to the Bogotá Health Secretariat clinical care guidelines, diagnosis is made in patients between 20 and 37 weeks of pregnancy, showing uterine activity of at least 4 contractions in 20 minutes, or 8 contractions in one hour, with intact membranes and cervical changes of 80% effacement and 2 cm dilation (1).

Preterm delivery treatment is indicated in patients between 20 and 37 weeks, with regular uterine activity. Tocolytic treatment is contraindicated in patients rupture of membranes, chorioamnionitis, congenital malformations and fetal demise (1). Treatment for preterm labor emphasizes hydration, since hypovolemia may be associated with increased uterine activity. However, tocolytic agents are used to inhibit uterine contractions with the purpose of delaying labor and achieving an effective maturation of the fetus (1, 2, 12). There are different drug families that may be used as tocolytic agents, including β_2-agonists, calcium channel blockers, oxytocin receptor antagonists, and cyclooxygenase inhibitors (13). The choice of a tocolytic agent is based on the patient's particular characteristics, and the drug's safety profile and effectiveness (14).

Atosiban is an oxytocin receptor antagonist, a tocolytic agent approved in 2007 by the National Food and Drug Surveillance Institute (Instituto Nacional de Vigilancia de Medicamentos y Alimentos - INVIMA) to delay imminent preterm delivery in pregnant women over the age of 18, with 24 to 33 complete weeks of pregnancy and normal fetal heart rate, presenting with threatened preterm delivery. INVIMA is the regulatory agency that issues approval for marketing medications in Colombia.

A review of meta-analyses found in the literature showed that none of the studies identified through database search assessed all outcomes or conditions of interest for our study, namely, maternal gestational age at the time of delivery, percentage of neonatal mortality, newborn respiratory distress syndrome, intraventricular bleeding, periventricular leukomalacia, necrotizing enterocolitis, percentage of maternal adverse events, and neonatal complications. Given the recognition that preterm delivery management is of paramount importance for reducing maternal and neonatal complications, this study focuses on evaluating the effectiveness and safety of atosiban versus nifedipine, indomethacin, terbutaline, fenoterol and placebo for the prevention of preterm delivery, taking perinatal and maternal outcomes into account.

MATERIALS AND METHODS

The final research question of this paper is shown in Table 1. This question was fine-tuned through expert consultation to define the need to limit the gestational age to that indicated by the National Food and Drug Surveillance Institute (INVIMA) (between 24 and 33 full weeks) and not consider magnesium sulphate as a comparator, as was initially suggested.

The inclusion criteria were the following:

Types of studies: Randomized clinical phase III trials with no publication date restriction, available in full text for comprehensive assessment when included in the review and meta-analysis.

Type of population: Studies that included adult pregnant patients with risk of imminent preterm

Table 1. PICOT structure assessment question	
P	Adult patients with risk of preterm labor between 24 and 33 weeks
I	Atosiban
C	Nifedipine, indometacine, terbutaline, fenoterol, placebo.
O	**Effectiveness** ***Primary*** Delivery delayed for more than 48 hours Delivery delayed for more than 7 days ***Secondary*** Gestational age at the time of birth **Safety** ***Primary*** Neonatal mortality rate Maternal adverse event rate ***Secondary*** Neonatal Respiratory Distress Syndrome Intraventricular Hemorrhage Periventricular Leukomalacia Rate of neonatal complications
T	According to reports in the trials

delivery, defined as regular uterine contractions at least 30 seconds in duration and a frequency of more than 4 contractions every 30 minutes; cervical dilation of 1 to 3 cm (0 to 3 cm for nulliparous women) and effacement > 50%; gestational age 24 to 33 full weeks and with normal fetal heart rate (110-160 bpm) according to the expert panel and the Colombian guidelines for the management of preterm delivery (1).

Type of intervention: The technology of interest was atosiban and the comparators were nifedipine, indomethacin, terbutaline, fenoterol, and placebo.

The primary effectiveness outcomes were absence of delivery at 48 hours and at 7 days, and secondary outcomes were the difference in gestational age at the time of delivery. Concerning safety, the primary outcomes were percentage of neonatal mortality and the proportion of maternal adverse events; the secondary outcomes were newborn respiratory distress syndrome, the frequency of intraventricular hemorrhage, the frequency of periventricular leukomalacia, and the percentage of total neonatal complications.

Any trials that were not available in full text but only as posters or abstracts were excluded because the complete information on the characteristics and outcomes of those references were not available for inclusion in the analysis.

Search Strategy

A literature search was conducted using the following databases: Medline via PubMed, EMBASE (Elsevier), Cochrane Database of Systematic Reviews (Wiley platform), Database of Abstracts of Reviews of Effects (DARE) (Wiley platform), Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid platform), Lilacs (Virtual Heal Library - VHL, iAHx interface), WHO International Clinical Trials Registry Platform ICTRP portal, and ClinicalTrials.gov (Annex 1).

The key words used for the search were defined based on the PICOT question (Table 1). The first step was the inclusion of the terms to define the population and then the search terms for the technologies involved.

The criteria for defining the population as free text and controlled vocabulary (MeSH, Emtree and DeCS) were: "Obstetric labor," "Premature" [Mesh] and "Preterm birth". The terms for the health technologies of interest that were associated with the Boolean operator *odds ratio* (OR) were: "Nifedipine," "Terbutaline," "Atosiban," "Indomethacin," "Fenoterol" and "placebo". Finally, the set of search terms that defined the population was combined with the terms of the health technologies of interest using the Boolean operator "AND".

The search terms used were adjusted according to the search platform of each electronic database. No filters were used for text availability (abstract), date of publication, type of study, or language (Annex 1).

Likewise, a manual "snowball" search was conducted based on the list of references of each article selected by the reviewers in search for other publications that met the previously defined search criteria.

Screening of references and selection of studies:

Prior to the start of the process, the selection criteria of the articles were shared and questions about the selection process were answered. The screening of references was conducted independently by two investigators (LS and PR), without knowing the results of the other. Afterwards, the articles selected by each reviewer were compared, any doubts regarding the selection of the articles were resolved by consensus between the reviewers, evaluating the new title and abstract, and in case additional information was required, the full text was obtained to finally make a decision of whether to include the articles or not. In case of disagreement, a third investigator was asked to participate (DR).

Assessment of the quality of the evidence

The assessment of the quality of the evidence and the risk of bias was evaluated for each article in a paired manner by both investigators (LS and PR). The articles selected were evaluated using the tool designed by the Cochrane Collaboration for identifying any risk of bias (15). This tool assesses the risk of the following biases: selection (random generation and blind assignment were taken into account); execution (blinding of the participants and the staff was evaluated); detection (outcome assessment risk was evaluated); attrition (the presence of incomplete data was assessed); and reporting (assessment for selective data reporting was performed). Based on these considerations, each article was categorized accordingly as: high, low or undetermined risk of bias. Disagreements were solved by a third researcher (DR).

Additionally, the tool developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group was used to assess the quality of the evidence set found for each outcome (16). This tool assesses the number of studies available for each outcome, study design, risk of bias, inconsistency in the results, the indirect nature of the results, inaccuracy, and other considerations (dose-response gradient and publication bias). Considerations for network meta-analysis assessment were taken into account (17). Summary tables for quality assessment were reported in accordance with the proposed network meta-analysis model (17).

Data extraction and evidence synthesis

For data extraction, the selected publications as well as the reports published as annexes and supplements were taken into consideration whenever it was necessary and depending on their availability. Extracted data included interventions, primary study inclusion and exclusion criteria, number of patients, age, clinical characteristics, type of analysis, outcomes assessed, ethical approval, site, and funding. Data for all the studies were uploaded to an

Excel® worksheet. Data extraction was conducted by searching for the information reported as part of the intention-to-treat analysis. When available, information derived from safety analysis was considered, specifically in relation to adverse events. The total number of patients in each arm and the number of patients analyzed were considered for data extraction for the arms in each of the studies. Following data extraction, quality control of the information obtained was performed by means of comparison with the records of the primary studies. For adverse event analysis, all reported maternal events for each of the studies, both in the intervention group as well as in the control group, were added and compared.

Statistical analysis. After collecting the studies, assessments to determine head-to-head comparisons were performed. In those cases in which direct information was not derived from a comparison, the possibility of indirect comparisons using network meta-analyses was evaluated. To this end, the first thing that was determined was whether there was a comparison network that could enable an indirect comparison. When that was the case, the characteristics of the populations and the methods of each study were verified in order to assess transitivity within the information set found. In those cases in which this was not possible, a narrative report of the outcomes was made based on the data reported in the primary studies. If not, a network meta-analysis was conducted using the R statistical tool (*R Development Core Team*), version 3.2.3 and the R package netmeta, version 0.9-2, which uses a frequency analytical method. For categorical outcomes in each study, event and population numbers, or the comparison measurement, were extracted: risk ratio (RR), hazard ratio (HR), odds ratio (OR), with their respective scatter or confidence interval measurement for assessment (15). For continuous outcomes, the mean for each group was extracted together with scatter or mean difference and confidence interval. *A priori* subgroup analyses were not considered.

This information was entered into the statistical software package using Microsoft Excel templates. Once the analysis was completed, the presence of I^2 statistical heterogeneity was verified, categorizing it as suggested in the Cochrane manual (18): not significant between 0 and 40%, moderate between 30 and 60%, substantial between 50 and 90%, and considerable between 75 and 100%. Additionally, the intra- and inter design Q test was performed in order to assess heterogeneity and consistency. Model consistency was verified by means of a comparison between direct available relationships and model estimates. The model contains estimates for all possible comparisons between all outcomes. Results were reported in league tables, showing the appropriate model estimates and direct results according to the outcome. Using a frequentist methodology similar to the Surface Undercumulative Ranking Curve (SUCRA), employed in Bayesian models and available in the netmeta package, the probability of being the best option among the ones used in the model was calculated.

Ethical considerations. Given that this research consists of a review of the literature and a meta-analysis, it is considered risk-free. Pursuant to Article 11 of Resolution 8430 of 1993 (19), risk-free research is described as consisting of "studies that use retrospective document review techniques and methods, and studies where no intervention or intentional modification to the biological, physiological or social variables of the subjects is performed. These include clinical record reviews, interviews, questionnaires and other studies which do not identify or deal with sensitive subject behavior considerations".

RESULTS

Overall, 5245 references were found as a result of the screening. After removing duplicates, a total of 4599 references were obtained. Of these, 30 which

met the inclusion criteria by title and abstract were included for full-text evaluation. Finally, 11 studies (20-30) corresponding to randomized clinical trials were selected for inclusion in the qualitative and quantitative analyses. The characteristics of the studies included are described in Annex 2; most were only two-arm studies. All the studies met the gestational age for inclusion in one of the following ways: consideration of the entire range of interest, partial consideration of the range of interest, consideration of a wider range, but reporting the information for the range of interest. The majority of the studies included a population of young women with a mean age ranging between 25 and 30 years. Singleton and twin pregnancies were considered in the majority of the studies. The reasons for reference exclusions are shown in Annex 3. Four records with no results were found in clinicaltrials.gov and 1 reference was a poster report and, for this reason, they were not considered in the results. For another study, there was a record stating that it had been withdrawn before the initiation of the trial. Of the remaining 9 studies, 9 did not represent the inclusion criteria for the populations (reports of gestational ages outside the range considered, excess cervical dilation), and two showed aggregate results for various comparators (beta-agonists together, medications and bedrest grouped together). Figure 1 shows the PRISMA reference screening flow diagram.

Risk of biases

The 11 phase III controlled clinical trials were assessed. (20-30) High risk of performance and detection biases was identified for 5 open-label studies (20, 21, 23, 24, 28). For the remaining studies, low or indeterminate risk of selection, performance, detection, attrition reporting and other forms of biases were found. Risk-of-bias summary tables are shown in Figure 2.

Quality of the evidence

Annex 4 shows GRADE evidence profiles for important outcomes with evidence summary tables, together with the network geometry.

Effectiveness

Delivery delay of more than 48 hours. 8 relevant studies were identified for this outcome, (20, 21, 23-26, 28, 30) for a total of 1436 randomized patients; a network meta-analysis was performed. The results are summarized in Table 2. No statistically significant differences are found between atosiban and fenoterol (RR = 1.26; 95% CI: 1-1.59, moderate certainty), nifedipine (RR = 1.02; 95% CI: 0.91-1.15, moderate certainty) and terbutaline (RR = 1.06; 95% CI: 0.93-1.21, moderate certainty). Similar results are observed in head-to-head comparisons. No significant differences are found either between fenoterol, nifedipine and terbutaline (Table 2). In this analysis, I^2 was 44.7% (moderate heterogeneity) with intra- and inter-design *p* value in the Q test of 0.11 and 0.24, respectively, that is, not statistically significant. No relevant inconsistencies were found for this analysis (Annex 4).

Regarding the comparison between atosiban and placebo, the head-to-head study (22) reports a composite result together with the outcome of not needing additional tocolytic agents at 48 hours. For this comparison in women between 28 and 33 full weeks of gestation, the study found an absolute risk difference of 14% (95% CI: 4-23).

Delivery delay of more than 7 days: 7 relevant studies were identified for this comparison (20, 21, 23-26, 29) with a total of 1305 randomized patients; a network meta-analysis was performed (Table 3). No statistically significant differences were found between atosiban and fenoterol (RR = 1.18; 95% CI: 0.71-1.95, moderate certainty), nifedipine (RR = 1.06; 95% CI: 0.82-1.37, moderate certainty) and terbutaline (RR = 1.37; 95% CI: 0.99-1.89, low

Table 2.
Delivery delay longer than 48 hours*

League Table								
Direct Estimators								
	Atosiban	1.26 (1.00-1.59)	1,00 (0.88-1.13)	1,10 (0.95-1.27)				
Model Estimators	1,26 (1.00-1.59)	**Fenoterol**	-	-				
	1,02 (0.91-1.15)	0,81 (0.62-1.05)	**Nifedipine**	0,92 (0.70-1.22)				
	1,06 (0.93-1.21)	0,84 (0.64-1.10)	1,04 (0.89-1.22)	**Terbutaline**				
Model Estimators, direct and indirect								
Comparison	**Number of direct studies**	**Proportion of data extracted from direct studies**	**Model Estimator**	**Direct estimator**	**Indirect estimator**	**Direct/indirect estimator ratio**	**Z**	**P value**
atosiban:fenoterol	1	1	1,26	1.26	ND	ND	ND	ND
atosiban:nifedipine	3	0.87	1.0204	0.9971	1.1857	0.8409	-0.99	0.3198
atosiban:terbutaline	2	0.82	1.0609	1.095	0.9209	1.1892	0.99	0.3198
fenoterol:nifedipine	0	0	0.8099	ND	0.8099	ND	ND	ND
fenoterol:terbutaline	0	0	0.842	ND	0.842	ND	ND	ND
nifedipine:terbutaline	2	0.32	1.0396	0.9236	1.0983	0.8409	-0.99	0.3198

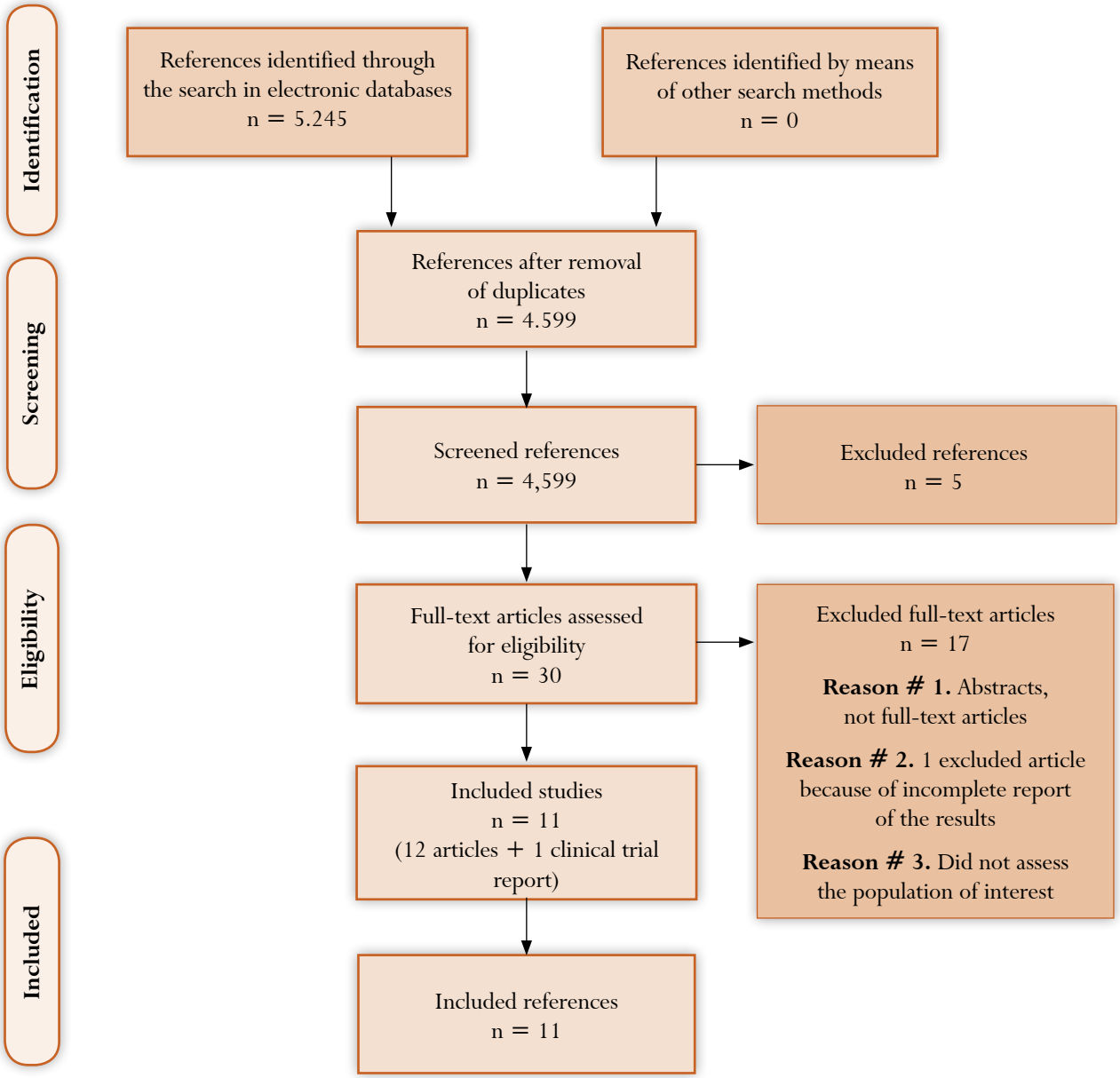
* We present the table with comparisons of each element reported in the column versus the element in every row. In the lower part are the model estimators; the direct tools are in the upper part, when available. The table including differences between direct and indirect estimators for each comparison is also reported with their respective statistical test.

certainty). Similar results are observed in head-to-head comparisons in all cases, except the comparison with terbutaline, where direct comparisons in 2 studies show a statistically significant difference. (RR = 1.61; 95% CI: 1.08-2.4) (Tabla 3). I^2 for this analysis was 82% with good Q test intra- and inter-design *p* values of 0.0003 and 0.052, respectively. This corresponds to moderate to severe heterogeneity (Annex 4).

As for the comparison with placebo, the head-to-head study (22) provides a composite result together with the outcome of not requiring additional tocolytic agents at 7 days. For this comparison, an absolute risk difference of 17% (95% CI: 7-26%) was found in pregnant women between 28 and 33 full weeks of gestation.

Gestational age at the time of delivery. Four relevant studies were identified for this outcome (23, 24, 27,

Figure 1.
PRISMA flow diagram for screening and selection of evidence (de novo search).

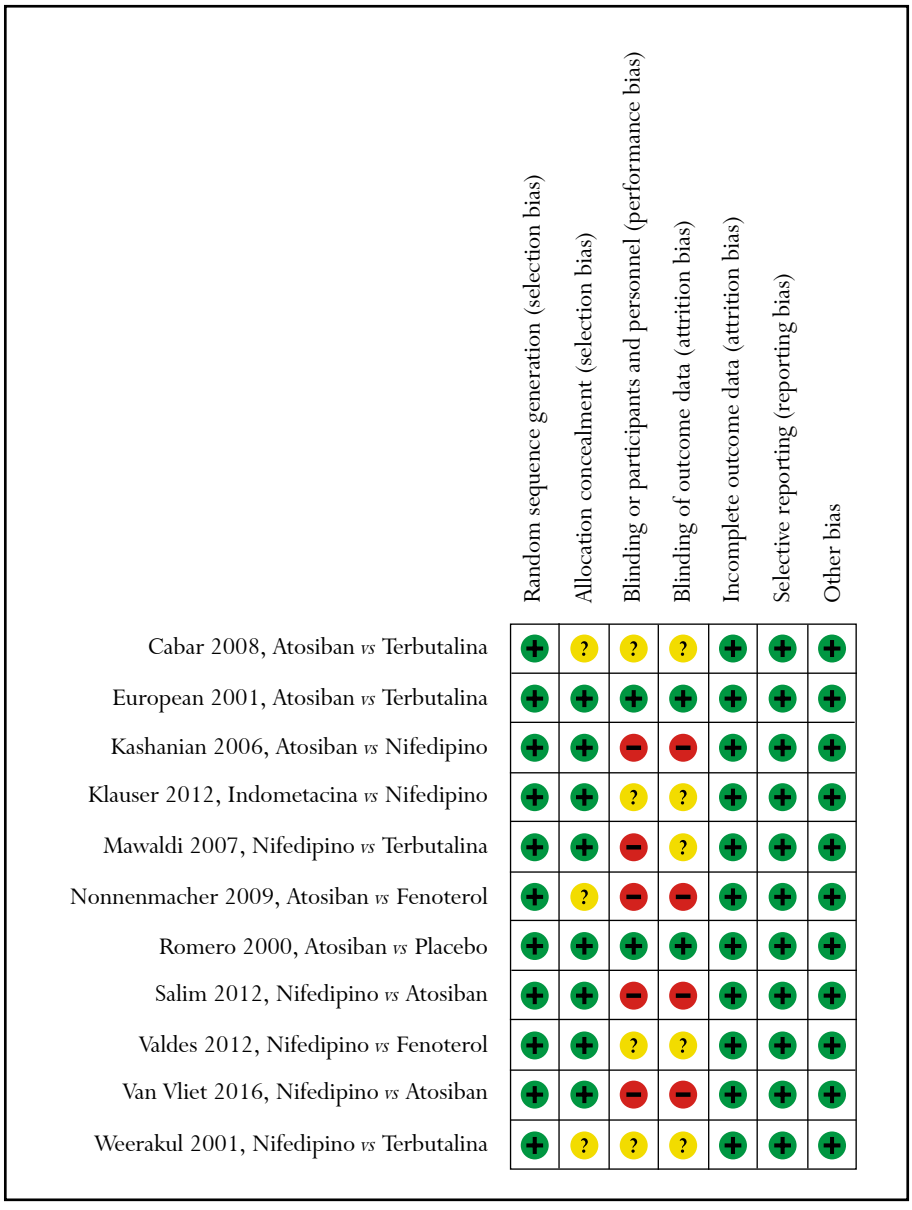


30), with a total of 849 randomized patients; a network meta-analysis was performed (Table 4). No statistically significant differences were found between atosiban and indomethacin (0.91; 95% CI: -7.74-5.92), nifedipine (-0,91; 95% CI: -3.54-1.71) and terbutaline (-0.13; 95% CI: -5-4.74). In this analysis, I^2 was 0%, with an intra-design *p* value of 0.85 in the Q test, and undetermined inter-design value. There is consistency of direct and indirect comparisons in this case, given the network structure.

Safety

Neonatal mortality. Three relevant studies were identified for this outcome (24, 25, 27). Based on the

Figure 2.
Risk of bias of primary studies included, Cochrane tool for risk



other studies with a total of 835 patients randomized, a network meta-analysis was performed (Table 5). A statistically significant difference was found between atosiban and indomethacin (RR = 0.21; 95% CI: 0.05-0.92, low certainty), but no significant differences were found with nifedipine (RR = 0.45; 95% CI: 0.19-1.1, low certainty) or terbutaline (RR = 0.5; 95% CI: 0.13-1.91, low certainty). No significant differences were found between indomethacin, nifedipine and terbutaline in the meta-analysis. Similar results are observed in the head-to-head comparisons (Table 5) (24, 25, 27). No significant differences were found between fenoterol, nifedipine and terbutaline. Given the

Table 3.
Delivery delay longer than 7 days*

League Table								
Direct Estimators								
Model Estimators	**Atosiban**	1.18 (0.71-1.95)	0.97 (0.73-1.29)	1.61 (1.08-2.40)				
	1.18 (0.71-1.95)	**Fenoterol**	-	-				
	1.06 (0.82-1.37)	0,90 (0.51-1.58)	**Nifedipine**	1,02 (0.63-1.64)				
	1.37 (0.99-1.89)	1.16 (0.64-2.11)	1.29 (0.92-1.82)	**Terbutaline**				
Model estimators, direct and indirect								
Comparison	**Number of direct studies**	**Proportion of data extracted from direct studies**	**Model Estimator**	**Direct estimator**	**Indirect estimator**	**Direct/indirect estimator ratio**	**Z**	**P value**
atosiban:fenoterol	1	1	1.18	1.18	ND	ND	ND	ND
atosiban:nifedipine	3	0.83	1.06	0.97	1.58	0.62	-1.39	0.1632
atosiban:terbutaline	2	0.66	1.37	1.61	0.99	1.62	1.39	0.1632
fenoterol:nifedipine	0	0	0.9	ND	0.9	ND	ND	ND
fenoterol:terbutaline	0	0	1.16	ND	1.16	ND	ND	ND
nifedipino:terbutaline	1	0.51	1.29	1.02	1.66	0.62	-1.39	0.1632

* We present the table with comparisons of each element reported in the column versus the element in every row. In the lower part are the model estimators; the direct tools are in the upper part, when available. The table including differences between direct and indirect estimators for each comparison is also reported with their respective statistical test.

structure of the evidence, I^2 and the Q test could not be calculated (see Annex 4).

Proportion of maternal adverse events. Five relevant studies were identified for this outcome (20, 21, 23, 26, 28), for a total of 588 randomized patients; a network meta-analysis was performed (Table 6). Statistically significant differences were found between atosiban and fenoterol (RR = 0.16; 95% CI: 0.08-0.31, moderate certainty), nifedipine (RR = 0.48; 95% CI: 0.3-0.78, moderate certainty) and terbutaline (RR = 0.44; 95% CI: 0.28-0.71, moderate certainty). Similar results were observed in head-to-head comparisons, except the direct comparison between atosiban and terbutaline (RR = 0.55; 95% CI: 0.3-1.00), where point estimation is similar but the confidence interval does not show statistical significance. In this analysis, I^2 is 0%, and the intra- and inter-design *p* values for the Q test are 0.61 and 0.24, respectively.

The evidence summary table for the network

Table 4.
Gestational age at the time of delivery*

League table								
		Direct Estimators						
Model estimators	**Atosiban**	-	-0.91 (-3.54-1.71)	-				
	-0.91 (-7.74-5.92)	**Indomethacin**	0.00 (-6.30-6.30)	-				
	-0.91 (-3.54-1.71)	0.00 (-6.30-6.30)	**Nifedipine**	0.78 (-3.33-4.89)				
	-0.13 (-5.00-4.74)	0.78 (-6.74-8.30)	0.78 (-3.33-4.89)	**Terbutaline**				

Model estimators, direct and indirect								
Comparison	**Number of direct studies**	**Rate of data extracted from direct studies**	**Model Estimator**	**Direct estimator**	**Indirect estimator**	**Direct/indirect estimation tool ratio**	**Z**	**P value**
atosiban:indometacine	0	0	-0.9115	ND	-0.9115	ND	ND	ND
atosiban:nifedipine	2	1	-0.9115	-0.9115	ND	ND	ND	ND
atosiban:terbutaline	0	0	-0.1315	ND	-0.1315	ND	ND	ND
indometacina:nifedipine	1	1	0	0	ND	ND	ND	ND
indometacina:terbutaline	0	0	0.78	ND	0.78	ND	ND	ND
nifedipino:terbutalina	1	1	0.78	0.78	ND	ND	ND	ND

* We present the table with comparisons of each element reported in the column versus the element in every row. In the lower part are the model estimators; the direct tools are in the upper part, when available. The table including differences between direct and indirect estimators for each comparison is also reported with their respective statistical test.

meta-analysis of this outcome is shown in Annex 4.

Given that aggregate adverse events are considered in this analysis, the broken down information reported in the primary studies is shown below.

Table 7 shows the specific adverse events reported in each study against atosiban, together with the reported statistical analysis. There is evidence of a statistically significant reduction between atosiban and nifedipine in terms of hypotension and overall events (23), a statistically significant reduction between atosiban and terbutaline in terms of tachycardia, tachypnea and dyspnea, and a statistically significant increase between atosiban and terbutaline in terms of nausea, vertigo and hot flashes (26). No reported statistical tests were found for the other outcomes.

For the remaining safety outcomes (neonatal respiratory distress syndrome, intraventricular

Table 5.
Neonatal mortality*

League Table								
		Direct Estimators						
	Atosiban	-	0.45 (0.19-1.10)	0.50 (0.13-1.91)				
Model Estimators	0.21 (0.05-0.92)	**Indomethacin**	2.20 (0.66-7.30)	-				
	0.45 (0.19-1.10)	2.20 (0.66-7.30)	**Nifedipine**	-				
	0.50 (0.13-1.91)	2.42 (0.33-17.96)	1.10 (0.22-5.48)	**Terbutaline**				
Model Estimators, direct and indirect								
Comparison	**Number of direct studies**	**Proportion of data extracted from direct studies**	**Model Estimator**	**Direct estimator**	**Indirect estimator**	**Direct/indirect estimator ratio**	**Z**	**P value**
atosiban:indomethacin	0	0	0.2066	ND	0.2066	ND	ND	ND
atosiban:nifedipine	1	1	0.4545	0.4545	ND	ND	ND	ND
atosiban:terbutaline	1	1	0.5	0.5	ND	ND	ND	ND
indomethacin:nifedipine	1	1	2.2	2.2	ND	ND	ND	ND
indomethacin:terbutaline	0	0	2.42	ND	2.42	ND	ND	ND
nifedipine:terbutaline	0	0	1.1	ND	1.1	ND	ND	ND

* We present the table with comparisons of each element reported in the column versus the element in every row. In the lower part are the model estimators; the direct tools are in the upper part, when available. The table including differences between direct and indirect estimators for each comparison is also reported with their respective statistical test.

hemorrhage, intraventricular leukomalacia and neonatal complications) a report of the information presented in the primary articles was prepared, considering that there was insufficient information for a network meta-analysis or a simple direct meta-analysis (Table 8). There are no statistically significant differences between atosiban and nifedipine in the four events evaluated. (24) No statistical analysis is reported for the comparison with terbutaline, although a lower frequency of neonatal respiratory distress, intraventricular hemorrhage (25), and total events (26) is reported.

DISCUSSION

This study is a systematic review of the literature comparing atosiban versus other treatments in patients between 24 and 33 completed weeks of gestation. As far as effectiveness is concerned, no statistically significant differences were found when compared with nifedipine, terbutaline and fenoterol

Table 6.
Maternal adverse events*

League table								
Direct estimators								
	Atosiban	0.16 (0.08-0.31)	0.39 (0.21-0.71)	0.55 (0.30-1.00)				
Model Estimators	0.16 (0.08-0.31)	**Fenoterol**	-	-				
	0.48 (0.30-0.78)	3,02 (1.34-6.82)	**Nifedipine**	0.79 (0.48-1.30)				
	0.44 (0.28-0.71)	2.77 (1.23-6.24)	0.92 (0.60-1.40)	**Terbutaline**				
Model Estimators. direct and indirect								
Comparison	**Number of direct studies**	**Proportion of data extracted from direct studies**	**Model Estimator**	**Direct estimator**	**Indirect estimator**	**Direct/indirect estimation tool ratio**	**Z**	**P value**
atosiban:fenoterol	1	1	0.16	0.16	ND	ND	ND	ND
atosiban:nifedipine	2	0.62	0.4834	0.3874	0.6962	0.5565	-1.17	0.2422
atosiban:terbutaline	1	0.63	0.443	0.55	0.3061	1.7971	1.17	0.2422
fenoterol:nifedipine	0	0	3.0211	ND	3.0211	ND	ND	ND
fenoterol:terbutaline	0	0	2.7685	ND	2.7685	ND	ND	ND
nifedipine:terbutaline	1	0.75	0.9164	0.79	1.4197	0.5565	-1.17	0.2422

* We present the table with comparisons of each element reported in the column versus the element in every row. In the lower part are the model estimators; the direct tools are in the upper part, when available. The table including differences between direct and indirect estimators for each comparison is also reported with their respective statistical test.

in terms of no delivery at 48 hours and at 7 days. These results are of moderate-to-low certainty in terms of evidence. When compared to placebo, one study reported significant differences in terms of the composite outcome of no delivery or need for additional tocolytic agents at 48 hours and at 7 days.

Concerning safety, lower neonatal mortality was found for atosiban when compared to indomethacin, and non-significant differences were found with nifedipine and terbutaline (low certainty). It is worth noting that it was possible to analyze this result from a network with a total of three primary studies. In terms of maternal adverse events, a probably lower frequency was found when compared to fenoterol, nifedipine and terbutaline (moderate certainty). It is worth highlighting that a combined analysis was performed for this outcome, probably combining adverse events of different nature. Consequently, it is reasonable to verify all the comparisons for each event in order

Table 7.
Maternal adverse event report, by studio

		Frequency of events, n (%)		P value
Studies and comparison	**Outcome**	**Atosiban**	**Reference**	
Kashanian, Atosiban vs. nifedipine (20)	Headache	3/40 (7.5 %)	3/40 (7.5 %)	Not reported
	Vertigo	3/40 (7.5 %)	9/40 (22.5 %)	Not reported
	Flank pain	1/40 (2.5 %)	0/40 (0 %)	Not reported
	Hypotension	0/40 (0 %)	11/40 (27.5 %)	Not reported
	Palpitations	0/40 (0 %)	3/40 (7.5 %)	Not reported
	Tachycardia	0/40 (0 %)	3/40 (7.5 %)	Not reported
Nonnenmacher, atosiban vs. fenoterol (21)	Cardiovascular	2/51 (4 %)	42/54 (78 %)	Not reported
Salim, atosiban vs. nifedipine (23)	Hypotension	2/70 (2.9 %)	8/75 (10,7 %)	0,07
	Tachycardia	1/70 (1.4 %)	3/75 (5.3 %)	0,24
	Palpitations	0/70 (0 %)	1/75 (1.3 %)	Not reported
	Headache	2/70 (2.9 %)	4/75 (5.3 %)	0,52
	Nausea	0/70 (0 %)	1/75 (1.3 %)	Not reported
	Vomiting	0/70 (0 %)	0/75 (0 %)	Not reported
	Itching	0/70 (0 %)	1/75 (1.3 %)	Not reported
	Local reaction	0/70 (0 %)	0/75 (0 %)	Not reported
	Rash	0/70 (0 %)	0/75 (0 %)	Not reported
	Any event	5/70 (7.1 %)	17/75 (22.7 %)	0.01
Cabar, atosiban vs. terbutaline (26)	Tachycardia	0/40 (0 %)	20/40 (50 %)	< 0.05
	Tachypnea	0/40 (0 %)	5/40 (12.5 %)	< 0.05
	Dyspnea	0/40 (0 %)	3/40 (12.5 %)	< 0.05
	Nausea	5/40 (17.5 %)	0/40 (0 %)	< 0.05
	Vertigo	3/40 (12.5 %)	0/40 (0 %)	< 0.05
	Headache	2/40 (5 %)	2/40 (5 %)	Not reported
	Hot flashes	1/40 (2.5 %)	0/40 (0 %)	< 0.05

to arrive at a more adequate personalization of the safety profile according to each individual patient. No significant differences were found in terms of neonatal respiratory distress, intraventricular hemorrhage, periventricular leukomalacia and neonatal complications.

How complete was the review in terms of the information obtained in terms of outcomes? Wide screening of

Table 8.
Information reported in primary studies regarding outcomes: Newborn Respiratory Distress Syndrome, intraventricular hemorrhage, periventricular leukomalacia and total neonatal complications

		Frequence of events, n (%)		Reported statistical test
Study	Challenge	Atosiban	Reference	
Newborn Respiratory Distress Syndrome				
European Atosiban study group 2001 (25)	Terbutaline	27/131 (20.6%)	47/153 (30.7%)	Not reported
Van Vliet* (24)	Nifedipine	21/294 (7%)	11/297 (4%)	RR of nifedipine vs. Atosiban 0.55 (95% CI: 0.27-1.15)
Intraventricular hemorrhage				
European Atosiban study group (25)	Terbutaline	7/131 (7.3%)	13/ 153 (8.5%)	Not reported
Van Vliet (24)	Nifedipine	2/294 (1%)	5/297 (2%)	RR of nifedipine vs. Atosiban 2.47 (95% CI: 0.48-12.75)
Periventricular Leukomalacia				
Van Vliet (24)	Nifedipine	2/294 (1%)	1/297 (<1%)	RR of nifedipine vs. Atosiban 0.49 (95% CI: 0.05-5.46)
Neonatal Complications				
Cabar (26)	Terbutaline	6/40 (15%)	8/40 (20%)	Not reported
Van Vliet (24)	Nifedipine	45/294 (15%)	42/297 (14%)	RR of nifedipine vs. atosiban 0.91 (95% CI: 0.61-1.37)

* Bronchopulmonary dysplasia is reported in this study.

the literature is designed to identify all the relevant data available in manuscripts published in journals or registry reports. It may be argued that the limitation in terms of gestational age between 24 and 33 full weeks may have limited the scope of the conclusions of this research, given that it meant that some studies were not included. However, we believe that this makes this review relevant for the local context, given that it focuses on the literature pertaining to the population for which atosiban is indicated in our setting.

Quality of the body of evidence. As reported in the evidence summary tables, the results showed medium-to-low accuracy. Regarding effectiveness outcomes, there are difficulties with the accuracy of the results in the report. They do not allow to differentiate clearly between the absence of a difference and lack of statistical precision for results

without mathematical significance. For such outcomes it is not considered that within the network there were some open studies.

Regarding the body of evidence available for neonatal mortality, certainty is low. This occurs because of problems related to the accuracy of the tools used for estimation and the structure of the network, which implies that some comparisons come exclusively from first degree loops. For maternal adverse events, the body of evidence is also limited to moderate certainty due to the risk of bias of some open studies that may be relevant both for detection and performance.

Applicability of the results based on the quality of the evidence. Considering all of the above, it may be said that there are no important differences in effectiveness when compared to other active references (moderate certainty). In terms of the results on neonatal mortality, even though they may show interesting information, it is likely that more and better primary evidence is needed to consider them directly for decision making. However, these results should not be ignored. Results on maternal adverse events show a moderate certainty. There is a decrease in such events when compared to other active comparators. This may have implications for clinical practice. A closer look at reported events (Table 7) clearly shows that the decrease in atosiban-related adverse events is cardiovascular, such as hypotension, tachycardia and the like. This is a potentially important aspect since there are cases in which severe hypotension in the mother is associated with an increase in neonatal morbidity and mortality due to the decrease in placental perfusion (2, 31). This could imply an assessment by the clinician in order to determine whether the differences in these events may favor atosiban instead of other options. A similar rationale can be used for other reported adverse events.

The main strength of this study is the use of a systematic review methodology for searching and synthesizing available evidence regarding a specific question. The fact that the review considers randomized clinical trials adds to the strength of the body of evidence, because these optimize bias control for intervention questions. The extensive search in medical literature, amplified through the "snowball", attempts to capture all relevant publications even though it cannot ensure absolute certainty. The use of evidence summary tables facilitates communication of results to clinicians. When reviewing meta-analyses available in the literature, none of those obtained in the database search assessed the full amount of the outcomes, or comparison markers of interest for our studies, for which a paper with incremental input to the existing literature could be considered. The population restriction to pregnancies between 24 and 33 complete weeks as indicated by INVIMA may help make the review more relevant from the local perspective.

Regarding its weaknesses, it is worth mentioning that the use of network meta-analyses may create weaknesses in the results, given that indirect evidence is of lower quality than direct evidence, broadly speaking. In this specific case, this effect is not necessarily large, given that in nearly all comparisons there was an important percentage of information coming from direct evidence. In addition, the network structure for some outcomes, such as neonatal mortality, implies many comparisons identical to those in direct studies, while indirect data are used only for notifying some outcomes which had no indirect comparison. The fact that Colombian populations are not included in the trials is a potential, though unavoidable limitation, and it possibly has a marginal effect on the results. The restriction of the population to pregnancies between 24 and 33 complete weeks could be considered as a limitation to the inclusion of relevant studies and generalizing results. This may translate into differences with other previous studies. For

example, some results differ from those obtained in the meta-analysis carried out by Flenady *et al.* (32), in which it was observed that there is no evidence suggesting atosiban is superior in terms of extending pregnancy when compared to placebo (32). The difference between the Flenady *et al*. meta-analysis and this trial may be due to the fact that this meta-analysis included two investigations in patients with gestational age outside the range of interest for the present study and outside the one set forth in the health registry. In this case, the information from the composite outcome resulting exclusively from a primary trial was included, which could limit the utility of this conclusion. However, it is useful because it sheds light on a potentially favorable effect of atosiban over placebo.

CONCLUSIONS

Atosiban probably shows no differences in effectiveness when compared to nifedipine, terbutaline and fenoterol in terms of labor delay at 48 hours and 7 days in pregnant women with risk of preterm labor between 24 and 33 weeks (moderate to low certainty). The comparison of atosiban against placebo based on a primary study, showing a possible improved performance of atosiban in terms of a composite outcome of labor delay and non use of tocolysis at 48 hours and at 7 days.

Regarding safety, there is possibly a lower frequency of events with atosiban when compared to indomethacin, whereas no statistically significant differences were found with nifedipine and terbutaline (low certainty).

Concerning maternal adverse events, potential reduction of events was found with atosiban compared to fenoterol, nifedipine and terbutaline. It is worth looking closely at the differences regarding specific adverse events versus each comparator to assess whether these have an impact on clinical behavior.

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ANNEXES

Annex 1.

Research strategies and results for each database

Research report # 1	
Type of search	New
Database	Medline
Platform	PubMed
Search date	08/06/2017
Date of search range	No restriction
Language restrictions	None
Other limits	None
Research strategy (results)	"Obstetric Labor, Premature"[Mesh] OR "Preterm birth"[All Fields] OR "Premature Birth"[Mesh] AND "Terbutaline"[Mesh] OR "KWD-2019"[All Fields] OR "Indomethacin"[Mesh] OR "Nifedipine"[Mesh] OR "nifedipine"[MeSH Terms] OR "nifedipine"[All Fields] OR "bay 1040"[All Fields] OR "fenoterol"[MeSH Terms] OR "fenoterol"[All Fields] OR "th"[All Fields] AND "1165a"[All Fields] OR "th 1165a"[All Fields] OR "Fenoterol"[Mesh] OR "atosiban"[Supplementary Concept] OR "atosiban"[All Fields] OR "rwj 22164"[All Fields] OR "atosiban"[Supplementary Concept] OR "atosiban"[All Fields] OR "orf 22164"[All Fields]
References identified	1097
References without duplicates	1074

Research report # 2	
Type of search	New
Databases	EMBASE
Platform	Elsevier
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	"prematurity"/exp OR "premature labor"/exp AND ("fenoterol"/exp OR "atosiban"/exp OR "indomethacin"/exp OR "terbutaline"/exp OR "nifedipine"/exp OR "terbutaline sulfate"/exp)
References identified	3958
References without duplicates	3894

Research report # 3	
Type of search	New
Databases	Cochrane Database of Systematic Reviews
Platform	Wiley
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	"Preterm birth" OR "Premature Birth" AND "Terbutaline" OR KWD-2019 OR "Indomethacin" OR "Nifedipine" OR bay 1040 OR th 1165a OR Fenoterol OR "atosiban" OR rwj 22164 OR orf 22164
References identified	21
References without duplicates	21

Research report # 4	
Type of search	New
Databases	Cochrane Database of Abstracts of Reviews of Effects (DARE)
Platform	Wiley
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	"Preterm birth" OR "Premature Birth" AND "Terbutaline" OR KWD-2019 OR "Indomethacin" OR "Nifedipine" OR bay 1040 OR th 1165a OR Fenoterol OR "atosiban" OR rwj 22164 OR orf 22164
References identified	0
References without duplicates	0

Research report # 5	
Type of search	New
Databases	Cochrane Central Register of Controlled Trials - CENTRAL
Platform	Ovid
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	"Preterm birth" OR "Premature Birth" AND "Terbutaline" OR KWD-2019 OR "Indomethacin" OR "Nifedipine" OR bay 1040 OR th 1165a OR Fenoterol OR "atosiban" OR rwj 22164 OR orf 22164
References identified	173
References without duplicates	171

Research report # 6	
Type of search	New
Databases	Lilacs
Platform	Virtual health library (VHL)
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	tw:Preterm birth OR Premature AND tw:Terbutaline OR tw: Indomethacin OR tw: Nifedipine OR tw: Fenoterol OR tw: atosiban
References identified	32
References without duplicates	32

Research report # 7	
Type of search	New
Databases	WHO International Clinical Trials Registry
Platform	ICTRP portal
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	Preterm birth OR Premature Birth AND Terbutaline OR KWD-2019 OR Indomethacin OR Nifedipine OR bay 1040 OR th 1165a OR Fenoterol OR atosiban OR rwj 22164 OR orf 22164
References identified	2
References without duplicates	2

Research report # 8	
Type of search	New
Databases	ClinicalTrials.gov
Platform	
Date of research	08/06/2017
Search date range	No restrictions
Language restrictions	None
Other limitations	None
Search strategy (results)	Preterm birth OR Premature Birth AND Terbutaline OR KWD-2019 OR Indomethacin OR Nifedipine OR bay 1040 OR th 1165a OR Fenoterol OR atosiban OR rwj 22164 OR orf 22164
References identified	66
References without duplicates	66

Annex 2.

Description of included trials

Author / year	Cabar (24)	European (23)
Type of study	Randomized clinical Trial	Randomized clinical Trial
Comparison/ Challenge	Atosiban vs. Terbutaline	Atosiban vs. Terbutaline
Dose	Atosiban bolus 6,75 mg, inf 300 µg/min x 3-5 h, 100 µg/min x 3.5 h	Atosiban bolus 6,75 mg, inf 300 µg/min x 3 h, 100 µg/min x 18 h
	Terbutaline 2,5 mg infusión en 500 mL glucose 5 % (20 mL/h)	Terbutaline 10-25 ug in dextrose at 5 %
Type of analysis	Intention to treat	-
Sample size	80	249
Location	São Paulo, Brazil	Czech Republic, Denmark, Sweden, United Kingdom
Inclusion criteria	Patients with singleton pregnancy, gestational age 23-33 weeks plus 6 days, intact membranes, live fetus, no maternal comorbidities, no fetoplacental disease condition, no intrauterine growth restriction, no fetal distress, no cervical incompetence, with amniotic fluid index between 5 and 25	Patients over 18 years of age with a gestational age between 23-33 full weeks, with preterm labor defined as the presence of 4 or morecontractions over a 30-minute time period lasting 30 or more seconds, 0-3 cm or 1-3 cm of cervical dilation in nulliparous and multiparous women, respectively, and effacement greater than 50%
Exclusion criteria	Not reported	Multiple gestation, rupture of membranes, vaginal bleeding, use of NSAIDs for tocolysis in the previous 12 hours, severe preeclampsia or hypertension, body temperature higher than 37.5 ºC, urinary infection, fetoplacental abnormalities, maternal comorbidities, contraindications for the use of terbutaline, alcohol or psychoactive substances use, hypersensitivity to the study agent, participation in a clinical trial in the previous month
Average age	28,4 years	--
Ovular membrane status	Intact	Intact
Gestational age at the start of tocolysis	23-33,6 weeks	23-33 complete weeks
Gestational age at delivery	28-40 weeks	35 weeks
Type of pregnancy	Single	Singleton and multiple

Author / year	Cabar (24)	European (23)
Outcomes	Time of delivery delay	Time of delivery delay
	Maternal adverse events	Maternal adverse events
	Neonatal complications	Neonatal complications that required NICU
Ethical approval	Ethics Committee for Research Project analysis (CAPPesq) of HC-FMUSP	Ethics Committee for each institution and in accordance with the declaration of Helsinki

Author / year	Mawaldi (26)	Klauser (25)
Type of study	Randomized clinical trial	Randomized clinical trial
Comparisons	Terbutaline, Nifedipine	Indomethacin, magnesium sulphate, nifedipine
Dose	Terbutaline, 0.25 mg loading dose, repeat every 45 minutes	Indomethacin 100 mg, followed by 50 mg every 6 h max 48 h
	Nifedipine 30 mg initial dose, 20 mg at 90 min followed by 20 mg every 8 h for 48 h	Magnesium sulphate 6 g, maintenance 4-6 g/h, followed by 20-30 mg every 4-6 h
		Nifedipine
Type of analysis	Intention to treat	NA
Sample size	Terbutaline 95, nifedipine 79	Indomethacin 34, magnesium sulphate 33, nifedipine 42
Location	Saudi Arabia	United States
Inclusion criteria	Patients with gestational age between 24 and 34 weeks with 1 to 3 uterine contractions in 10 min for 1 h, cervix dilation at 0-3 cm for first pregnancies and 1-3 cm for multiparous women, cervical effacement under 50 %	Patients with gestational age between 20 and 32 weeks with risk of preterm delivery, integral membranes, single pregnancies or twin pregnancies, cervix dilation 1 to 6 cm and cervix effacement.
Exclusion criteria	Pregnancies with more than 2 fetuses, severe hemorrhage, membrane ruptures, maternal comorbidities, temperature greater than 37.5 °C, hypotension, major malformations.	Preeclampsia, abruptio placentae, major fetal malformations, chorioamnionitis, intrauterine growth restriction, fetal suffering.
Average age	Terbutaline 25.3 (5.6), nifedipine 25.4 (5.8)	NA
Ovular membranes	Intact	Intact

Author / year	Mawaldi (26)	Klauser (25)
Gestational age at the start of tocolysis	Terbutaline 30.6 (2.4), Nifedipine 30.4 (2.1)	NA
Gestational Age at the start of delivery	NA	Indomethacin 31.8 (4.2), magnesium sulphate 31.2 (3.9), nifedipine 31.8 (4.5)
Type of gestation	Terbutaline: singleton 83 (87.4), twin 12 (12.6), Nifedipine: single 67 (84.8), twin 12 (15.2)	Twin: indomethacin 16, magnesium sulphate 10, nifedipine 15
Outcomes	Prolongation of pregnancy, delivery at 48 h, complications after 3 h of treatment	Neonatal morbidity, neonatal deaths, days required under artificial ventilation in newborns, days required at neonatal ICU
Ethical Approval	Ethics Committee of King Abdulaziz Medical City Research	Not reported
Financing	Not reported	No reported

Author / year	Valdes (27)	Weerakul (28)	Romero (22)
Type of study	Randomized clinical trial	Randomized clinical trial	Randomized clinical trial
Comparisons	Nifedipine, fenoterol	Nifedipine, terbutaline	Atosiban vs. placebo
Dose	Nifedipine 20 mg initially with a possibility to readminister up until 60 mg in 1 h. Maintenance dose of 20 mg every 6 h.	nifedipine initial dose 10 mg with repetition cada 30 min up until 40 mg. Maintenance dose between 60-120 mg/day	Atosiban: bolus infusion at 6.25 mg, followed by 300 μg/min infusion for 3 h and then 100 μg-min for up to 45 hours; Placebo: equal volumes and flow rate as atosiban
	Fenoterol 1 μg/min initial dose, maximum 4 μg/min. Maintenance dose 0,5-1 μg/min	Terbutaline initial dose 0.25 μg, maintenance 5 μg/min maximum 15 μg/min	
Type of analysis	Intention to treat	Intention to treat	Intention to treat
Sample size	132	89	Atosiban 246, placebo 255
Location	Chile	Bangkok, Thailand	United States
Inclusion criteria	Singleton pregnancy, patients with risk of preterm delivery, gestational age between 22 and 34 weeks with integral membranes.	Patients with risk of preterm delivery and gestational age between 28 and 34 complete weeks.	Patients with risk of preterm delivery with intact membranes and cervical dilation under 3 cm in pregnancies between 20 weeks and 33 weeks plus 6 days

Author / year	Valdes (27)	Weerakul (28)	Romero (22)
Exclusion criteria	Intrauterine infection, major fetal malformations, abruptio placentae, intrauterine growth restriction, counterindications for tocolysis therapy, rupture pf membranes	Not reported	Presence of fetal or placental abnormalities, suboptimal fetal status, clinical suspicion of chorioamnionitis, maternal indications for delivery, urinary tract infection,clinical manifestations of substance abuse
Average age	Nifedipine 26.2 (6.1), Fenoterol 25.5 (6.9)	Nifedipine 27.96 (4.78), Terbutaline 28,52 (5.34)	Not reported
Ovular membranes	Intact	Intact	Intact
Gestational age at the start of tocolysis	Nifedipine 31.7 (2.7), Fenoterol 31.2 (2.4)	Nifedipine 31.8 (1.49), Terbutaline 31.18 (2.5)	Atosiban 30.3 (3.07), placebo 31.0 (2.52)
Gestational age at the start of delivery	NA	NA	Not reported
Type of pregnancy	NA	NA	Atosiban single dose 210/246 multiple dose 36/246, placebo single 212/255, multiple 43/255
Assessed outcomes	Effectiveness of tocolytic agent as first line treatment. Delivery before 24 h, between 24 and 48 h, after 48 h, after 7 days. Prolongation of pregnancy. Maternal adverse events. Discontinuation of medication. Perinatal and neonatal outcomes.	Prolongation of delivery, delivery after 48 h, delivery before week 34, delivery after week 37, gestational age at birth, weight at birth.	Time to therapeutic failure or delivery, percentage of successful treatment at 24 hours, 48 hours and 7 days, maternal and fetal adverse events.
Ethical approval	Not reported	Not reported	Approval of each participating institution
Funding	National Fund for Health Research	Not reported	Not reported

Annex 3.

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Annex 4.

Evidence summary tables and GRADE qualification for NMA

Effect estimators, confidence intervals and certainty in evidence for the use of atosiban in treatment of adult pregnant patients with threatened preterm delivery.

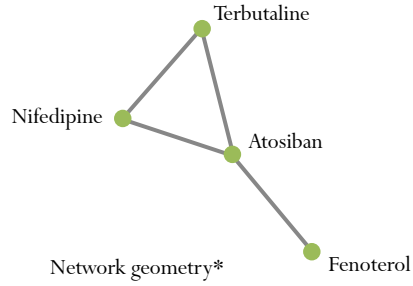
SOF- NMA

Type of population: adult pregnant patients with threatened preterm delivery

Interventions: atosiban

Comparison (reference): fenoterol, nifedipine, terbutaline

Environment: patient



Outcome : time delay until delivery > 48 hours						
Total studies: 8 studies Total participants: 1436 patients	Relative effect** (95% CrL)	Absolute anticipated effects*** (95% CrL)			Certainty of evidence	Ranking****
		Without intervention	With intervention	Difference		
Atosiban	-	-	680/1000	-	-	P = 1 0.8059
vs. Fenoterol	1.26 (1 a 1.59) Network estimate	540/1000	680/1000	140 more per 1000 (from 0 plus to 252 plus)	⊕⊕⊕O[1,2,3, 5] Moderate	P = 4 0.0620
vs. Nifedipine	1,02 (0,91 a 1,15) Network estimate	667/1000	680/1000	13 more per 1000 (from 67 minus to 89 plus)	⊕⊕⊕O[1,2,4, 5] Moderate	P = 2 0.6649
vs. Terbutaline	1.06 (0.93 a 1.21) Network estimat	641/1000	680/1000	38 more per 1000 (from 51 minus to 118 plus)	⊕⊕⊕O[1,2,4] Moderate	P = 3 0.4672

Definition table of MAR-TRH

* Lines represent direct comparisons

** Estimators of the meta-analysis with confidence interval. Bayes method.

*** Absolute anticipated effects calculated for the trials Van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, et al. Nifedipine vs. atosiban for threatened preterm birth (APOSTEL III): A multicentre, randomized controlled trial. Lancet. 2016; 21; 387(10033): 2117-24. doi: 10.1016/S0140-6736(16)00548-1.

**** **Statistic ranking:** P score. Probability values of likelihood of being the best therapeutic course.

Certainty of evidence (GRADE system)

High quality: high confidence that the real effect is found near the estimated effect.

Moderate quality: moderate confidence in the estimated effect: there is a possibility that the real effect is found near the estimated effect, however, they possibly differ in a substantial way.

Low quality: the confidence of the estimated effect is limited: the real effect may be substantially different to the estimated.

Very low quality: there is very little confidence in the estimated effect: the real effect is likely very different from the estimated effect.

Explanations

1. This effect was determined by a random factor of the model due to heterogeneity (I2 = 44,7).
2. Coherence: consistency between the effects of interventions from direct and indirect comparisons.
3. Indirect evidence: indirect evidence for this comparison is found in a first degree connection.
4. Indirect evidence: indirect evidence for this comparison is found in a second degree connection, even though most of the estimation comes-from direct evidence.
5. Imprecision: the 95% CI considers there is no effect/clinically relevant effect.

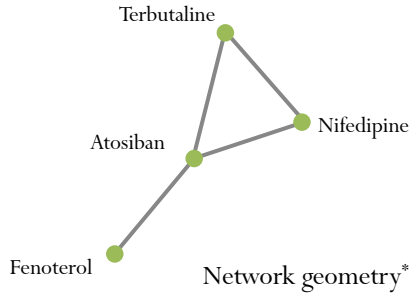
Effect estimators, confidence intervals and certainty in evidence for the use of atosiban in treatment of adult pregnant patients with threatened preterm delivery.

SOF- NMA

Type of population: Adult pregnant patients with threatened preterm delivery.

Interventions: atosiban

Comparison: fenoterol, nifedipine, terbutaline.



Network geometry*

Environment: patient

Outcome: time delay for delivery > 7 days						
Total studies: 7 studies Total participants: 1305 patients	Relative effect** (95% CrL)	Absolute anticipated effects *** (95% CrL)			Certainty of evidence	Ranking****
		Without intervention	With intervention	Difference		
Atosiban	-	-	510/1000	-	-	P = 1 0.79
vs. Fenoterol	1,18 (0.71 a 1.95) Network estimate	432/1000	510/1000	78 more per 1000 (from 208 minus to 248 plus)	⊕⊕⊕O1,2,4 Moderate	P = 3 0.43
vs. Nifedipine	1,06 (0.82 a 1.37) Network estimate	481/1000	510/1000	29 more per 1000 (from 112 minus to 138 plus)	⊕⊕⊕O1,2,5 Moderate	P = 2 0.63
vs. Terbutaline	1.37 (0.99 a 1.89) Network estimate	372,3/1000	510/1000	138 more per 1000 (from 5 minus to 240 plus)	⊕⊕OO1,2,5 Low	P = 4 0.13

Definition table of MAR-TRH

* Lines represent direct comparisons

** Estimators of the meta-analysis with confidence interval. Bayesian method.

*** Absolute anticipated effects calculated for the trials Van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, et al. Nifedipine vs. atosiban for threatened preterm birth (APOSTEL III): A multicentre, randomized controlled trial. Lancet. 2016; 21; 387(10033): 2117-24. doi: 10.1016/S0140-6736(16)00548-1.

**** Statistic ranking: P score. Probability values of likelihood of being the best therapeutic course..

Certainty of evidence (GRADE system)

High quality: high confidence that the real effect is found near the estimated effect.

Moderate quality: moderate confidence in the estimated effect: there is a possibility that the real effect is found near the estimated effect, however, they possibly differ in a substantial way.

Low quality: the confidence of the estimated effect is limited: the real effect may be substantially different to the estimated.

Very low quality: there is very little confidence in the estimated effect: the real effect is likely very different from the estimated effect.

Explanations

1. This effect was determined by a random factor of the model due to heterogeneity (I2 = 82,2).
2. Coherence: consistency between the effects of interventions from direct and indirect comparisons.
3. Indirect evidence: indirect evidence for this comparison is found in a first degree connection.
4. Indirect evidence: indirect evidence for this comparison is found in a second degree connection, even though most of the estimation comes from direct evidence.
5. Imprecision: the 95% CI considers there is no effect/clinically relevant effect.

Effect estimators, confidence intervals and certainty in evidence for the use of atosiban in treatment of adult pregnant patients with risk of preterm delivery.

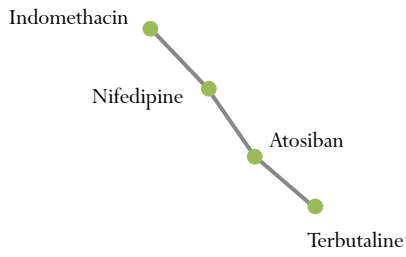
SOF- NMA

Type of population: adult pregnant patients with threatened preterm delivery.

Intervenciones: atosiban

Comparison (reference): fenoterol, nifedipine, terbutaline

Environment: patient



Network geometry*

Outcome : Neonatal mortality						
Total studies: 3 studies Total participants: 835 patients	Relative effect** (95% CrL)	Absolute anticipated effects*** (95% CrL)			Certainty of evidence	Ranking****
		Without intervention	With intervention	Difference		
Atosiban	-	-	50/1000	-	-	P = 1 0.9284
vs. Indomethacin	0.21 (0.05 a 0.92) Network estimate	238/1000	50/1000	188 less per 1000 (from 4 minus to 950 minus)	⨁⨁OO1,3,4 Low	P = 4 0.1038
vs. Nifedipine	0.45 (0.19 a 1.1) Network estimate	111/1000	50/1000	61 menos por 1000 (de 213 menos a 5 más)	⨁⨁OO 1,2,5 Low	P = 3 0.4651
vs. Terbutaline	0.5 (0.13 a 1.91) Network estimate	100/1000	50/1000	50 less per 1000 (from 335 minus to 24 plus)	⨁⨁OO,1,2,5 Low	P = 2 0.5027

Definition table of MAR-TRH
* Lines represent direct comparisons
** Estimators of the meta-analysis with confidence interval. Bayesian method.
*** Absolute anticipated effects calculated for the trials Van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, et al. Nifedipine vs. atosiban for threatened preterm birth (APOSTEL III): A multicentre, randomized controlled trial. Lancet. 2016; 21; 387(10033): 2117-24. doi: 10.1016/S0140-6736(16)00548-1.
**** Statistic ranking: P score. Probability values of likelihood of being the best therapeutic course.

Certainty of evidence (GRADE system)
High quality: high confidence that the real effect is found near the estimated effect.
Moderate quality: moderate confidence in the estimated effect: there is a possibility that the real effect is found near the estimated effect, however, they possibly differ in a substantial way.
Low quality: the confidence of the estimated effect is limited: the real effect may be substantially different to the estimated.
Very low quality: there is very little confidence in the estimated effect: the real effect is likely very different from the estimated effect.

Explanations
1. Heterogeneity is null (I2 = 0).
2. Coherence: consistency between the effects of interventions from direct and indirect comparisons.
3. Indirect evidence: indirect evidence for this comparison is found in a first degree connection.
4. Indirect evidence: indirect evidence for this comparison is found in a second degree connection, even though most of the estimation comes from direct evidence.

Effect estimators, confidence intervals and certainty in evidence for the use of atosiban for the treatment of adult pregnant patients with threatened preterm delivery

SOF- NMA

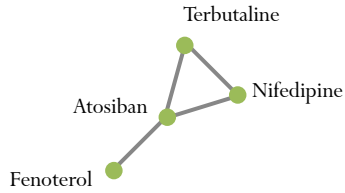
Type of population: adult pregnant patients with threatened preterm delivery.

Intervenciones: atosiban

Comparison (reference): fenoterol, nifedipine, terbutaline

Outcome: maternal adverse events

Environment: patient



Network geometry*

Maternal adverse events						
Total studies: 5 studies Total participants: 588 patients	Relative effect** (95% CrL)	Absolute anticipated effects*** (95% CrL)			Certainty of evidence	Ranking****
		Without intervention	Difference	Difference		
Atosiban	-	-	60/1000	-	-	P = 1 0.99
vs. Fenoterol	0.16 (0.08 to 0,31) Network estimate	375/1000	60/1000	315 less per 1000 (from 134 minus to 690 plus)	⨁⨁⨁O1,2, 4 Moderate	P = 4 0.004
vs. Nifedipine	0.48 (0.3 a 0.78) Network estimate	125/1000	60/1000	65 less per 1000 (from 17 minus to 140 minus)	⨁⨁⨁O1,2, 4 Moderate	P = 2 0.55
vs. Terbutaline	0.44 (0,28 a 0,71) Network estimate	136/1000	60/1000	76 less per 1000 (from 25 minus to 154 minus)	⨁⨁⨁O1,2, 3 Moderate	P = 3 0.45

Definition table of MAR-TRH

* Lines represent direct comparisons

** Estimators of the meta-analysis with confidence interval. Bayesian method.

*** Absolute anticipated effects calculated for the trials Van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, et al. Nifedipine vs. atosiban for threatened preterm birth (APOSTEL III): A multicentre, randomized controlled trial. Lancet. 2016; 21; 387(10033): 2117-24. doi: 10.1016/S0140-6736(16)00548-1.

**** **Statistic ranking:** P score. Probability values of likelihood of being the best therapeutic course.

Certainty of evidence (GRADE system)

High quality: high confidence that the real effect is found near the estimated effect.

Moderate quality: moderate confidence in the estimated effect: there is a possibility that the real effect is found near the estimated effect, however, they possibly differ in a substantial way.

Low quality: the confidence of the estimated effect is limited: the real effect may be substantially different to the estimated.

Very low quality: there is very little confidence in the estimated effect: the real effect is likely very different from the estimated effect.

Explicaciones

1. Heterogeneity is null (I2 = 0).
2. Direct evidence: evidence is based completely in direct evidence.
3. Indirect evidence: the model estimation considers a first degree indirect comparison, but most of the data comes from direct comparison.
4. Risk of bias: for this outcome, it is considered important for open studies as input in this comparison.