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NIFEDIPINE FOR THE MANAGEMENT OF PRETERM LABOR: A SYSTEMATIC REVIEW AND METAANALYSIS

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Abstract

OBJECTIVE—To determine the efficacy and safety of nifedipine as tocolytic agent in women with preterm labor.

STUDY DESIGN—Systematic review and metaanalysis of randomized controlled trials.

RESULTS—Twenty-six trials involving 2179 women were included. Nifedipine was associated with a significant reduction in the risk of delivery within 7 days of initiation of treatment (relative risk [RR], 0.82; 95% confidence interval [CI], 0.70–0.97) and before 34 weeks' gestation (RR, 0.77; 95% CI, 0.66–0.91), respiratory distress syndrome (RR, 0.63; 95% CI, 0.46–0.86), necrotizing enterocolitis (RR, 0.21; 95% CI, 0.05–0.94), intraventricular hemorrhage (RR, 0.53; 95% CI, 0.34–0.84), neonatal jaundice (RR, 0.73; 95% CI, 0.57–0.93), and admission to neonatal intensive care unit (RR, 0.76; 95% CI, 0.62–0.93) when compared to β_2 -adrenergic-receptor agonists. Sensitivity analysis restricted to high quality trials confirmed these results. There was no difference between nifedipine and magnesium sulfate for delivery within 48 hours of treatment, or birth before 34 or 37 weeks. Nifedipine was associated with a lower risk in maternal adverse events and discontinuation of treatment than tocolysis with β_2 -adrenergic-receptor agonists and magnesium sulfate. Maintenance tocolysis with nifedipine was ineffective in prolonging gestation or improving neonatal outcomes when compared to placebo or no treatment.

CONCLUSION—Nifedipine appears to be superior to β_2 -adrenergic-receptor agonists and magnesium sulfate and should be considered as the first-line tocolytic agent for the management of preterm labor.

Keywords

Calcium channel blocker; preterm labor; preterm birth; tocolysis; neonatal morbidity; tocolysis; preterm birth; randomized clinical trials

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INTRODUCTION

The World Health Organization has estimated that 12.9 million births, or 9.6% of all births worldwide, were preterm in 2005.¹ In the United States, the preterm birth rate has risen over the last two decades. In 2007, preterm births constituted 12.7% of live births, an increase of 20% since 1990, and 36% since the early 1980s.² Trends, in most other high-income countries, are similar to those in the United States.^{3,4} Preterm birth is the leading cause of perinatal morbidity and mortality⁴ and one of the leading causes of infant mortality.² Despite the improvement in survival rates of preterm neonates, they are at increased risk of long-term neurodevelopmental disabilities, and respiratory and gastrointestinal complications.⁵

Since uterine contractions are the most frequently recognized symptom and sign of preterm birth, inhibition of uterine contractions with tocolytic agents to prolong pregnancy and reduce neonatal complications has been and continues to be the focus of treatment of preterm labor. Tocolytic agents are intended to arrest uterine contractions during an episode of preterm labor (acute tocolysis) or maintain uterine quiescence after an acute episode (maintenance tocolysis). Several agents have been used for the inhibition of preterm labor but, unfortunately, it is still no clear what the first-line tocolytic agent should be:⁶ 1) β_2 -adrenergic-receptor agonists reduce the risk of delivery within 48 hours of initiation of treatment.⁷ Nevertheless, there is no evidence that this delay in the timing of birth leads to improvements in neonatal outcomes, and maternal adverse events are substantial;⁷ 2) magnesium sulfate is ineffective in delaying birth or preventing preterm birth, and its use could be associated with an increased risk of fetal, neonatal and infant mortality;⁸ 3) there is not enough evidence of whether prostaglandin-synthesis inhibitors reduce the risk of preterm birth because studies have limited sample size;⁹ 4) the oxytocin receptor antagonist, atosiban, was found to increase the proportion of patients remaining undelivered and not requiring an alternate tocolytic at 7 days when compared with placebo; yet, this was not associated with an improvement in neonatal outcomes which has been attributed to the complex design and interpretation of trials of tocolysis that involve a rescue maneuver.¹⁰ Yet, this agent has become the agent of choice in many European countries based on the results of comparative trials with beta-adrenergic agents. Barusiban, a selective oxytocin antagonist, was no more effective than placebo in delaying delivery for 48 hours;¹¹ 5) there is currently insufficient evidence to support the use of nitric oxide donors as a tocolytic drug;¹² and 6) maintenance tocolysis with β_2 -adrenergic-receptor agonists¹³ and oral magnesium sulfate¹⁴ is ineffective in prolonging gestation or reducing adverse neonatal outcomes. Atosiban maintenance treatment can delay the interval of time to the next episode of preterm labor, but does not reduce the rate of preterm delivery or improve infant outcomes.¹⁵

Some authors have proposed that nifedipine, a calcium channel blocker, could be used as a first-line tocolytic agent.^{16–18} The most recent substantial update of the Cochrane review regarding calcium channel blockers for acute tocolysis in preterm labor included 12 randomized controlled trials (10 using nifedipine) involving 1029 patients.¹⁹ This review concluded that, when compared with any other tocolytic agent (mainly beta-mimetics), calcium channel blockers (mainly nifedipine) reduce the risk of delivery within 7 days of initiation of treatment and delivery before 34 weeks of gestation with improvement in some clinically important neonatal outcomes such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal jaundice. A second review from the Cochrane database on maintenance tocolysis reported that, compared with no treatment, nifedipine neither reduces the risk of preterm birth before 37 weeks of gestation nor improves neonatal outcomes.²⁰ However, this review included only 1 trial of 74 women. The literature searches that are the basis for these two reviews were performed in

2002 and 2004, respectively. Since that time, additional randomized controlled trials with nifedipine have been published; therefore, this requires a re-assessment of the efficacy and safety of this agent.

We conducted a systematic review and metaanalysis of all available randomized controlled trials to determine the efficacy and safety of nifedipine as a tocolytic agent in patients with preterm labor.

MATERIALS AND METHODS

The systematic review was conducted following a prospectively prepared protocol and reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for metaanalysis of randomized controlled trials.²¹

Search

We searched (without language restrictions) the following computerized databases using the terms “nifedipine”, “calcium channel blocker”, “calcium antagonist”, “tocolysis”, “preterm labor”, “premature” and their associated medical subject headings (MeSH): MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to June 30, 2010), the Cochrane Central Register of Controlled Trials ([http://www.mrw.interscience.wiley.com/cochrane/clcentral_articles_fs.html](http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles_fs.html)) (1960 to June 30, 2010), ISI Web of Science (<http://www.isiknowledge.com>) (1960 to June 30, 2010), Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.anzctr.org.au, <http://www.nihr.ac.uk>, and www.umin.ac.jp/ctr), and Google scholar. To ensure maximum sensitivity we placed no limits or filters on the searches. Proceedings of the Society for Maternal-Fetal Medicine and international meetings on preterm birth and tocolysis, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. For studies with multiple publications, the data from the most complete report were used and supplemented if additional information appeared in other publications.

Study selection

We included randomized controlled trials in which nifedipine was used for tocolysis in patients with preterm labor compared with alternative tocolytic agents, placebo or no treatment. Trials were excluded if they were quasi-randomized, or if they only compared different doses of nifedipine or other calcium channel blockers, or if nifedipine was given in addition to or following failure of another tocolytic drug. Published abstracts alone were excluded if additional information on methodological issues and results could not be obtained. We classified trials according to aim of the treatment with nifedipine into two groups: “acute tocolysis” and “maintenance tocolysis”. Two reviewers independently evaluated studies for inclusion. Disagreements were resolved through consensus among reviewers. Authors of selected studies were contacted to complement data on trial methods and/or outcomes.

Outcome measures

The primary outcomes of interest were delivery within 48 hours and 7 days of treatment for acute tocolysis, delivery before 34 and 37 weeks of gestation for maintenance tocolysis, and perinatal death, admission to neonatal intensive care unit (NICU), neurodevelopmental disability at 2 years of age, and severe maternal adverse drug reactions for both acute and maintenance tocolysis. Secondary outcomes included the interval between trial entry and delivery, gestational age at delivery, maternal adverse events, discontinuation of treatment

because of adverse events, birth weight, Apgar score at 5 minutes, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, neonatal jaundice, neonatal sepsis, fetal death, neonatal death, length of stay in NICU, long term psychosocial and motor function, and pregnancy/neonatal outcomes among women enrolled at less than 32 weeks of gestation.

Study quality assessment

We conducted quality assessment according to a modified scoring system proposed by Jadad et al.²² which considers four items: randomization, blinding, follow-up, and concealment of allocation. We assigned points to each trial as follows: (1) quality of randomization (2 points: computer-generated random numbers or similar; 1 point: not described; 0 points: quasi-randomized or not randomized [we excluded such studies]); (2) double blinding (2 points: neither the person doing the assessments nor the study participant could identify the intervention being assessed; 1 point: not described; 0 points: no blinding or inadequate method); (3) follow-up (2 points: number or reasons for dropouts and withdrawals described, and assessment of primary outcomes in 95% of randomized women; 1 point: number or reasons for dropouts and withdrawals described but assessment of primary outcomes in <95% of randomized women; 0 points: number or reasons for dropouts and withdrawals not described); and (4) concealment of allocation (2 points: adequate method [central randomization; or drug containers or opaque, sealed envelopes that were sequentially numbered and opened sequentially only after they have been irreversibly assigned to the participant]; 0 points: no concealment of allocation or inadequate method or not described). Thus, the total score ranged from 0 (lowest quality) to 8 (highest quality). Studies that scored 6 points were considered to be of high quality. Two investigators (A.C.-A. and J.P.K.) independently assessed study quality, and discrepancies were resolved through discussion.

Data extraction

Two reviewers (A.C.-A. and J.P.K.) independently extracted data from each eligible study using a standardized data abstraction form. There was no blinding of authorship. From each article, we extracted data on study characteristics (randomization procedure, blinding of providers, patients and outcome assessors, follow up period, intention to treat analysis, losses to follow up, exclusions, and concealment allocation method), participants (inclusion and exclusion criteria, definition of preterm labor, cervical dilatation and effacement at trial entry, gestational age at randomization, numbers of women randomized, baseline characteristics, and country and date of recruitment), details of intervention (aim, loading and maintenance dose, route, duration, retreatment, use of alternative tocolytic therapy, and routine administration of antenatal corticosteroids), and outcomes (number of outcome events and/or mean $\pm$ standard deviation for each outcome). Unpublished additional data used in other metaanalysis¹⁹ were included. Studies reporting preterm birth before 36 weeks' gestation as outcome measure were included into the group of studies reporting preterm birth before 37 weeks of gestation in our data synthesis because of the relatively similar neonatal outcomes. Disagreements in extracted data were resolved by discussion among the authors.

Statistical analysis

All statistical analyses were performed according to the guidelines of the Cochrane Collaboration.²³ We analyzed outcomes on an intention-to-treat basis. If this was not clear from the original article then we carried out re-analysis when possible. If we found no evidence of a substantial difference in study populations, interventions, or outcome measurements, we performed metaanalysis. We calculated the summary relative risk (RR) for dichotomous data and weighted mean difference (WMD) for continuous data with

associated 95% confidence interval (CI). Four pre-specified subgroup analyses were performed to compare nifedipine with other tocolytic agents (β_2 -adrenergic-receptor agonists, magnesium sulfate, atosiban, and nitric oxide donors) for acute tocolysis and one to compare nifedipine with placebo or no treatment for maintenance tocolysis. The subgroup analyses comparing nifedipine versus placebo or no treatment for acute tocolysis were not performed because trials addressing these comparisons were not identified.

Heterogeneity of the results among studies was tested with the quantity I^2 , which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.²⁴ A value of 0% indicates no observed heterogeneity whereas I^2 values of 50% or more indicate a substantial level of heterogeneity.²⁴ We planned to pool data across studies using the fixed-effects models if substantial statistical heterogeneity was not present. We used random-effects models to pool data across studies if I^2 values $\geq 50\%$. A predefined sensitivity analysis was performed to explore the impact of study quality on the effect size for the main outcomes. This was performed by excluding trials with modified Jadad score <6 . We conducted additional analyses stratified according to the following characteristics: definition of preterm labor (based on uterine contractions plus cervical changes versus based on uterine contractions alone), mean or median cervical dilatation at trial entry (<2 versus ≥ 2 cm), membranes status (intact versus ruptured), plurality (singleton versus twin pregnancy), mean gestational age at trial entry (≤ 30 weeks versus >30 weeks), study setting (developed versus developing countries), maintenance therapy in studies evaluating acute tocolysis (yes versus no/not reported), use of alternative tocolytic therapy (yes versus no/not reported), and antenatal corticosteroid therapy (yes versus no/not reported). The meta-analyses according to plurality of pregnancy and membranes status, however, were not undertaken due to insufficient data. Univariable random-effects meta-regression models²³ were used to examine whether effect sizes were affected by these study characteristics.

We assessed publication and related biases visually by examining the symmetry of funnel plots and statistically by using the Egger test.²⁵ The larger the deviation of the intercept of the regression line from zero, the greater was the asymmetry and the more likely it was that the metaanalysis would yield biased estimates of effect. We considered $P < 0.1$ to indicate significant asymmetry, as suggested by Egger.

We also calculated the number needed to treat (NNT) for an additional beneficial outcome with its 95% CI for outcomes in which the treatment effect was significant at the 5% level (the 95% CI for the absolute risk difference did not include zero).²⁶ NNT was computed from the results of metaanalysis of relative risks as follows:

$$NNT = \left| \frac{1}{\text{Control group event rate} \times (1 - \text{relative risk})} \right|$$

In this review, NNT for an additional beneficial outcome is the number of women in preterm labor who need to be treated with nifedipine rather than with other tocolytic agents, placebo or no treatment to prevent one case of delivery within 48 hours or 7 days, or before 34 or 37 weeks, or adverse neonatal outcome.

Analyses were performed with the Review Manager (RevMan) software version 5.0.23 (The Nordic Cochrane Centre, Denmark), StatsDirect version 2.7.8 (StatsDirect Ltd, United Kingdom), and Stata, version 10.0 (StataCorp, College Station, Texas).

RESULTS

We identified 1527 studies in our literature search and considered 61 to be potentially eligible (Figure 1). Twenty-six studies, including 2179 women, fulfilled inclusion criteria of which 23 evaluated acute tocolysis^{27–49} and 3 evaluated maintenance tocolysis.^{50–52} There was strong agreement on the inclusion of studies ($\kappa = 0.89$). Additional neonatal data and long term follow up data for 1 trial³² were reported in 2 additional publications.^{53,54} Of the 23 trials on acute tocolysis, 16 evaluated nifedipine versus β_2 -adrenergic-receptor agonists (11 studies using ritodrine,^{27–34,36,39,42} 3 studies using terbutaline,^{37,40,41} and 2 studies using isoxsuprine^{35,38}), 5 evaluated nifedipine versus magnesium sulfate,^{43–47} and 1 each evaluated nifedipine versus atosiban⁴⁸ and nifedipine versus nitric oxide donors.⁴⁹ There were no trials in which nifedipine was compared with placebo or no treatment in acute tocolysis. Of the 3 trials on maintenance tocolysis, 2 evaluated nifedipine versus no treatment^{50,51} and 1 evaluated nifedipine versus placebo.⁵² In the study by Koks et al,³³ only the subset of patients who were not treated with β_2 -adrenergic-receptor agonists before trial entry was included (57 of 102 women). Thirty-four studies were excluded for the following reasons: initially available in abstract form and subsequently published as a full-length report (N=12); only available in abstract form with insufficient information on methods and results (N=6); method of generation of allocation to treatment was quasi-randomized (N=4); unclear method of randomization (N=3); study did not report relevant outcomes (N=4); nifedipine was used in combination with other tocolytic agents (N=2); comparison of two calcium channel blockers (N=1); comparison of two dose regimens of nifedipine (N=1); non-randomized trial (N=1); and women were enrolled only after subcutaneous terbutaline failed to inhibit contractions (N=1). The list of excluded studies is available from the authors upon request.

Characteristics of the studies included in the review are summarized in Table 1. Seven studies were conducted in the United States,^{28,30,43,44,47,50,52} 11 in Asian countries,^{31,35–38,40,41,45,46,48,51} 7 in European countries,^{27,29,32–34,39,42} and 1 in Brazil.⁴⁹ The sample size ranged from 40^{27,40} to 192⁴⁷ (median, 74). Preterm labor was consistently defined as presence of uterine contractions with evidence of cervical changes in 16 trials.^{28–31,36–38,40,41,43,44,48–52} Ten studies did not include cervical changes in the diagnosis of preterm labor.^{27,32–35,39,42,45–47} Nineteen studies were limited to women with intact membranes,^{27,30,31,34–39,41,43–46,48–52} 7 included also women with ruptured membranes,^{28,29,32,33,40,42,47} and 8 included women with a twin pregnancy.^{31,33,38,41,47,48,51,52} Standard maternal and fetal contraindications to tocolysis were reported as exclusion criteria in the great majority of included studies.

The gestational age at inclusion varied from 20 to 36 weeks. The minimum gestational age at trial entry ranged from 20 to 28 weeks, and the maximum from 33 to 36 weeks. Most trials included women between 24 and 34 weeks of gestation. Mean gestational age at trial entry varied from 29.1 to 32.4 weeks.

For studies evaluating acute tocolysis, nifedipine dosing regimens were similar across the trials with loading doses of 10 to 30 mg administered orally or sublingually, followed by 10 to 20 mg orally every four to eight hours for 24 to 72 hours. Twelve studies^{28,32,35,37,38,40,42,43,45–48} repeated a loading dose every 15 to 20 minutes to a maximum of 40 mg during the first hour of treatment if contractions persisted. Eleven trials^{29–33,35,36,42–44,47} reported maintenance therapy, 9^{27,28,34,37,40,41,45,46,49} did not, and 3^{38,39,48} stated there was no maintenance therapy. Seven studies^{31–33,35,36,43,44} used oral maintenance therapy in both treatment groups until 34 to 37 weeks of gestation. All but 3 trials^{30,34,36} reported the total duration of treatment. All studies evaluating maintenance tocolysis^{50–52} used nifedipine 20 mg orally every 4 to 6 hours until 37 weeks of gestation or

delivery, whichever occurred first. Use of alternative tocolytic therapy was explicitly mentioned in 18 studies^{27–34,39,40,42,43,46,47,49–52}. Twenty trials^{28,31–38,40–43,46–52} reported administration of antenatal corticosteroids for all women enrolled. In the remaining 6 trials^{27,29,30,39,44,45} antenatal corticosteroids use was not reported.

Table 2 shows quality assessment of included studies. All but 5 studies^{35,38,43,45,51} had adequate generation of allocation sequence. Sixteen studies^{28–30,32–34,37,39,41–44,47,49,50,52} reported adequate concealment of allocation. For all of the 23 studies evaluating acute tocolysis, blinding of the intervention was not performed and blinding assessment of outcomes was not reported. Only 1 study⁵² evaluating maintenance tocolysis was double-blinded. Eighteen trials reported assessment of primary outcomes in 95% of randomized women.^{27–35,37,39,41,42,44,45,47,51,52} Thirteen trials (50%) had a modified Jadad score of 6 or more.^{28–30,32–34,37,39,41,42,44,47,52}

Acute tocolysis

1. Nifedipine versus β_2 -adrenergic-receptor agonists—This subgroup analysis included data from 16 trials with a total of 1278 women. Compared with women receiving β_2 -adrenergic-receptor agonists, those using nifedipine had a statistically significant reduction in the risk of delivery within 7 days of initiation of treatment (37.1% vs 45.0%; RR, 0.82; 95% CI, 0.70–0.97; $P=0.00$) (Table 3). The number of women with preterm labor who need to be treated (NNT) with nifedipine rather than with β_2 -adrenergic-receptor agonists to prevent one case of delivery within 7 days of treatment is 12 (95% CI, 7–63). Nifedipine was also associated with a decreased risk of delivery before 34 weeks of gestation (48.4% vs 62.2%; RR, 0.77; 95% CI, 0.66–0.91; $P=0.00$; NNT for benefit, 7; 95% CI, 5–24), maternal adverse events (19.5% vs 56.1%; RR, 0.31; 95% CI, 0.18–0.54; $P=84.0\%$; NNT for benefit, 3; 95% CI, 2–5), and discontinuation of treatment because of adverse events (0.6% vs 8.8%; RR, 0.14; 95% CI, 0.06–0.31; $P=0.00$; NNT for benefit, 13; 95% CI, 12–21). A significant increase in gestational age at birth (weighted mean difference [WMD] 0.7 weeks; 95% CI, 0.3–1.2; $P=0.00$), interval between trial entry and delivery (WMD, 5.8 days; 95% CI, 1.4–10.2; $P=63.0\%$), and birth weight (WMD, 178.8 gm; 95% CI, 84.1–273.6; $P=31.0\%$) was also shown. No difference was seen for the risk of delivery within 48 hours of initiation of treatment or before 37 weeks of gestation.

Treatment with nifedipine was associated with an overall reduction in respiratory distress syndrome (10.9% vs 16.8%; RR, 0.63; 95% CI, 0.46–0.86; $P=0.00$; NNT for benefit, 16; 95% CI, 11–51), necrotizing enterocolitis (0.4% vs 3.4%; RR, 0.21; 95% CI, 0.05–0.94; $P=0.00$; NNT for benefit, 37; 95% CI, 31–514), intraventricular hemorrhage (8.5% vs 16.5%; RR, 0.53; 95% CI, 0.34–0.84; $P=0.00$; NNT for benefit, 13; 95% CI, 9–42), neonatal jaundice (43.2% vs 60.6%; RR, 0.73; 95% CI, 0.57–0.93; $P=48.0\%$; NNT for benefit, 6; 95% CI, 4–30), admission to NICU (26.6% vs 34.3%; RR, 0.76; 95% CI, 0.62–0.93; $P=0.00$; NNT for benefit, 12; 95% CI, 7–48), and NICU length of stay (WMD, –7.2 days; 95% CI, –11.2 to –3.3; $P=0.00$). No statistically significant differences were seen for perinatal mortality, fetal and neonatal death, neonatal sepsis, Apgar score <7 at 5 minutes, retinopathy of prematurity, neurodevelopmental delay at 2 years of age, and psychosocial and motor function at 9–12 years of age.

2. Nifedipine versus magnesium sulfate—Five trials contributed data which included 556 women. There was no overall difference between nifedipine and magnesium sulfate for delivery within 48 hours of treatment, or before 34 or 37 weeks of gestation, gestational age at birth or in time from trial entry to delivery (Table 4). Nifedipine was associated with a significant reduction in maternal adverse events (23.5% vs 35.6%; RR, 0.63; 95% CI, 0.48–0.82; $P=48.0\%$; NNT for benefit, 8; 95% CI, 5–19). In addition, one trial⁴⁷ reported that

severe maternal adverse effects were significantly less frequent among women receiving nifedipine than among women receiving magnesium sulfate (10.0% vs 21.7%; RR, 0.46; 95% CI, 0.23–0.93).

There were no significant differences between the groups in the risk of major adverse neonatal outcomes, although a significant reduction was seen in the risk of admission to NICU (37.3% vs 51.9%; RR, 0.72; 95% CI, 0.53–0.97; NNT for benefit, 7; 95% CI, 4–69) and NICU length of stay (WMD, –2.2 days; 95% CI, –3.4 to –1.1; $I^2=42.0\%$) in the nifedipine group compared with the magnesium sulfate group.

3. Nifedipine versus atosiban—This comparison included 1 trial⁴⁸ involving only 40 women in each group. No difference was shown for the risk of delivery within 48 hours of treatment (25.0% vs 17.5%; RR, 1.43; 95% CI, 0.60–3.38) or within 7 days (35.0% vs 25.0%; RR, 1.40; 95% CI, 0.71–2.77) for women receiving nifedipine compared with atosiban. Maternal side effects secondary to study medication were significantly more common among women allocated to nifedipine rather than atosiban (40% vs 17.5%; RR, 2.29; 95% CI, 1.06–4.95).

4. Nifedipine versus nitric oxide donors—There was only 1 trial⁴⁹ that compared these two agents, involving a total of 50 women. No statistically significant differences were found between nifedipine and transdermal nitroglycerin for delivery within 48 hours of treatment or maternal adverse drug reaction.

Table 5 displays the sensitivity analysis for the comparison of nifedipine with β_2 -adrenergic-receptor agonists and magnesium sulfate in acute tocolysis. The effects of nifedipine on reduction of delivery within 7 days of initiation of treatment and before 34 weeks of gestation, maternal adverse drug reaction, discontinuation of treatment because of adverse effects, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, admission to NICU, and NICU length of stay did not change after sensitivity analysis limited to trials with high methodological quality (modified Jadad score 6). However, the increase in gestational age at birth for women receiving nifedipine compared with β_2 -adrenergic-receptor agonists was not demonstrated after the sensitivity analysis (WMD, 0.6 weeks; 95% CI, 0.0–1.2; $I^2=0.0\%$). Additional sensitivity and subgroup analyses for the comparison of nifedipine with β_2 -adrenergic-receptor agonists and magnesium sulfate in acute tocolysis showed that estimates of effect sizes varied to some degree depending on the definition of preterm labor used and use of maintenance therapy, but the CIs were wide and tests for interaction were not statistically significant (data not shown). In addition, univariable meta-regression analyses indicated no association between effect sizes and study characteristics considered.

Maintenance tocolysis

1. Nifedipine versus placebo or no treatment—Three trials, which recruited 215 women, were included. No significant differences were seen between nifedipine maintenance therapy and placebo or no treatment for preterm birth before 34 or 37 weeks of gestation, gestational age at birth, episodes of recurrent preterm labor, and adverse neonatal outcomes. Nifedipine was associated with a significant increase in pregnancy prolongation (WMD, 6.3 days; 95% CI, 1.2–11.4; $I^2=22.0\%$) (Table 6). Outcomes were similar for subgroup of women enrolled at less than 32 weeks of gestation.

All funnel plots showed no asymmetry, either visually or in terms of statistical significance ($P>.10$ for all, by Egger test).

COMMENT

In this metaanalysis we found no significant differences between nifedipine and both β_2 -adrenergic-receptor agonists and magnesium sulfate in reducing the risk of delivering within 48 hours of initiation of treatment and before 37 weeks of gestation. However, when compared with β_2 -adrenergic-receptor agonists, nifedipine was associated with a significant reduction in preterm birth within 7 days of initiation of treatment and before 34 weeks of gestation (approximately 20%) which led to significant improvements in clinically important neonatal outcomes such as respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, admission to NICU, and length of stay in NICU. Moreover, nifedipine was less likely than β_2 -adrenergic-receptor agonists and magnesium sulfate to cause maternal adverse events, and its use was associated with a significant decrease in discontinuation of treatment because of adverse events when compared with β_2 -adrenergic-receptor agonists. There were no significant differences between children exposed *in utero* to either nifedipine or β_2 -adrenergic-receptor agonists in neurodevelopmental status at 2 years of age or psychosocial and motor functioning at 9–12 years of age. The paucity of trials precluded drawing conclusions about comparisons between nifedipine and atosiban or nitric oxide donors for acute tocolysis. Maintenance tocolysis with nifedipine was ineffective in prolonging gestation or reducing any adverse neonatal outcomes when compared with placebo or no treatment.

The strength of our findings is based on the use of the most rigorous methodology for performing a systematic review of randomized controlled trials, a broad literature search, the inclusion of a relatively large number of studies in meta-analyses, the study quality assessment which was based on a widely used and validated scale, the relatively narrow confidence intervals obtained which made our results more precise, the evidence of clinical and statistical homogeneity in the results of the trials for most of the outcomes evaluated, the sensitivity analyses restricted to high quality trials that were consistent with (and thus supportive of) our overall findings, the subgroup and meta-regression analyses that failed to show any significant influence of study characteristics on effect size, and the symmetrical funnel plots that suggested absence of publication and related biases in our meta-analyses.

Our study also has some limitations. First, no placebo-controlled trial has studied the efficacy and safety of nifedipine for acute tocolysis in preterm labor. Compared with placebo, β_2 -adrenergic-receptor agonists reduced the risk of delivery within 48 hours of initiation of treatment (RR, 0.63; 95% CI, 0.53–0.75) and within 7 days of treatment (RR, 0.78; 95% CI, 0.68–0.90).⁷ Since the present metaanalysis has showed that nifedipine is as effective as β_2 -adrenergic-receptor agonists to reduce risk of delivery within 48 hours, and more effective to reduce risk of delivery within 7 days of treatment with a significantly better adverse-event profile, it is unlikely that a placebo-controlled trial involving nifedipine in acute tocolysis will be performed. Second, only half of the trials included herein were considered of high-quality and just one was double-blind. Nevertheless, sensitivity analyses restricted to high quality trials showed no significant differences with overall meta-analyses. In addition, assessment and measurement of most outcomes included in our review are considered objective in nature and thereby, not likely to be influenced by lack of blinding. Third, several studies failed to report results on some outcome measures considered in our review. Thus, our metaanalysis may be underpowered for some outcomes and it is possible that if these results were reported more consistently, effect sizes might be different. Finally, we could not fully address the potential for performance bias by extracting consistent data on concomitant co-interventions. The difference in frequency of use and/or type of alternative tocolytic therapy between groups could have increased the apparent benefit of nifedipine compared with β_2 -adrenergic-receptor agonists.

We were unable to determine the efficacy of nifedipine for acute tocolysis in women with twin pregnancies or with preterm premature rupture of membranes due to a paucity of data. Two studies^{31,33} reported data for women with twin pregnancies (N=35) and two^{28,33} reported data for women with premature rupture of membranes (N=58). There were no statistically significant differences between nifedipine-treated and ritodrine-treated groups for delivery within 48 hours and 7 days of initiation of treatment, and preterm birth before 34 and 36 weeks of gestation.

Some serious adverse effects such as myocardial infarction,^{55,56} severe maternal dyspnea,⁵⁷ maternal hypoxia,⁵⁸ severe maternal hypotension with fetal death,⁵⁹ and atrial fibrillation⁶⁰ have been reported during tocolytic therapy with nifedipine. A case series study reported that six out of seven cases of nifedipine-associated severe maternal dyspnea occurred in women with twin pregnancies and recommended caution when administering nifedipine to patients with compromised cardiovascular function, mainly those with a twin gestation, cardiac disease, maternal hypertension, and intrauterine infection.⁵⁷ A recent multicenter prospective cohort study from the Netherlands and Belgium, in which an independent panel evaluated the recorded adverse events without knowledge of the type of tocolytic used, reported that among 542 women treated with nifedipine, five (0.9%) had a serious adverse side effect and six (1.1%) had a mild adverse side effect.⁶¹ In our review, nifedipine was associated with a significant decreased risk in maternal adverse effects when compared with β_2 -adrenergic-receptor agonists and magnesium sulfate, and a significant reduction in discontinuation of treatment because of adverse effects when compared with β_2 -adrenergic-receptor agonists. Moreover, nifedipine had no effects on fetal and neonatal death. However, consideration of randomized control trials alone is insufficient to determine the range and severity of adverse events and both, observational studies and case reports, must be employed to assess safety data. Recently, Khan et al.⁶² published a systematic review and meta-regression analysis of randomized controlled trials, observational studies, and case series which evaluated the fetomaternal safety of calcium channel blockers when used in pregnancy, not just for the treatment of preterm labor but also for use in the treatment of hypertension in pregnancy. These authors reported that adverse events were highest among women who received more than 60 mg total dose of nifedipine (odds ratio, 3.78; 95% CI, 1.27–11.2) and in reports from case series compared to controlled studies (odds ratio, 2.45; 95% CI, 1.17–5.15).

The ideal tocolytic agent should be myometrium-specific, easy to administer, inexpensive, effective in preventing preterm birth and improve neonatal outcomes, with few maternal, fetal, and neonatal side effects, and without long-term adverse effects. Since nifedipine meets most of these requirements, it should be considered as a first-line agent in the management of preterm labor. In addition, a cost-decision analysis of 4 tocolytic drugs (indomethacin, magnesium sulfate, nifedipine, and terbutaline) based on safety and cost found that nifedipine and indomethacin are the most cost-effective tocolytics used in the United States.⁶³ The optimal dose of nifedipine for the treatment of preterm labor is yet to be determined. In most studies included in our review, the initial dose was 10 mg orally or sublingually. If contractions persisted, this dose was repeated every 15–20 minutes up to a maximal total dose of 40 mg during the first hour of treatment. Then, 20 mg orally every 6–8 hours for 2–3 days.

In summary, nifedipine appears to be a more effective tocolytic agent than β_2 -adrenergic-receptor agonists with improvement in neonatal outcomes, and it is better tolerated than β_2 -adrenergic-receptor agonists and magnesium sulfate. Currently, there is insufficient evidence to justify the routine use of nifedipine as long-term maintenance tocolytic after an episode of preterm labor. Further adequately powered studies are needed to assess the optimal dose of nifedipine, its efficacy and safety in women with multiple gestations, premature rupture of

membranes, and lower gestational ages, its effectiveness as maintenance therapy after preterm labor has been arrested, the cost-effectiveness of intervention, and the long term consequences of exposure for infants. We were not able to compare efficacy and safety of nifedipine and atosiban because of the paucity of data.

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Figure 1.
Study selection process

TABLE 1

Characteristics of studies included in the systematic review

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
ACUTE TOCOLYSIS					
NIFEDIPINE COMPARED WITH β_2-ADRENERGIC-RECEPTOR AGONISTS					
Read, ²⁷ 1986	United Kingdom	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: multiple pregnancy, polyhydramnios, premature rupture of membranes, history of cervical surgery, history of mid-trimester abortion or previous preterm delivery, history of any medical condition which would contraindicate the use of either of the drugs, chorioamnionitis, any irregularity of the fetal heart rate, and cervical dilatation >4 cm.	20–35	Nifedipine (N=20): 30 mg orally. Then 20 mg orally every 8 h for 3 days. Ritodrine (N=20): 50 μ g/min IV increasing by 50 μ g every 10 min to a maximum of 300 μ g for 24 h. Then 10 mg orally oral every 4 h for 48 h.	Ritodrine in nifedipine group
Ferguson, ²⁸ 1990	United States	Inclusion: women with singleton pregnancy in preterm labor irrespective of the membranes status. Exclusion: previous treatment with tocolytics in current pregnancy, diabetes, hyperthyroidism, cardiac disease, severe preeclampsia, eclampsia, placental abruption, chorioamnionitis, multiple pregnancy, polyhydramnios, cervical dilatation >4 cm, fetal distress, severe intrauterine growth retardation, fetal death, and fetal anomaly incompatible with life.	20–36	Nifedipine (N=33): 10 mg sublingually. If uterine contractions persisted after 20 min, a similar dose was repeated at intervals of 20 min, up to a maximal total dose of 40 mg during the first h of treatment. Then 20 mg orally every 4–6 h. Ritodrine (N=33): 50 μ g/min IV increasing by 50 μ g every 15–30 min up to a maximum of 350 μ g/min. Then 10–20 mg orally every 4–6 h.	Alternate regimen and terbutaline
Janky, ²⁹ 1990	France	Inclusion: women with singleton pregnancy in preterm labor. Exclusion: chorioamnionitis, fetal death, fetal anomaly incompatible with life, medical condition contraindicating the use of betamimetics, cervix >4 cm, and premature rupture of membranes after 34 weeks.	28–36	Nifedipine (N=30): 10 mg sublingually. Then 20 mg orally every 8 h for 7 days. Ritodrine (N=32): 200–300 μ g/min IV until contractions ceased. Then 100 μ g/min for 24 h. Thereafter 20 mg orally every 4–6 h for 6 days.	Permitted but unspecified
Bracero, ³⁰ 1991	United States	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: multiple pregnancy, premature rupture of membranes	20–36	Nifedipine (N=26): 30 mg orally. Then 20 mg orally every 6 h for 24 h, then decreased to 8-hour intervals for an additional 24 h. Thenceforth, 20 mg every 8–12 h. No data on duration of treatment. Ritodrine (N=23): 100 μ g/min IV increasing by 50 μ g/min every 10 min to a maximum of	Ritodrine and magnesium sulfate in nifedipine group and magnesium sulfate in ritodrine group

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Kupferminc, ³¹ 1993	Israel	Inclusion: women with singleton or twin pregnancy in preterm labor and intact membranes. Exclusion: polyhydramnios, placental abruption, hypertension, infection, any medical condition that would contraindicate tocolytic therapy, cervical dilatation >4 cm, and premature rupture of membranes.	26–34	350 µg/min. Thirty min prior to discontinuation of IV ritodrine, 10 mg orally every 2 h for 24 h. Then 10 mg every 4 h for 24 h. Then 20 mg every 8–12 h. Thereafter, 10–20 mg orally every 4–6 h. No data on duration of treatment.	Ritodrine in nifedipine group
Papatsonis, ³² 1997	The Netherlands	Inclusion: women with singleton pregnancy in preterm labor irrespective of the membranes status. Exclusion: multiple pregnancy, intrauterine infection, fetal congenital anomalies, abruption placenta, severe fetal growth restriction, and any contraindication for the use of beta-adrenergic drugs.	20–33 4/7	Nifedipine (N=95): 10 mg sublingually. If contractions persisted, this dose was repeated every 15 min to maximum of 40 mg during the first hour of treatment. Then 60–160 mg/day of slow-release nifedipine until 34 weeks. Ritodrine (N=90): 383 µg/min IV after which the infusion rate was determined by the time lag after which tocolysis is established (minimum 100 µg/min) for at least 3 days. Then ritodrine 40 mg orally every 8 h until 34 weeks in two of the three participating hospitals.	Nifedipine in ritodrine group; Indomethacin in both groups
Koks, ^{33d} 1998	The Netherlands	Inclusion: women with singleton or twin pregnancy in preterm labor irrespective of the membranes status. Exclusion: any contraindication for the use of nifedipine or betamimetic, intrauterine infection, irregular fetal heart rate, antepartum hemorrhage, and polyhydramnios.	24–34	Nifedipine (N=32): 30 mg sublingually. Then 20 mg orally every 6–12 h which was reduced to 20 mg every 8 h until 34 weeks. Ritodrine (N=25): 200 µg/min IV up to maximum of 400 µg/min. Then 80 mg orally every 8 h until 34 weeks.	Indomethacin in both groups
García-Velasco, ³⁴ 1998	Spain	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: previous tocolytic treatment, cervical dilatation 3 cm, maternal infection, vaginal bleeding, and any medical or obstetrical condition contraindicating tocolytic therapy.	26–34	Nifedipine (N=26): 30 mg (20 mg orally and 10 mg sublingually). Then 10–20 mg every 4–6 h. No data on duration of treatment or maintenance therapy. Ritodrine (N=26): 50 µg/min IV increasing by 50 µg/min every 20 min to a maximum of 350 µg/min for 12 h. Then 5 mg orally every 3 h. No data on duration of treatment or maintenance therapy.	Indomethacin in both groups
Ganla, ³⁵ 1999	India	Inclusion: women with singleton pregnancy in preterm labor. No data on membranes status.	26–36	Nifedipine (N=50): 5 mg sublingually. If contractions persisted, this dose was repeated every 15 min to maximum of 40 mg during the	Not reported

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Al-Qattan, ³⁶ 2000	Kuwait	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: multiple pregnancy, cardiac disease, placental abruption, hyperthyroidism, severe preeclampsia, eclampsia, infection, cervical dilatation >4 cm, polyhydramnios, fetal pathology, premature rupture of membranes, breech presentation, fetal death, fetal distress, and congenital malformation.	24–34	first two hours of treatment. Then 10 mg orally every 8 h for 48 h. Thereafter 10–20 mg orally every 12 h until 36 weeks. Isoxsuprine (N=50): 0.5 mg/min IV increasing to a maximum of 10 mg/min for 12 h. Then 10 mg IM every 8 h for 48 h. Thereafter 10–20 mg orally every 8 h until 36 weeks.	Not reported
Weerakul, ³⁷ 2002	Thailand	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: multiple pregnancy, premature rupture of membranes, previous tocolytics, cervical dilatation >3 cm, chorioamnionitis, infection, fetal distress, fetal anomalies, and medical or obstetrical complications.	28–34	Nifedipine (N=45): 10 mg sublingually. If contractions persisted after 15 min, a second dose of 10 mg was given. Then 20 mg after 30 min to a maximum in the first hour of 40 mg. Then 60–120 mg orally per day for 3 days. No data on maintenance therapy. Terbutaline (N=44): 0.25 mg IV followed by continuous IV infusion started at 5 µg/min and increased by 5 µg/min every 15 min up to a maximum of 15 µg/min. Then the infusion was maintained at the same rate for 2 h, after which the treatment was continued with subcutaneous injection of 0.25 mg every 4 h for 24 h. No data on maintenance therapy.	Not reported
Rayamahji, ³⁸ 2003	Nepal	Inclusion: women with singleton or twin pregnancy in preterm labor and intact membranes. Exclusion: premature rupture of membranes, advanced labor, preeclampsia, eclampsia, cardiac disease, thyroid disorder, antepartum hemorrhage, polyhydramnios, chorioamnionitis, severe fetal growth restriction, fetal death, oligoamnios, fetal anomalies incompatible with life.	28–36	Nifedipine (N=32): 10 mg sublingually. This dose was repeated every 20 min to maximum of 40 mg during the first hour of treatment. Then 10–20 mg orally every 6–8 h for up to 7 days. Isoxsuprine (N=30): 0.08 mg/min IV increasing to a maximum of 0.24 mg/min. Then 10 mg orally every 8 h for up to 7 days.	Not reported
Curarach, ³⁹ 2006	Spain	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: cervical dilatation >5 cm, polyhydramnios, fetal anomalies, fetal	22–35	Nifedipine (N=40): 30 mg (20 mg orally and 10 mg sublingually). Then 20 mg orally every 6 h for 48 h. There was no maintenance therapy.	Alternate regimen and indomethacin

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Laopapojanart, ⁴⁰ 2007	Thailand	Inclusion: women with singleton pregnancy in preterm labor irrespective of the membranes status. Exclusion: multiple pregnancy, heart or renal disease, hypertension, chorioamnionitis, placental abruption, placenta previa, preeclampsia, diabetes, and thyrotoxicosis.	24–36	Ritodrine (N=40): 100 µg/min IV increasing by 50 µg/min every 20 min to a maximum of 350 µg/min for 48 h followed by 10 mg orally every 6 h until discharge. There was no maintenance therapy. Nifedipine (N=20): 10 mg orally. If contractions persisted, 10 mg orally every 4 h to a maximum in the first hour of 40 mg. Then 20 mg every 4 h for 3 days. No data on maintenance therapy. Terbutaline (N=20): 10 µg/min IV followed by continuous IV infusion with an increment 5 µg/min every 10 min until 25 µg/min was reached. Then subcutaneous injection of 0.25 mg every 4 h for 24 h. No data on maintenance therapy.	Alternate regimen and indomethacin
Mawaldi, ⁴¹ 2008	Saudi Arabia	Inclusion: women with singleton or twin pregnancy in preterm labor and intact membranes. Exclusion: women carrying more than 2 fetuses; major antepartum hemorrhage, premature rupture of membranes, major medical disorder, temperature >37.5 °C, blood pressure <90/50 mm Hg, compromised fetus, and lethal fetal anomalies	24–34	Nifedipine (N=79): 30 mg orally followed by 20 mg after 90 min. If contractions persisted, 20 mg orally every 8 h for 48 h. No data on maintenance therapy. Terbutaline (N=95): 0.25 mg subcutaneous repeated every 45 min if the uterine contractions persisted. No data on maintenance therapy.	Not reported
Van De Water, ⁴² 2008	The Netherlands	Inclusion: women with singleton pregnancy in preterm labor irrespective of the membranes status. Exclusion: multiple pregnancy, intrauterine infection, fetal congenital defects, placental abruption, diabetes mellitus, cardiovascular diseases, hyperthyroidism, and preeclampsia.	24–34	Nifedipine (N=48): 20 mg orally. If contractions persisted after 30 min, a second dose of 20 mg was given. Then 90–120 mg orally per day for 48 h. Thereafter 90 mg/day for 7 days. Ritodrine (N=43): 200 µg/min IV increasing by 50 µg/min every 30 min until quiescence was achieved for 48 h. Then 80 mg orally every 8 h for a total duration of 7 days.	Indomethacin
NIFEDIPINE COMPARED WITH MAGNESIUM SULFATE					
Glock, ⁴³ 1993	United States	Inclusion: primigravid women with singleton pregnancy in preterm labor and intact membranes Exclusion: multiple pregnancy, premature rupture of membranes, known tocolytic drug exposure during the study pregnancy, diabetes, hyperthyroidism, cardiac disease, preeclampsia, abruptio placentae, chorioamnionitis, hydramnios, renal failure, cervical dilation >4 cm, fetal distress, severe intrauterine growth	20–34	Nifedipine (N=39): 10 mg sublingually. If contractions persisted, this dose was repeated every 20 min to maximum of 40 mg during the first hour of treatment. Once contractions ceased, 20 mg orally every 4 h for 48 h, then 10 mg orally every 8 h until 34 weeks. Magnesium sulfate (N=41): 6-g bolus then 2 g/h, increased to maximum of 4 g/h, until quiescence for 24 h. Then, weaned at 0.5 g every 4–6 h. Thereafter terbutaline 5 mg orally every 6 hours until 34 weeks.	Intravenous ritodrine

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Floyd, ⁴⁴ 1995	United States	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: Previous tocolytic therapy in current pregnancy, allergy to either study drug, medical or obstetric complications precluding treatment with either drug, and chorioamnionitis.	20–34	Nifedipine (N=50): 30 mg orally followed by 20 mg every 8 h until quiescence. Then 20 mg orally every 8 h until 37 weeks or delivery, whichever occurred first. Magnesium sulfate (N=40): 4-g bolus then 4–6 g/h continued for 6 h after quiescence. Then magnesium gluconate 2 g orally every 4 h until 37 weeks or delivery, whichever occurred first.	Not reported
Haghighi, ⁴⁵ 1999	Iran	Inclusion: women with singleton pregnancy in preterm labor and intact membranes Exclusion: known tocolytic drug exposure during the study pregnancy, diabetes, hyperthyroidism, cardiac disease, preeclampsia, placental abruption, chorioamnionitis, polyhydramnios, renal failure, cervical dilation 4 cm, fetal distress, severe intrauterine growth restriction, and fetal anomaly incompatible with life	23–36	Nifedipine (N=34): 10 mg sublingually. If contractions persisted, this dose was repeated every 20 min to maximum of 40 mg during the first hour of treatment. Once contractions ceased, 20 mg orally every 6 h during the first 24 h and 20 mg every 8 h the second day. No data on maintenance therapy. Magnesium sulfate (N=40): 6-g bolus then 2 g/h, increased to maximum of 4 g/h, until quiescence for up to 48 h. Then, terbutaline 5 mg orally every 6 h. No data on maintenance therapy.	Not reported
Taherian, ⁴⁶ 2007	Iran	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: taking other tocolytic agents, cervical dilatation 5 cm or obstetrical contraindications for tocolysis such as severe preeclampsia, lethal fetal anomalies, chorioamnionitis, significant antepartum hemorrhage, and maternal cardiac or liver diseases.	26–36	Nifedipine (N=57): 10 mg orally every 20 min (maximal dose of 40 mg in first hour). Once contractions ceased, 10–20 mg orally every 6 h. No data on duration of treatment or maintenance therapy. Magnesium sulfate (N=63): 4-g bolus then 2–3 g/h. No data on duration of treatment or maintenance therapy.	Ritodrine or indomethacin (18% in nifedipine group and 13% in magnesium sulfate group)
Lyell, ⁴⁷ 2007	United States	Inclusion: women with singleton or twin pregnancy in preterm labor irrespective of the membranes status. Exclusion: placental abruption, placenta previa, non reassuring fetal status, intrauterine growth restriction, chorioamnionitis, and maternal medical disease.	24–33	Nifedipine (N=100): 10 mg sublingually every 20 min for three doses total, followed by 20 mg orally every 4–6 h until at least 12 h of uterine quiescence occurred within the first 48 h. Maintenance therapy with nifedipine in 42% of women. Magnesium sulfate (N=92): 4-g bolus then 2 g/h, increased to maximum of 4 g/h, until at least 12 h of uterine quiescence occurred within the first 48 h. Maintenance therapy with nifedipine in 38% of women.	Permitted but unspecified

NIFEDIPINE COMPARED WITH ATOSIBAN

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Kashanian, ⁴⁸ 2005	Iran	Inclusion: women with singleton or twin pregnancy in preterm labor and intact membranes. Exclusion: premature rupture of membranes, vaginal bleeding, fetal death, fetal distress, fetal growth restriction, history of trauma, cervical dilatation >3 cm, maternal systemic disorders, uterine anomaly, and blood pressure <90/50 mm Hg.	26–34	Nifedipine (N=40): 10 mg sublingually every 20 min to a maximum in the first hour of 40 mg. Then 20 mg orally every 6 h for the first 24 h, and then every 8 h for the following 24 h. Thereafter, 10 mg orally every 8 h for the last 24 h. There was no maintenance therapy. Alosiban (N=40): 300 µg/min IV, continued for a maximum of 12 h, or 6 h after contractions were inhibited. There was no maintenance therapy.	Not reported
NIFEDIPINE COMPARED WITH NITRIC OXIDE DONORS					
Amorim, ⁴⁹ 2009	Brazil	Inclusion: women with singleton pregnancy in preterm labor and intact membranes. Exclusion: premature rupture of membranes, preeclampsia, diabetes, placental abruption, fetal malformation, and previous treatment with tocolytics.	24–34	Nifedipine (N=24): 10 mg sublingually repeated after 30 min. Then 20 mg orally every 6 h for at least 24 h. No data on maintenance therapy. Nitroglycerin (N=26): 10 mg transdermal patch. If contractions persisted after 6 h, a second patch of 10 mg was placed (maximum dose of 20 mg/24 h). No data on maintenance therapy.	Terbutaline
MAINTENANCE TOCOLYSIS					
NIFEDIPINE COMPARED WITH PLACEBO/NO TREATMENT					
Carr, ⁵⁰ 1999	United States	Inclusion: women with singleton pregnancy who had been in active preterm labor successfully arrested with IV magnesium sulfate. Exclusion: cervical dilatation 5 cm, obstetric contraindications to tocolysis (severe preeclampsia, lethal fetal anomalies, chorioamnionitis, significant antepartum hemorrhage), or maternal cardiac or liver disease.	24–33	Nifedipine (N=37): 20 mg orally every 4–6 h until 37 weeks. It was initiated after discontinuation of acute IV tocolysis. Control (N=37): no treatment	Magnesium sulfate or terbutaline
Sayin, ⁵¹ 2004	Turkey	Inclusion: women with singleton or twin pregnancy and intact membranes who had been in active preterm labor successfully arrested with IV ritodrine and verapamil. Exclusion: cervical dilatation 4 cm, triple or higher order pregnancy, intrauterine infection, fetal congenital anomalies, fetal growth restriction, and any contraindication to betamimetics such as diabetes mellitus, cardiac disease, or hyperthyroidism.	Not stated	Nifedipine (N=37): 20 mg orally every 6 h until 37 weeks. It was initiated after discontinuation of acute IV tocolysis. Control (N=36): no treatment	Ritodrine and verapamil

First author, year	Location	Inclusion/exclusion criteria	Gestational age (weeks)	Interventions (sample size)	Alternative tocolytic therapy
Lyell, ⁵² 2008	United States	Inclusion: women with singleton or twin pregnancy and intact membranes who had been in active preterm labor successfully arrested with IV magnesium sulfate or oral nifedipine. Exclusion: placental abruption, placenta previa, fetal anomaly incompatible with life, triple or higher-order multiple pregnancies, intrauterine infection, or a maternal medical contraindication to ongoing tocolysis.	24–34	Nifedipine (N=33): 20 mg orally every 6 h until 37 weeks. It was initiated after discontinuation of acute IV tocolysis. Control (N=35): placebo	Magnesium sulfate

^aWomen receiving β_2 -agonists immediately before randomization (N=45) were excluded from analyses

TABLE 2

Methodological quality assessment (modified Jadad scoring system²²) of included studies

Study	Randomization	Blinding	Follow-up	Allocation concealment	Total score
Read ²⁷	2	0	2	0	4
Ferguson ²⁸	2	0	2	2	6
Janky ²⁹	2	0	2	2	6
Bracero ³⁰	2	0	2	2	6
Kupferminc ³¹	2	0	2	0	4
Papatsonis ³²	2	0	2	2	6
Koks ³³	2	0	2	2	6
García-Velasco ³⁴	2	0	2	2	6
Ganla ³⁵	1	0	2	0	3
Al-Qattan ³⁶	2	0	1	0	3
Weerakul ³⁷	2	0	2	2	6
Rayamahil ³⁸	1	0	1	0	2
Cararach ³⁹	2	0	2	2	6
Laohapojanart ⁴⁰	2	0	1	0	3
Mawaldi ⁴¹	2	0	2	2	6
Van De Water ⁴²	2	0	2	2	6
Glock ⁴³	1	0	1	2	4
Floyd ⁴⁴	2	0	2	2	6
Haghighi ⁴⁵	1	0	2	0	3
Taherian ⁴⁶	2	0	1	0	3
Lyell ⁴⁷	2	0	2	2	6
Kashanian ⁴⁸	2	0	0	0	2
Amorim ⁴⁹	2	0	1	2	5
Carr ⁵⁰	2	0	1	2	5
Sayin ⁵¹	1	0	2	0	3

Study	Randomization	Blinding	Follow-up	Allocation concealment	Total score
Lyell ⁵²	2	2	2	2	8

Scores: 0=lowest quality, 8=highest quality

TABLE 3

Acute tocolysis: nifedipine compared with β_2 -adrenergic-receptor agonists

Outcome	Number of events/total number or Total number			
	No of trials	Nifedipine	β ₂ -agonists	Relative risk or Mean difference (95% CI) I ² (%)
Pregnancy outcomes				
Delivery within 48 hours of treatment	13 ^{27,28,31–34,36–42}	114/535	126/524	0.84 (0.68, 1.05)
Delivery within 7 days of treatment	10 ^{28,31–33,36–40,42}	153/410	171/380	0.82 (0.70, 0.97)
Preterm birth <34 weeks' gestation	5 ^{32,33,36,37,42}	121/250	140/225	0.77 (0.66, 0.91)
Preterm birth <37 weeks' gestation	9 ^{28,31,32,34,36–40}	214/356	206/336	0.97 (0.87, 1.08)
Pregnancy prolongation (days)	9 ^{27,29,30,32,34,35,37–39}	360	350	5.8 (1.4, 10.2)
Gestational age at birth (weeks)	8 ^{30,32,33,36–40}	319	291	0.7 (0.3, 1.2)
Maternal adverse drug reaction	9 ^{27,28,31,32,37,39–42}	81/415	235/419	0.31 (0.18, 0.54)
Discontinuation of treatment because of adverse effects	13 ^{28–39,42}	3/522	44/498	0.14 (0.06, 0.31)
Perinatal and neonatal outcomes				
Birthweight (grams)	10 ^{27,30,32–34,36–40}	365	335	178.8 (84.1, 273.6)
Apgar score <7 at 5 minutes	2 ^{31,32}	6/137	10/130	0.6 (0.2, 1.5)
Respiratory distress syndrome	13 ^{28–37,39,40,42}	56/516	81/483	0.63 (0.46, 0.86)
Necrotizing enterocolitis	5 ^{30,32,37,39,42}	1/250	8/235	0.21 (0.05, 0.94)
Intraventricular hemorrhage	6 ^{28,32,36,37,40,42}	23/271	41/249	0.53 (0.34, 0.84)
Retinopathy of prematurity	2 ^{32,42}	0/143	5/133	0.15 (0.02, 1.28)
Neonatal jaundice	2 ^{30,32}	51/118	66/109	0.73 (0.57, 0.93)
Neonatal sepsis	6 ^{29,30,32,37,39,42}	27/280	37/267	0.70 (0.45, 1.09)
Perinatal mortality	11 ^{27–32,34,36–39}	12/415	11/396	1.02 (0.49, 2.14)
Fetal death	11 ^{27–32,34,36–39}	1/415	1/396	1.00 (0.14, 6.96)
Neonatal death	14 ^{27–34,36–40,42}	15/518	13/483	1.03 (0.53, 2.02)
Admission to NICU	9 ^{29–34,37,40,42}	97/364	116/338	0.76 (0.62, 0.93)
NICU stay (days)	2 ^{30,42}	71	62	−7.2 (−11.2, −3.3)
Any mental retardation at 2 years of age	1 ⁴²	9/28	12/35	0.94 (0.46, 1.90)
				NA

Outcome	No of trials	Number of events/total number or Total number		Relative risk or Mean difference (95% CI)	<i>P</i> (%)
		Nifedipine	β_2 -agonists		
Behavioral-emotional functioning score at age 9–12 years	1 ³²	45	51	–1.5 (–4.7, 1.8)	NA
Quality of life score at age 9–12 years	1 ³²	44	50	–0.3 (–0.7, 0.1)	NA

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit

TABLE 4

Acute tocolysis: nifedipine compared with magnesium sulfate, atosiban, and nitric oxide donors

Outcome	Number of events/total number or Total number			Relative risk or Mean difference (95% CI)	I ² (%)
	No of trials	Nifedipine	Other tocolytic		
NIFEDIPINE COMPARED WITH MAGNESIUM SULFATE					
Pregnancy outcomes					
Delivery within 48 hours of treatment	4 ^{43,45-47}	41/230	53/236	0.84 (0.60, 1.18)	0
Preterm birth <34 weeks' gestation	3 ^{43,44,46}	57/146	60/144	0.99 (0.76, 1.29)	0
Preterm birth <37 weeks' gestation	3 ^{43,44,47}	93/189	92/173	0.94 (0.77, 1.14)	0
Pregnancy prolongation (days)	1 ⁴⁴	50	40	-5.8 (-18.6, 7.0)	NA
Gestational age at birth (weeks)	2 ^{43,47}	139	133	-0.1 (-0.9, 0.7)	19
Maternal adverse drug reaction	4 ^{43,45-47}	54/230	84/236	0.63 (0.48, 0.82)	48
Severe maternal adverse drug reaction	1 ⁴⁷	10/100	20/92	0.46 (0.23, 0.93)	NA
Discontinuation of treatment because of adverse effects	2 ^{43,45}	0/73	4/81	0.12 (0.01, 2.10)	NA
Perinatal and neonatal outcomes					
Birthweight (grams)	4 ^{43,45-47}	240	250	-5.6 (-67.5, 56.4)	0
Apgar score at 5 minutes	3 ^{43,45,46}	130	144	0.0 (-0.4, 0.4)	0
Apgar score <7 at 5 minutes	1 ⁴⁴	7/50	6/40	0.93 (0.34, 2.56)	NA
Respiratory distress syndrome	2 ^{44,47}	26/160	28/146	0.87 (0.54, 1.40)	0
Intraventricular hemorrhage	1 ⁴⁷	2/110	3/106	0.64 (0.11, 3.77)	NA
Neonatal sepsis	1 ⁴⁷	3/110	5/106	0.58 (0.14, 2.36)	NA
Perinatal mortality	3 ^{43,44,47}	3/199	1/187	1.71 (0.37, 7.88)	0
Fetal death	3 ^{43,44,47}	1/199	0/187	2.41 (0.10, 57.65)	NA
Neonatal death	3 ^{43,44,47}	2/199	1/187	1.51 (0.26, 8.74)	36
Admission to NICU	1 ⁴⁷	41/110	55/106	0.72 (0.53, 0.97)	NA
NICU stay (days)	2 ^{45,47}	144	146	-2.2 (-3.4, -1.1)	42
NIFEDIPINE COMPARED WITH ATOSIBAN					
Delivery within 48 hours of treatment	1 ⁴⁸	10/40	7/40	1.43 (0.60, 3.38)	NA
Delivery within 7 days of treatment	1 ⁴⁸	14/40	10/40	1.40 (0.71, 2.77)	NA

Outcome	No of trials	Number of events/total number or Total number		Relative risk or Mean difference (95% CI)	I ² (%)
		Nifedipine	Other tocolytic		
Maternal adverse drug reaction	1 ⁴⁸	16/40	7/40	2.29 (1.06, 4.95)	NA
NIFEDIPINE COMPARED WITH OXIDE NITRIC DONORS (NITROGLYCERIN)					
Delivery within 48 hours of treatment	1 ⁴⁹	3/24	4/26	0.81 (0.20, 3.26)	NA
Maternal adverse drug reaction	1 ⁴⁹	5/24	9/26	0.60 (0.23, 1.54)	NA

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit

TABLE 5
Acute tocolysis: Sensitivity analysis including only studies with high methodological quality (modified Jadad score = 6)

Outcome	Number of events/total number or Total number				Relative risk or Mean difference (95% CI)	I ² (%)
	No of trials	Nifedipine	β ₂ -agonists			
NIFEDIPINE COMPARED WITH β ₂ -ADRENERGIC-RECEPTOR AGONISTS						
Delivery within 48 hours of treatment	8 ^{28,32–34,37,39,41,42}	83/397	78/394		1.00 (0.76, 1.31)	48
Delivery within 7 days of treatment	6 ^{28,32,33,37,39,42}	106/292	122/274		0.81 (0.66, 0.98)	31
Preterm birth <34 weeks' gestation	4 ^{32,33,37,42}	106/220	122/202		0.79 (0.67, 0.94)	0
Preterm birth <37 weeks' gestation	5 ^{28,32,34,37,39}	137/238	131/232		1.01 (0.88, 1.17)	26
Pregnancy prolongation (days)	6 ^{29,30,32,34,37,39}	258	250		5.8 (1.8, 9.9)	49
Gestational age at birth (weeks)	5 ^{30,32,33,37,39}	237	220		0.6 (0.0, 1.2)	0
Maternal adverse drug reaction	6 ^{28,32,37,39,41,42}	54/339	175/344		0.28 (0.15, 0.53)	78
Discontinuation of treatment because of adverse effects	9 ^{28-30,32–34,37,39,42}	1/374	31/355		0.11 (0.04, 0.31)	0
Birth weight (grams)	6 ^{30,32,33,34,37,39}	263	246		139.9 (13.9, 265.8)	48
Respiratory distress syndrome	9 ^{28–30,32–34,37,39,42}	44/374	61/354		0.67 (0.47, 0.94)	0
Necrotizing enterocolitis	5 ^{30,32,37,39,42}	1/250	8/235		0.21 (0.05, 0.94)	0
Intraventricular hemorrhage	4 ^{28,32,37,42}	23/221	38/210		0.58 (0.36, 0.91)	0
Neonatal jaundice	2 ^{30,32}	51/118	66/109		0.73 (0.57, 0.93)	48
Admission to NICU	7 ^{29,30,32–34,37,42}	84/302	99/282		0.77 (0.62, 0.96)	18
NICU stay (days)	2 ^{30,42}	71	62		−7.2 (−11.2, −3.3)	0
NIFEDIPINE COMPARED WITH MAGNESIUM SULFATE						
Delivery within 48 hours of treatment	1 ⁴⁷	8/100	7/92		1.05 (0.40, 2.78)	NA
Preterm birth <34 weeks' gestation	1 ⁴⁴	10/50	8/40		1.00 (0.44, 2.30)	NA
Preterm birth <37 weeks' gestation	2 ^{44,47}	70/150	68/132		0.91 (0.72, 1.16)	0
Pregnancy prolongation (days)	1 ⁴⁴	50	40		−5.8 (−18.6, 7.0)	NA
Gestational age at birth (weeks)	1 ⁴⁷	100	92		0.2 (−0.7, 1.1)	NA
Maternal adverse drug reaction	1 ⁴⁷	34/100	60/92		0.52 (0.38, 0.71)	NA
Severe maternal adverse drug reaction	1 ⁴⁷	10/100	20/92		0.46 (0.23, 0.93)	NA

Outcome	No of trials	Number of events/total number or Total number		Relative risk or Mean difference (95% CI)	I ² (%)
		Nifedipine	β ₂ -agonists		
Admission to NICU	1 ⁴⁷	41/110	55/106	0.72 (0.53, 0.97)	NA
NICU stay (days)	1 ⁴⁷	110	106	-4.6 (-8.3, -0.9)	NA

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit

TABLE 6

Maintenance tocolysis: nifedipine compared with placebo/no treatment

Outcome	Number of events/total number or Total number		Relative risk or Mean difference (95% CI)	I ² (%)	
	No of trials	Nifedipine Placebo/no treatment			
Pregnancy outcomes					
Preterm birth <34 weeks' gestation	1 ⁵⁰	12/37	9/37	1.33 (0.64, 2.78)	NA
Preterm birth <37 weeks' gestation	3 ⁵⁰⁻⁵²	59/107	69/108	0.87 (0.69, 1.08)	32
Pregnancy prolongation (days)	3 ⁵⁰⁻⁵²	107	108	6.3 (1.2, 11.4)	22
Gestational age at birth (weeks)	3 ⁵⁰⁻⁵²	107	108	0.7 (-0.7, 2.1)	66
At least 1 episode of recurrent preterm labor	2 ^{50,51}	16/69	20/68	1.19 (0.19, 7.30)	66
More than 1 episode of recurrent preterm labor	2 ^{51,52}	21/70	18/71	1.21 (0.72, 2.03)	15
Perinatal and neonatal outcomes					
Birthweight (grams)	3 ⁵⁰⁻⁵²	125	120	-29.4 (-209.1, 150.4)	0
Respiratory distress syndrome	2 ^{50,51}	7/77	9/77	0.78 (0.31, 1.98)	0
Necrotizing enterocolitis	2 ^{50,51}	2/77	1/77	1.67 (0.23, 12.33)	0
Intraventricular hemorrhage	2 ^{50,51}	2/77	3/77	0.71 (0.14, 3.54)	30
Neonatal sepsis	1 ⁵¹	2/40	1/40	2.00 (0.19, 21.18)	NA
Neonatal death	1 ⁵¹	0/40	2/40	0.20 (0.01, 4.04)	NA
Admission to NICU	2 ^{50,51}	22/77	19/77	1.16 (0.68, 1.96)	0
NICU stay (days)	3 ⁵⁰⁻⁵²	125	120	-0.3 (-2.1, 1.4)	0
Preterm birth <34 weeks' gestation among women enrolled at <32 weeks' gestation	1 ⁵⁰	8/25	8/24	0.96 (0.43, 2.15)	NA
Preterm birth <37 weeks' gestation among women enrolled at <32 weeks' gestation	2 ^{50,52}	34/50	38/52	0.93 (0.72, 1.20)	0
Pregnancy prolongation (days) among women enrolled at <32 weeks' gestation	3 ⁵⁰⁻⁵²	66	75	11.0 (-2.1, 24.2)	73
Gestational age at birth (weeks) among women enrolled at <32 weeks' gestation	2 ^{50,52}	50	52	0.2 (-1.2, 1.6)	0
Birthweight among women enrolled at <32 weeks' gestation	1 ⁵⁰	25	24	122.0 (-308.0, 552.0)	NA
Admission to NICU among women enrolled at <32 weeks' gestation	1 ⁵⁰	5/25	6/24	0.80 (0.28, 2.28)	NA

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit