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Effect of Maintenance Tocolysis With Nifedipine in Threatened Preterm Labor on Perinatal Outcomes
A Randomized Controlled Trial

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Importance In threatened preterm labor, maintenance tocolysis with nifedipine, after an initial course of tocolysis and corticosteroids for 48 hours, may improve perinatal outcome.

Objective To determine whether maintenance tocolysis with nifedipine will reduce adverse perinatal outcomes due to premature birth.

Design, Setting, and Participants APOSTEL-II (Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labor) is a double-blind, placebo-controlled trial performed in 11 perinatal units including all tertiary centers in the Netherlands. From June 2008 to February 2010, women with threatened preterm labor between 26 weeks (plus 0 days) and 32 weeks (plus 2 days) gestation, who had not delivered after 48 hours of tocolysis and a completed course of corticosteroids, were enrolled. Surviving infants were followed up until 6 months after birth (ended August 2010).

Intervention Randomization assigned 406 women to maintenance tocolysis with nifedipine orally (80 mg/d; n=201) or placebo (n=205) for 12 days. Assigned treatment was masked from investigators, participants, clinicians, and research nurses.

Main Outcome Measures Primary outcome was a composite of adverse perinatal outcomes (perinatal death, chronic lung disease, neonatal sepsis, intraventricular hemorrhage >grade 2, periventricular leukomalacia >grade 1, or necrotizing enterocolitis). Analyses were completed on an intention-to-treat basis.

Results Mean (SD) gestational age at randomization was 29.2 (1.7) weeks for both groups. Adverse perinatal outcome was not significantly different between groups: 11.9% (24/201; 95% CI, 7.5%-16.4%) for nifedipine vs 13.7% (28/205; 95% CI, 9.0%-18.4%) for placebo (relative risk, 0.87; 95% CI, 0.53-1.45).

Conclusions and Relevance In patients with threatened preterm labor, nifedipine-maintained tocolysis did not result in a statistically significant reduction in adverse perinatal outcomes when compared with placebo. Although the lower than anticipated rate of adverse perinatal outcomes in the control group indicates that a benefit of nifedipine cannot completely be excluded, its use for maintenance tocolysis does not appear beneficial at this time.

Trial Registration trialregister.nl Identifier: NTR1336.

P RETERM BIRTH IS THE MOST COM-mon cause of neonatal morbidity and mortality worldwide. Almost 75% of perinatal deaths occur in infants born before 37 weeks' gestation.[1] Consequently, preterm birth is associated with a large burden of disease, high costs for medical care, special education, and institutionalized care for disabled infants.[2]

In threatened preterm labor before 34 weeks, delay of delivery for 48 hours allows antenatal corticosteroid treatment to improve fetal maturity and transfer of the pregnant woman to a center with a neonatal intensive care unit.[3] For initial tocolysis, nifedipine is comparable with magnesium sulfate[4] and superior to ritodrine[5] and atosiban.[6] Because perinatal morbidity and

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mortality are inversely related to gestational age,[7] delay of delivery for more than 48 hours may improve perinatal outcome.

However, the effectiveness of maintenance tocolysis, after an initial course of tocolysis and corticosteroids for 48 hours, on pregnancy and perinatal outcome has not been demonstrated. Three meta-analyses failed to show any beneficial effect of maintenance tocolysis with β-mimetics, oxytocin antagonists, or magnesium sulfate.[8-10] Maintenance tocolysis with nifedipine has been assessed in 3 small trials that showed contradictory results. In one study, Sayin et al[11] reported a significant increase in mean gestational age at delivery, whereas 2 other studies[12,13] did not demonstrate a beneficial effect on gestational age at delivery (pooled mean difference, −0.14; 95% CI, −1.2 to 0.95). These studies were not powered to detect effects on perinatal outcome, but only to detect an effect on prolongation of pregnancy. Yet reduction of perinatal mortality and morbidity should be the primary goal of maintenance tocolysis. Therefore, we evaluated the effectiveness of maintenance tocolysis with nifedipine on perinatal outcome.

METHODS

We performed a multicenter, double-blind, placebo-controlled trial in 11 perinatal units including all tertiary centers in the Netherlands. Randomization of participants occurred between June 2008 and February 2010; follow-up was completed in August 2010. The complete study protocol is reported elsewhere.[14] Written informed consent was obtained from all participants. The trial was approved by each institutional review board.

Study Population

Women with threatened preterm labor and a gestational age between weeks 26 (plus 0 days) and 32 (plus 2 days), who had not delivered after a complete 48-hour course of tocolytics and corticosteroids, were eligible for participation. The diagnosis of threat-

ened preterm labor was based on changes in cervical length, progression in dilatation in combination with contractions, or on ruptured membranes. The initial tocolytic was usually nifedipine or atosiban, according to local protocol. We included women with singleton and multiple pregnancies with and without ruptured membranes. Women who were transferred to a tertiary center during the first 48 hours could be included. In case of transfer, the diagnosis of threatened preterm labor was established by confirmation of ruptured membranes, measurement of the cervical length by ultrasound, dilatation at vaginal examination, or a combination of these factors. Threatened preterm labor was considered to remain present in all women who had not delivered in the first 48 hours after admission.

Maternal exclusion criteria were signs of intrauterine infection, hypertension (≥140/90 mm Hg), preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), placenta previa, and contraindications for nifedipine. Fetal exclusion criteria included signs of fetal distress, known lethal congenital anomalies, and intrauterine death.

Randomization

Women were randomly assigned to receive nifedipine or placebo (allocation ratio 1:1) for 12 days. Group assignment was based on a computer-generated random sequence in blocks of 4 participants. Treatment assignment and block size were blinded to investigators, participants, clinicians, and research nurses. For additional tocolysis or unblinding of treatment allocation (possible for reasons of safety), the study group provided 24-hour telephone service.

To demonstrate generalizability of findings, the outcome of women who refused randomization (nonrandomization group) was assessed separately. This group was treated according to local protocol. Women in the nonrandomization group gave written informed consent for follow-up of their data.

Interventions

Study medication was 20 mg of nifedipine slow-release tablets every 6 hours, resulting in a total daily dose of 80 mg of nifedipine or placebo tablets. Initiation of study medication was 48 to 72 hours after the start of initial tocolysis. Study protocol allowed treating physicians to decrease the dosing interval of the study drug to every 4 hours based on the patient's symptoms. Study medication was phased out from day 10 (total daily dose of 60 mg) until day 12 (total daily dose of 20 mg) and discontinued on day 13. Maintenance nifedipine therapy was limited to 12 days following 2 days of initial tocolysis and corticosteroids, based on the assumption that 2 weeks' prolongation of pregnancy in threatened preterm labor patients, if clinically relevant, should show an effect on perinatal outcome.

We studied the effect with nifedipine for 12 days with duration extending to a maximal gestational age of 34 weeks. This method of intervention was implemented for 2 reasons. First, the Dutch national guideline on preterm labor considers the risk of adverse perinatal outcome after 34 weeks' gestation too small to warrant tocolysis. Second, any beneficial effect of maintenance tocolytic therapy should be more easily demonstrated in a group of cases at high risk of adverse perinatal outcome than in a group with high- and low-risk cases combined. Once study medication was completed, a repeat course of tocolysis and corticosteroids for 48 hours was allowed in case of recurrence of threatened preterm labor.

Study Outcome

The primary outcome measure was a composite of adverse perinatal outcomes due to premature birth, defined as perinatal mortality and serious morbidity including chronic lung disease, neonatal sepsis (proven with a positive blood culture), severe intraventricular hemorrhage greater than grade 2, periventricular leukomalacia greater than grade 1, and necrotizing enterocolitis. Chronic lung disease was defined as oxygen dependency at 28

days of life.[15] We included chronic lung disease instead of respiratory distress syndrome in our composite adverse perinatal outcome, since presence of chronic lung disease is of more prognostic importance for long-term outcome. Intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis were defined according to previously described classifications.[16-18] The status of the primary outcome was evaluated for as long as 6 months after birth. All infants hospitalized for prematurity or any other reason within the first 6 months of life visited our outpatient clinic at aged 6 months.

Secondary outcome measures were gestational age at delivery, birth weight, days using ventilation support, length of stay in neonatal intensive care, and total days in hospital until 3 months corrected age. Posthoc exploratory analyses examined prolongation of pregnancy, maternal mortality, maternal blood loss, and infant respiratory distress syndrome. All outcomes were collected for both the randomized and nonrandomized groups and included in the web-based database by research nurses and midwives before the randomization code of the trial was broken.

Prespecified subgroup analyses were performed to assess the consistency of a treatment effect among subgroups defined by singleton or multiple gestation, gestational age at randomization, and absence or presence of ruptured membranes.

Statistical Analysis

The trial was designed to detect a reduction from 25% in the composite neonatal outcome in the placebo group (based on 3 earlier trials on maintenance tocolysis with nifedipine[11-13] and 1 trial of nifedipine initial tocolysis performed in the Netherlands[5]) to 14% in the nifedipine maintenance tocolysis group (11% difference based on a 2-week increase in gestational age showed by Sayin et al[11] and on perinatal data of 1 of our participating centers). We needed to enroll 406 women to obtain a power of 80% at a signifi-

cance level of .05 (2-sided). An independent data and safety monitoring committee reviewed the data after randomization of 200 women.

Data analysis was performed according to the intention-to-treat principle, ie, participants were analyzed in the allocated group even in case of discontinuation of intervention. Data were collected from participants and their infants who discontinued intervention; there were no missing data. Continuous variables are presented as means with standard deviations, as geometric means with 95% CIs, or as medians with interquartile ranges (IQRs) whenever appropriate. The primary outcome was measured per pregnancy, ie, 1 or more of the components of the primary outcome in 1 or more of the infants was counted as 1 primary outcome. The effectiveness of nifedipine was assessed by calculating relative risks (RRs) with 95% CIs and determined with a log-binomial model. The outcome of the study was dichotomous and the association of interest RR could be simply calculated from a 2×2 table. Instead, we chose to calculate the association using a log-binomial regression model, which is similar to a χ^2 test on a 2×2 table, which corresponded with the sample size calculation.

Secondary outcomes were measured per infant. For dichotomous secondary outcomes, the RR was determined using binomial generalized estimating equations (GEEs) with a log-link function. GEEs were used to account for outcomes in multiple pregnancies by considering the mother as a cluster variable.[19] For continuous secondary outcomes, negative binomial GEEs with a log-link function were used. The effectiveness of nifedipine was assessed by calculating hazard ratios (HRs) with 95% CIs, geometric mean differences with 95% CIs, or incidence rate ratios (IRRs) with 95% CIs. Pregnancy outcomes were compared using log-binomial logistic regression for dichotomous outcomes and the Mann-Whitney U test for outcomes that did not show a normal distribution. Time to delivery was assessed with Kaplan-Meier analysis and Cox proportional

hazard analysis. A P value of less than .05 was considered significant (2-sided). The statistical software used was R, version 2.15.1 (R Foundation for Statistical Computing).

RESULTS

Study Population

We approached 636 eligible women, of whom 406 agreed to participate. Baseline characteristics of the 230 women in the nonrandomized group were comparable with those of the randomized group except for maternal age, with those in the nonrandomized group being on average 1 year younger (P = .01; TABLE 1). The data and safety monitoring committee evaluated the data after inclusion of 200 women and recommended continuing the study.

Of the 406 participants, 201 were assigned to the nifedipine group and 205 to the placebo group (FIGURE 1). Table 1 summarizes the baseline characteristics of the randomized population. Mean (SD) gestational age at randomization was 29.2 (1.7) weeks for both groups. Twenty-two percent of the participants had a multiple pregnancy and 25% had ruptured membranes. Initial tocolysis was provided with atosiban in 40% of the women and with nifedipine in all others.

Nine women, 3 in the nifedipine and 6 in the placebo group, never started study medication for the following reasons: withdrawal (n=6), need for emergency tocolysis for transfer to another center (n=1), complete dilatation at study entry (n=1), and signs of intrauterine infection (n=1).

Additional tocolysis, needed for transfer to another perinatal center, was given to 12 (6.0%) women in the nifedipine group and to 9 women (4.4%) in the placebo group (Table 1). Treatment allocation was never unblinded during the study.

Primary Outcome

Adverse perinatal outcome was not significantly different between the groups, with 24 (11.9%; 95% CI, 7.5%-16.4%) cases in the nifedipine group and 28 (13.7%; 95% CI, 9.0%-18.4%) in the

placebo group (RR, 0.87; 95% CI, 0.53-1.45; TABLE 2), risk difference 1.8% (95% CI, −4.7 to 8.3%). Perinatal death occurred in 5 (2.5%) in the nifedipine group and in 4 (2.0%) in the placebo group (RR, 1.3; 95% CI, 0.35-4.7). The rates of chronic lung disease, proven neonatal sepsis, intraventricular hemorrhage greater than grade 2, periven-

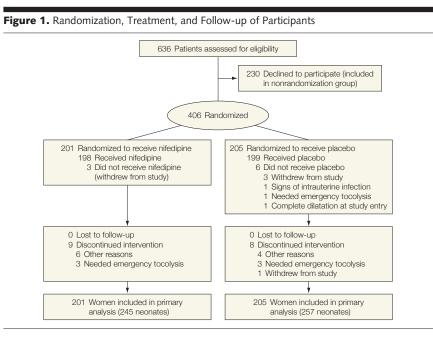tricular leukomalacia greater than grade 1, and necrotizing enterocolitis were comparable between both groups.

Secondary Outcome

Mean (SD) gestational age at delivery was comparable for both groups: 34.1 (4.0) weeks for the nifedipine group and 34.2 (4.0) weeks for the placebo group

(HR, 1.0; 95% CI, 0.83-1.2; TABLE 3). Birth weight was not significantly different between the 2 groups, with a geometric mean difference of 27 g (95% CI, −128 to 195). Neonatal intensive care unit admission occurred in 100 of 245 neonates (40.8%) in the nifedipine group and in 102 of 257 (39.7%) in the placebo group. The length of neonatal intensive care unit admission was 10 days for both groups (IRR, 0.92; 95% CI, 0.70-1.2). Ventilation support for the nifedipine group was provided for 2 days (IQR, 1-4) and for the placebo group for 3 days (IQR, 1-6) (IRR, 0.74; 95% CI, 0.43-1.3). Total hospital admission was 23 days for both groups (IRR, 0.97; 95% CI, 0.82-1.1).

Prespecified subgroup analysis of women randomized between 26 weeks (plus 0 days) and 27 weeks (plus 6 days), 28 weeks (plus 0 days) and 29 weeks (plus 6 days), and 30 weeks (plus 0 days) and 32 weeks (plus 1 day) of gestation revealed no differences in either perinatal mortality, composite adverse perinatal outcome, gestational age at delivery, or birth weight between the groups (eTable 1, eTable 2, and eTable 3 available at http://www.jama.com). Similarly, subgroup analyses among women with singleton and multiple pregnancies and among women with and without ruptured membranes revealed no differences.

Exploratory Outcomes

Prolongation of pregnancy was comparable between groups (HR, 1.0; 95% CI, 0.84-1.2), and the Kaplan-Meier curve indicated no difference (log-rank P, .85; FIGURE 2). Delivery prior to 32 weeks (plus 0 days) gestation occurred in 66 (32.8%) women in the nifedipine group and 71 (34.6%) women in the placebo group (RR, 0.95; 95% CI, 0.73-1.3). Infant respiratory distress syndrome treated with surfactant occurred in 12 of 201 (6.0%) pregnancies in the nifedipine group and in 14 of 205 (6.8%) in the placebo group (RR, 0.87; 95% CI, 0.41-1.8).

Maternal mortality did not occur in either group. In both groups, 1 participant was admitted to the intensive care

Table 1. Baseline Demographics and Clinical Characteristics

Characteristics	Participants by Study Group, No. (%)		
	Nifedipine (n = 201)	Placebo (n = 205)	Nonrandomization (n = 230)
Age, mean (SD), y	30.2 (5.1)	30.2 (5.1)	28.7 (5.5)[a]
Body mass index, mean (SD)[b]	23.3 (4.7)	23.3 (4.3)	23.5 (5.0)
White race	166 (82.6)	155 (75.6)	166 (72.2)
Nulliparous	116 (57.7)	106 (51.7)	134 (58.3)
Prior preterm birth	39 (19.4)	55 (26.8)	40 (17.4)
Gestational age at study entry, mean (SD), wk	29.2 (1.7)	29.2 (1.7)	29.2 (1.9)
Multiple gestation	42 (20.9)	48 (23.4)	45 (19.6)
Twins	40 (19.9)	44 (21.5)	42 (18.3)
Triplets	2 (1.0)	4 (1.9)	3 (1.5)
pPROM at study entry	53 (26.4)	48 (23.4)	44 (19.1)
Vaginal bleeding at study entry	38 (18.9)	38 (18.5)	43 (18.7)
Additional tocolysis	12 (6.0)	9 (4.4)	NA
Vaginal examination at study entry	(n = 134)	(n = 132)	(n = 111)
Dilatation, median (IQR), cm	0 (0-1)	1 (0-2)	1 (0-1)
Cervical length, median (IQR), mm	25 (15-35)	23 (15-30)	24 (17-31)

Abbreviations: IQR, interquartile range; NA, not applicable; pPROM, premature rupture of the membranes before 37 weeks' gestation.
[a] P = .01.
[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

Figure 1. Randomization, Treatment, and Follow-up of Participants

636 Patients assessed for eligibility

230 Declined to participate (included in nonrandomization group)

406 Randomized

201 Randomized to receive nifedipine
198 Received nifedipine
3 Did not receive nifedipine (withdrew from study)

205 Randomized to receive placebo
199 Received placebo
6 Did not receive placebo
3 Withdrew from study
1 Signs of intrauterine infection
1 Needed emergency tocolysis
1 Complete dilatation at study entry

0 Lost to follow-up
9 Discontinued intervention
6 Other reasons
3 Needed emergency tocolysis

0 Lost to follow-up
8 Discontinued intervention
4 Other reasons
3 Needed emergency tocolysis
1 Withdrew from study

201 Women included in primary analysis (245 neonates)

205 Women included in primary analysis (257 neonates)

unit because of severe bleeding during the third stage of labor. Cesarean deliveries were performed in 53 (26.4%) women in the nifedipine group and in 56 (27.3%) women in the placebo group (RR, 0.97; 95% CI, 0.70-1.3). Vaginal blood loss during the third stage was not significantly different with geometric mean values of 403 mL (nifedipine) and 353 mL (placebo). Severe blood loss of greater than 1000 mL occurred in 22 of 201 (11.1%) women in the nifedipine group and in 15 of 205 (7.3%) women in the placebo group (RR, 1.5; 95% CI, 0.80-2.8).

In 120 participants who delivered while still using study medication, women receiving nifedipine had significantly more blood loss than those in the placebo group: 432 ml vs 307 mL, with a geometric mean difference of 125 mL (95% CI, 3-295; P, .045). Severe blood loss of greater than 1000 mL occurred in 8 of 59 (13.6%) women in the nifedipine group and in 3 of 61 (4.9%) women in the placebo group (RR, 2.6; 95% CI, 0.73-9.3).

COMMENT

Our randomized placebo-controlled trial in women with threatened preterm labor showed that nifedipine maintenance tocolysis for 12 days did not result in a significant reduction in adverse perinatal outcomes when compared with placebo.

Our study has several strengths. We chose a clinically important end point; conducted a large, nationwide study in which all 10 perinatal centers in the Netherlands participated; and included high-risk participants, more than two-thirds of whom delivered preterm. Only tocolytic maintenance was studied (independent of initial tocolysis) and few women received additional tocolysis (5%), which was lower than the 8% to 42% reported in the previous trials with nifedipine.[11-13] The study likely represents the population at risk of threatened preterm labor. Most of the participating women were referred from regional hospitals where the decision for referral and start of the initial treatment was taken unaffected by the incentive to recruit women for the study. Two-thirds of the 636 eligible women consented to randomization and the relevant baseline characteristics of women who declined randomization were not different from those of the study groups, except for maternal

age (the nonrandomized group was 1 year younger).

The limitations of our study include lower than planned power for primary and secondary end points in the study design due to a lower than anticipated control event rate. The primary outcome in our study was a composite of adverse perinatal outcomes. Previous studies evaluating interventions thought to improve perinatal outcome, such as progestagens in multiple pregnancy, were powered on duration of pregnancy.[20,21] The reason for choosing neonatal outcome as the primary outcome was that this is the relevant clinical outcome and not gestational age per se. This is a strength, as prolongation of pregnancy is not a goal in itself but only a step in the pathway to reduce adverse perinatal outcomes. However, the 14% adverse outcome in the placebo group was low in comparison to the anticipated rate of 25%. This can be explained by improved neonatal care over the last decades and differences with the studies used to estimate this anticipated rate. If the true RR were as low as the lower bound of the 95% CI (0.53), the absolute risk reduction could be 6.5%, which would be considered as irrelevant by

Table 2. Perinatal Outcome

Primary Outcome	Participants by Study Group, No. (%)		RR (95% CI)	IRR (95% CI)
	Nifedipine (n = 201)	Placebo (n = 205)		
Adverse perinatal outcome[a]	24 (11.9)	28 (13.7)	0.87 (0.53-1.45)	
Perinatal death	5 (2.5)	4 (2.0)	1.3 (0.35-4.7)	
Chronic lung disease	5 (2.5)	6 (2.9)	0.85 (0.26-2.7)	
Neonatal sepsis	16 (8.0)	18 (8.8)	0.91 (0.48-1.7)	
IVH >grade 2	2 (1.0)	5 (2.4)	0.41 (0.08-2.1)	
PVL >grade 1	0	0	NA	
Necrotizing enterocolitis	5 (2.5)	3 (1.5)	1.7 (0.41-7.0)	
Secondary outcome	(n = 245)	(n = 257)		
Geometric birth weight, mean (95% CI), g[b]	2047 (1950-2149)	2035 (1938-2138)		
Neonatal intensive care unit admission, No. (%)	100 (40.8)	102 (39.7)	0.99 (0.78-1.3)	
Length, median (IQR), d	10 (6-19)	10 (5-24)		0.92 (0.70-1.2)
Ventilation support, No. (%)	35 (14.3)	34 (13.2)	1.1 (0.67-1.7)	
Length, median (IQR), d	2 (1-4)	3 (1-6)		0.74 (0.43-1.3)
Total hospital admission, No. (%)	216 (88.2)	220 (85.6)	1.0 (0.95-1.1)	
Length, median (IQR), d	23 (5-42)	23 (4-45)		0.97 (0.82-1.1)

Abbreviations: IQR, interquartile range; IRR, incidence rate ratio; IVH, intraventricular hemorrhage; NA, not applicable; PVL, periventricular leukomalacia; RR, relative risk.
[a] Adverse perinatal outcome was a composite of perinatal death, chronic lung disease, neonatal sepsis, IVH greater than grade 2, PVL greater than grade 1, and necrotizing enterocolitis.
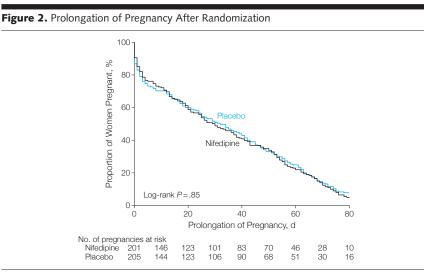[b] The geometric mean differerence is 27 g (95% CI, −128 to 195).

Table 3. Maternal Outcome

Total Randomized Groups	No. (%)		HR (95% CI)	RR (95% CI)	Geometric Difference, Mean (95% CI)
	Nifedipine (n = 201)	Placebo (n = 205)			
Secondary outcome					
Gestational age at delivery, mean (SD), wk	34.1 (4.0)	34.2 (4.0)	1.0 (0.83-1.2)		
Exploratory outcomes					
Prolongation of pregnancy, median (IQR), d	30 (7-56)	32 (4-59)	1.0 (0.84-1.2)		
Delivery, wk[a]					
<32	66 (32.8)	71 (34.6)		0.95 (0.73-1.3)	
<34	96 (47.8)	96 (46.8)		1.0 (0.83-1.3)	
<37	137 (68.2)	137 (66.8)		1.0 (0.89-1.2)	
Serious adverse events[b]	6 (3.0)	5 (2.4)		1.2 (0.38-4.0)	
Intrauterine infection	13 (6.5)	15 (7.3)		0.88 (0.43-1.8)	
Cesarean delivery	53 (26.4)	56 (27.3)		0.97 (0.70-1.3)	
Hemorrhage >1000 mL	22 (11.1)	15 (7.3)		1.5 (0.80-2.8)	
Geometric blood loss at delivery, mean (95% CI), mL	403 (360-452)	353 (319-391)			50 (−8 to 118)
Subgroups delivered within study period	(n = 59)	(n = 61)			
Hemorrhage >1000 mL	8 (13.6)	3 (4.9)		2.6 (0.73-9.3)	
Geometric blood loss at delivery, mean (95% CI), mL	432 (343-544)	307 (248-379)			125 (3-295)[c]

Abbreviations: HR, hazard ratio; IQR, interquartile range; RR, relative risk.
[a] No. (%) of women in whom delivery was delayed are reported as cumulative values from less than 32 weeks to less than 34 weeks and from less than 34 weeks to less than 37 weeks.
[b] Serious adverse events are maternal mortality, perinatal mortality, and severe maternal morbidity with admittance to the intensive care unit or critical care unit.
[c] Statistically significant in favor of placebo.

Figure 2. Prolongation of Pregnancy After Randomization

No. of pregnancies at risk									
Nifedipine	201	146	123	101	83	70	46	28	10
Placebo	205	144	123	106	90	68	51	30	16

Data are based on Kaplan-Meier analysis. Hazard ratio of time to delivery 1.0 (95% CI, 0.84 to 1.2).

come.[11-13] It seems likely that the absence of any effect is not due to ineffectiveness of nifedipine as a uterine relaxant. Other commonly used tocolytic agents, including β-mimetics, oxytocin antagonists, and magnesium sulfate, were equally ineffective as maintenance therapy in prolonging pregnancy or improving perinatal outcome.[8-10] Apparently, symptomatic treatment of uterine contractions with any uterine relaxant is ineffective when used as maintenance therapy. The etiology of threatened preterm labor is multifaceted and includes subclinical intrauterine infection.[22] Future research should be directed toward therapies tailored to the specific underlying causes of preterm labor.

most patients and clinicians unless the harms and costs of treatment were negligible. Although this implies that our data cannot exclude that maintenance tocolysis with nifedipine could improve perinatal outcome, we found no benefit of maintenance tocolysis on any secondary, subgroup, or exploratory analysis.

Another limitation is the inclusion of both singletons and multiples in the study. A differential effect is possible because multiples have an increased risk of delivering preterm. We did not observe any difference between the subgroups, but the numbers per subgroup were too small to exclude a possible difference.

This study confirms the findings of 3 previous smaller trials, all of which did not show an effect of nifedipine maintenance tocolysis on perinatal out-

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