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Nifedipine versus placebo in the treatment of preterm prelabor rupture of membranes: a randomized controlled trial
Assessment of perinatal outcome by use of tocolysis in early labor—APOSTEL IV trial

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ABSTRACT

Objective: Preterm birth is the most common cause of neonatal morbidity and mortality. Around one third of preterm deliveries starts with preterm prelabor rupture of membranes (PPROM). The aim of this trial was to study the effect of prolonged tocolysis with nifedipine versus placebo in women with PPROM on perinatal outcome and prolongation of pregnancy.

Study design: The Apostel IV was a nationwide multicenter randomized placebo controlled trial. We included women with PPROM without contractions between 24^{+0} and 33^{+6} weeks of gestation. Participants were randomly allocated to daily 80 mg nifedipine or placebo, until the start of labor, with a maximum of 18 days. The primary outcome measure was a composite of poor neonatal outcome, including perinatal death, bronchopulmonary dysplasia, periventricular leukomalacia > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis > stage 1 and culture proven sepsis. Secondary outcomes were gestational age at delivery and prolongation of pregnancy. Analysis was by intention to treat. To detect a reduction of poor neonatal outcome from 30% to 10%, 120 women needed to be randomized. Trial registry: NTR 3363.

Results: Between October 2012 and December 2014 we randomized 25 women to nifedipine and 25 women to placebo. Due to slow recruitment the study was stopped prematurely. The median gestational age at randomization was 29.9 weeks (IQR 27.7–31.3) in the nifedipine group and 27.0 weeks (IQR 24.7–29.9) in the placebo group. Other baseline characteristics were comparable. The adverse perinatal outcome occurred in 9 neonates (33.3%) in the nifedipine group and 9 neonates (32.1%) in the placebo group (RR 1.04, 95% CI 0.49–2.2). Two perinatal deaths occurred, both in the nifedipine group. Bronchopulmonary dysplasia was seen less frequently in the nifedipine group (0% versus 17.9%; $p = 0.03$). Prolongation of pregnancy did not differ between the nifedipine and placebo group (median 11 versus 8 days, HR 1.02; 95% CI 0.58–1.79).

Conclusion: This randomized trial did not show a beneficial effect of prolonged tocolysis on neonatal

Abbreviations: BPD, Broncho pulmonary disease; CI, confidence interval; GA, gestational age; IQR, inter quartile range; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PPROM, preterm prelabor rupture of membranes; PVL, periventricular leukomalacia; RR, relative risk; SD, standard deviation.

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outcomes or prolongation of pregnancy in women with PPROM without contractions. However, since results are based on a small sample size, a difference in effectiveness cannot be excluded.

Background

Preterm birth is the most common cause of neonatal morbidity and mortality worldwide and accounts for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities [1–3]. Around one third of preterm deliveries starts with preterm prelabor rupture of membranes (PPROM) [4]. Despite the high prevalence of preterm birth following PPROM, the optimal management of PPROM remains a topic of debate and is hindered by a lack of evidence.

After rupture of the membranes, there is a high risk that labor will follow within days. Most women with PPROM who receive conservative management deliver within one week. Most clinical guidelines advise to administer a 48 h course of corticosteroids and transfer to a tertiary care center to improve neonatal outcome [5–8]. One mechanism by which tocolysis might improve outcome is to delay delivery during this 48 h period. However, the use of tocolysis in this period, but especially after 48 h, is subject to debate. The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery declining from 77% at 24 to 27 weeks to less than 2% from 34 weeks onwards [9]. Administration of tocolytic drugs after the 48 h period may further increase the latency period and thereby improve gestational age at delivery. However, prolongation of pregnancy in PPROM does not automatically lead to an improvement of neonatal outcome. As infection is detected in a major part of all women with PPROM, prolongation of pregnancy may result in longer exposure of the fetus to a harmful infective environment. Therefore, the benefit of postponing delivery must be weighed against the potential harm of the increased risk on maternal and perinatal infection.

A recent Cochrane review indicated that, when compared to placebo, tocolysis in PPROM is associated with an average 73 h longer latency of delivery (95% confidence interval (CI) 20–126; three trials, 198 women) and fewer births within 48 h (RR 0.55; 95% CI 0.32–0.95; six trials, 354 women). However, tocolysis was also associated with an increased risk of a 5 min Apgar score under 7 and an increased need for ventilation support. Different tocolytic drugs were compared, mostly betamimetics (ritodrine) [10]. In a subgroup analysis, including three trials with 137 women with PPROM and no or minimal uterine contractions, tocolysis significantly increased the duration of pregnancy without any significant effects on maternal and neonatal outcomes. In a subgroup analysis (5 studies, 291 women) of women with PPROM before 34 weeks of gestation tocolysis increased the rate of chorioamnionitis (RR 1.79; 95% CI 1.02–3.14), neonatal outcome was comparable [10].

As the goal of tocolysis is to improve neonatal outcomes, we performed a multicenter randomized trial comparing nifedipine versus placebo in women with PPROM without contractions in terms of perinatal outcomes and prolongation of pregnancy.

Methods

Trial design

We performed a multicenter randomized placebo controlled trial, the APOSTEL IV study: Assessment of Perinatal Outcome by uSe of Tocolysis in Early Labor. It was conducted in eight Dutch perinatal centers with NICU facilities. The trial was conducted within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. The study has been approved by the ethics committee of the Academic Medical Centre in Amsterdam (Reference number 2011-092) and by the boards of management of all participating hospitals. This trial was registered in the Netherlands Trial Register, trial number 3363. The study was not funded. The study is reported according to the CONSORT guidelines [11].

Participants

Women, aged ≥18 years, with a gestational age between $24^{+0/7}$ and $33^{+6/7}$ weeks with ruptured membranes without signs of active labor were eligible for the trial. Exclusion criteria were (1) ≥3 contractions per 10 min (2) previous treatment with tocolysis in the last 7 days (tocolysis for <6 h for transportation was allowed) (3) symptoms justifying start of tocolysis (4) ruptured membranes ≥72 h (5) signs of chorioamnionitis or intra uterine infection (6) signs of fetal distress (7) fetal major congenital anomaly (8) contraindication for the use of nifedipine (9) maternal disease as reason for delivery (such as hypertension, HELLP syndrome or preeclampsia).

Procedures, recruitment and randomization

Eligible women were identified by the staff and/or local research coordinator of the participating hospitals. After counseling and reading the patient information form, patients were asked for written informed consent. We provided patient information in Dutch and English. After informed consent, baseline demographics of the patient were entered in a web-based database. Randomization was performed per center by a web based computerized program in a 1:1 ratio, using permuted blocks of 4, rendered by an independent data manager. The study was double blind; research staff, clinicians and participants were blinded for treatment allocation.

Interventions

Study medication consisted of one tablet every six hours, administered orally, containing 20 mg nifedipine slow release or placebo. The medication was given until the start of active labor (>3 contractions per 30 min), with a maximum of 18 days or until gestational age of 34^{+0} weeks. The length of the therapy was limited to 18 days, based on the assumption that prolongation of pregnancy of more than two weeks, if clinically relevant, should show an effect on perinatal outcome. The medication package was stored by the patient, and the administration of the study medication was noted in her medical record. Antenatal corticosteroids were administered according to national guidelines, advising antenatal corticosteroids to women in preterm labor <34 weeks of gestation [8]. Prophylactic antibiotic therapy and magnesium sulphate were administered according to local protocol, as was maternal and fetal monitoring.

Outcome measures

Primary outcome measures

The primary outcome was a composite of adverse perinatal outcome, including perinatal death, bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL) > grade 1,

intraventricular hemorrhage > grade 2, necrotizing enterocolitis (NEC) > stage 1 and culture proven sepsis.

The diagnosis of BPD was made according to the international consensus guideline as described by Jobe and Bancalari at time of discharge to home or at 36 weeks of corrected gestational age [12]. PVL > grade 1 and IVH > grade 2 were diagnosed by repeated neonatal cranial ultrasound by the neonatologist according to the guidelines on neuroimaging described by de Vries et al. and Ment et al. [13,14] NEC was diagnosed according to Bell > stage 1 [15]. Culture proven sepsis was diagnosed by the combination of clinical signs of sepsis and positive blood cultures.

Secondary outcome measures

Secondary outcomes were birth weight, gestational age at delivery, prolongation of pregnancy, number of days on ventilation support, number of days in NICU and total days in hospital. Furthermore discontinuation of study medication due to progression of labor, side effects or signs of intra uterine infection was noted.

We registered maternal morbidity, mortality or complications that might have been related to the use of tocolytics during the study. An expert panel subsequently judged whether the complication was related to the use of tocolytics or not.

Statistical analysis

Sample size

To detect a reduction in adverse perinatal outcome from 30% in the placebo group to 10% in the nifedipine group, 120 women (60 per arm) were needed (two sided test, type I error rate = 0.05, power 80%).

Data analysis

Data were analyzed according to the intention to treat principle. Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on their distribution. Categorical and dichotomous variables are presented as a number and percentage of the total allocation group. The perinatal outcomes were assessed on child level (in case of twins both children were taken into account). The main outcome variable, 'adverse perinatal outcome', and secondary neonatal outcomes were assessed by calculating rates in the two groups, relative risks and 95% confidence intervals. The maternal outcome was assessed on maternal level.

Prolongation of pregnancy was evaluated by Cox proportional hazards regression and Kaplan-Meier estimates, and tested with the Log rank test.

Results

After consultation of the Data Safety Monitoring Committee, it was decided to end the study on December 10th, 2014 due to slow recruitment.

Study population

Between October 2012 and December 2014 we included 50 women, of whom 25 were allocated to nifedipine and 25 to placebo (Fig. 1). Outcomes were available for all 25 women in both groups, corresponding with 27 children in the nifedipine group and 28 children in the placebo group. Table 1 shows that baseline characteristics of both groups were comparable, except for gestational age at study entry: median (IQR) 29.9 weeks (27.7–31.3) in the nifedipine group versus 27.0 weeks (24.7–29.9) in the placebo group.

Primary outcome

Adverse perinatal outcome occurred in 9 (33.3%) children in the nifedipine group versus 9 children (32.1%) in the placebo group (RR 1.04; 95% CI 0.43–2.5). BPD occurred significantly less frequent in the nifedipine group (no children in the nifedipine group compared with five (17.9%) in the placebo group, $p = 0.03$). Other components were not significantly different (Table 2). Because there was a difference in gestational age at study entry between the arms, we performed a sensitivity analysis in which we corrected for gestational age at study entry. Results showed that the composite of adverse perinatal outcome remained comparable between the groups after adjusting for differences in gestational age at study entry (adjusted RR 1.03; 95% CI 0.51–2.1)

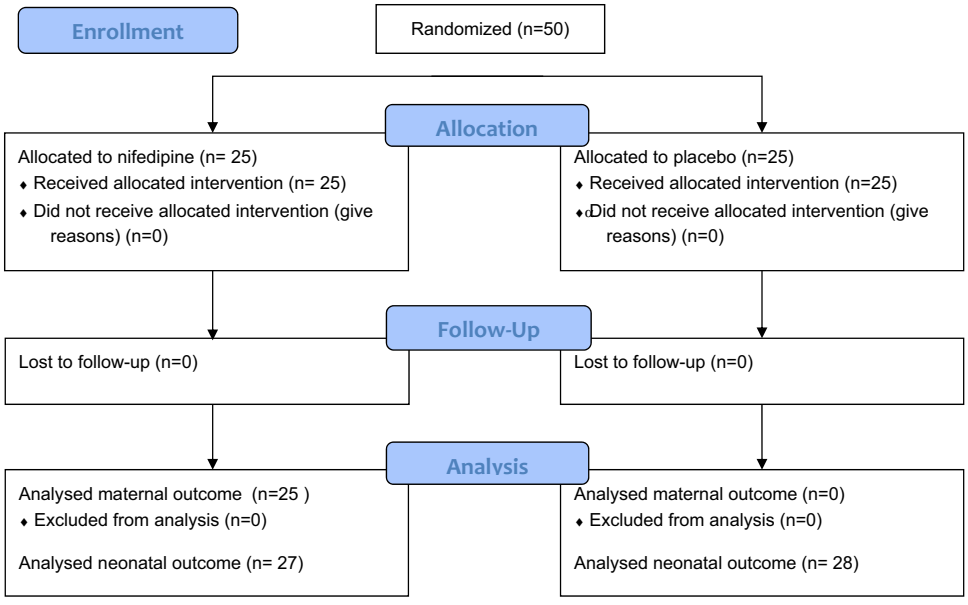

Fig. 1. Flow chart.

Table 1
Baseline characteristics.

	Nifedipine ($n=25$)	Placebo ($n=25$)
Gestational age at study entry, median (IQR), weeks	29.9 (27.7–31.3)	27.0 (24.7–29.9)
Maternal age, median (IQR), years	33.4 (30.3–35.7)	32.9 (27.7–36.3)
Body mass index, median (IQR)	22.7 (20.8–26.4)	23.8 (20.8–31.4)
Caucasian, *n* (%)	19 (76.0)	19 (76.0)
Nulliparous, *n* (%)	16 (64.0)	14 (56.0)
Smoking, *n* (%)	4 (16.0)	3 (12.0)
Prior preterm birth, *n* (%)	5 (20.0)	3 (12.0)
Twin gestation, *n* (%)	2 (8.0)	3 (12.0)
Laboratory results at entry		
Leukocytes, median (IQR), $\times 10^9$/L	12.5 (10.4–13.3)	11.1 (9.7–12.7)
CRP, median (IQR), mg/L	7.0 (5.0–12.0)	5.0 (3.0–12.0)
Prophylactic antibiotic therapy, *n* (%)	15 (60.0)	14 (56.0)
Corticosteroids administered, *n* (%)	25 (100)	24 (96.0)

IQR: inter quartile range; CRP: c-reactive protein.

Perinatal deaths

Two perinatal deaths occurred, both in the nifedipine group. In the first woman, PPROM occurred at 24^{+1} weeks of gestation. Five days later a boy was born, after a vaginal breech delivery. Birth weight was 730 g. Apgar scores after respectively 1, 5 and 10 min were 0, 5 and 9. After seven days the boy died of NEC followed by septic shock. In the second woman PPROM occurred at 25^{+4} weeks of gestation. After three days, an emergency cesarean section was performed because of signs of uterine infection and suspected fetal distress. Birth weight was 900 g. Apgar scores after respectively 1 and 5 min were 0 and 6. After one day he died as a result of respiratory insufficiency due to sepsis.

Secondary outcomes

Median gestational age at delivery was 32.0 weeks (IQR 29.1–33.3) in the nifedipine group compared with 30.0 weeks (IQR 26.3–32.1) in the placebo group ($p=0.15$)). Prolongation of pregnancy was also comparable median 11 days (IQR 4–19) in the nifedipine group compared with 8 days (IQR 5–25) in the placebo group, HR 1.02; 95% CI 0.58–1.79). In women treated with nifedipine 92% was still pregnant 48 h after initiation of study medication, compared with 100% in the placebo group (RR 0.92; 95% CI 0.92–1.05). After seven days 64% of the women in the nifedipine group was still pregnant, compared with 60% in women in the placebo group (RR 1.07; 95% CI 0.67–1.7). The Kaplan-Meier survival analysis on the

Table 2
Primary and secondary outcomes.

Primary outcome (child level)	Nifedipine ($n=27$)	Placebo ($n=28$)	RR (95% CI)	*p*-value
Adverse perinatal outcome, *n* (%)	9 (33.3)	9 (32.1)	1.04 (0.43–2.5)	0.58
Perinatal mortality, *n* (%)	2 (7.4)	0 (0)	NA	0.24
Broncho pulmonary dysplasia, *n* (%)	0 (0)	5 (17.9)	NA	0.03
PVL > grade I, *n* (%)	0 (0)	0 (0)	NA	NA
IVH > grade II, *n* (%)	1 (3.7)	0 (0)	NA	0.49
NEC > grade I, *n* (%)	3 (11.1)	0 (0)	NA	0.11
Culture proven sepsis, *n* (%)	6 (22.2)	7 (25.0)	0.89 (0.29–2.6)	0.53

Sensitivity analysis	Adjusted RR (95% CI)	*p*-value
Adverse perinatal outcome	1.03 (0.51–2.1)	0.93

Secondary outcomes (child level)	Nifedipine ($n=27$)	Placebo ($n=28$)	RR (95% CI)	
Birth weight, grams median (IQR)	1745 (1250–1920)	1424 (945–1963)		0.34
NICU admittance, *n* (%)	20 (74.1)	23 (82.1)	0.90	0.35
Length in days, median (IQR)	11 (3–22)	11 (5–55)	(0.69–1.2)	0.24
Ventilation support, *n* (%)	5 (18.5)	6 (21.4)	0.86	0.53
Length in days, median (IQR)	1 (1–9)	4 (1–8)	(0.25–2.9)	0.93
Total days in hospital until 3 months corrected age Days, median (IQR)	32 (22–56)	48 (30–90)		0.04

Secondary outcomes (maternal level)	Nifedipine ($n=25$)	Placebo ($n=25$)	HR (95% CI)/RR (95% CI)	
Gestational age at delivery, mean (SD), weeks	32.0 (29.1–33.3)	30.0 (26.3–32.1)	NA	0.15
Prolongation of pregnancy				
Days, median (IQR)	11 (4–19)	8 (5–25)	1.02 (0.58–1.8)	0.92
≥48 h, *n* (%)	23 (92.0)	25 (100)	0.92 (0.92–1.05)	0.25
≥7 days, *n* (%)	16 (64.0)	15 (60.0)	1.07 (0.67–1.7)	0.50
Maternal mortality, *n* (%)	0 (0)	0 (0)	NA	NA
Discontinuation of study medication, *n* (%)	19 (76.0)	18 (72.0)	1.06 (0.74–1.5)	0.40
Due to progression into labor, *n* (%)	15 (60.0)	14 (56.0)	1.07 (0.63–1.8)	0.50
Due to side effects, *n* (%)	2 (8.0)	0 (0)	NA	0.49
Due to signs of intra uterine infection, *n* (%)	6 (24.0)	8 (32.0)	0.75 (0.26–2.1)	0.38

RR: relative risk; CI: confidence interval; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; IQR: inter quartile range; NICU: neonatal intensive care unit; HR: hazard ratio.

prolongation of pregnancy revealed no differences between nifedipine and placebo (Fig. 2, log rank test, $p = 0.94$).

Birth weight, number of days on ventilation support and NICU were comparable between the groups. Total days in hospital until 3 months corrected age was significantly lower in the nifedipine group (32 days versus 48 days). Maternal mortality did not occur. Due to progression into labor within 18 days after starting treatment, study medication was discontinued in 15 women (60.0%) in the nifedipine group and in 14 women (56.0%) in the placebo group (RR 1.07; 95% CI 0.63–1.8). Two women (8.0%) in the nifedipine group discontinued study medication because of side effects, compared with no women in the placebo group (Table 2). Side effects included an allergic reaction and palpitations.

Comment

In this randomized clinical trial among women with PPROM without contractions, we found no significant differences between treatment with nifedipine or placebo in terms of perinatal outcomes and prolongation of pregnancy. However, the trial was underpowered as only 50 of the targeted 120 women could be included.

Our results are in line with previous studies in which women with PPROM did not seem to benefit from treatment with prolonged tocolysis [10]. Our study has several strengths. The trial was a randomized, double-blind, placebo controlled trial, thereby minimizing the risk of bias. Furthermore our primary outcome was a composite of adverse perinatal outcomes, which we believe reflects the main goal of tocolysis: improving neonatal outcome. Our study has limitations as well. The most important limitation is the small sample size due to premature ending of the study. We planned to recruit 120 women, but recruitment was stopped after 50 women had been included. Our sample size only had a 45% power to detect a 20% reduction in adverse perinatal outcome. Thus, although we found a comparable rate of composite adverse perinatal outcome, arguably our small sample size indicates that we might have missed a relevant difference. Therefore, it may still be possible that use of nifedipine results in a clinically relevant difference in perinatal outcomes in women with PPROM without contractions. Other studies performed on tocolysis in women with PPROM all have small sample sizes and are mostly dated from the 1980s and 1990s. Results of a Cochrane review showed no improvement in neonatal outcomes, however not all trials used standard corticosteroid therapy and antibiotics [10].

An additional argument against a potential effect of nifedipine in otherwise symptom free women with PPROM is that we found no effect from nifedipine on time to delivery. Furthermore the number of women that discontinued study medication because of progression into labor was high, and comparable between the groups (60% in the nifedipine group versus 56% in the placebo group). In absence of such an effect on duration of pregnancy, it is unlikely that children born from women with PPROM will benefit directly from nifedipine. This is in line with our previous study on prolonged tocolysis in women with arrested preterm labor, the APOSTEL II study, that did not show a difference in short term perinatal outcome or at 2 year follow-up [16,17]. Two deaths occurred in the nifedipine group and although no causal relation could be determined between the two deaths and possible side effects of nifedipine, we cannot exclude an indirect effect. It may be hypothesized that the administration of nifedipine in pregnant women has an adverse effect on the fetus, for example by lowering maternal blood pressure and reducing placental perfusion. However, previous studies have shown contradictory results, thus no final conclusions can be drawn [18–22].

Looking at separate components, we found a significantly lower rate of BPD in women treated with nifedipine (0% in the nifedipine

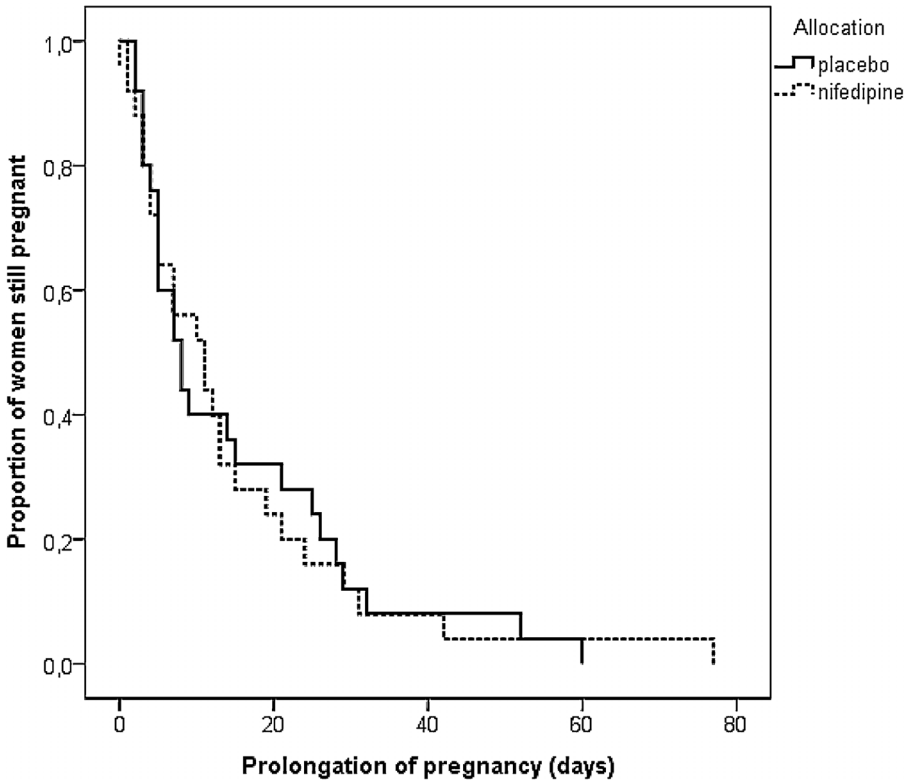

Fig. 2. Kaplan-Meier curve for prolongation of pregnancy.

group compared to 18% in the placebo group). This has not been reported in previous studies. A possible explanation for this difference could be the higher gestational age at study entry and delivery in the nifedipine group, since the occurrence of BPD decreases with increasing gestational age at delivery [12]. All cases of BPD occurred in neonates born before 30 weeks of gestation. In addition there were two perinatal deaths in the nifedipine group at 24^{+1} and 25^{+4} weeks. BPD can only be diagnosed if survival occurs to a corrected age of 36 weeks of gestation [12].

In conclusion, this randomized clinical did not show a beneficial effect of prolonged tocolysis with nifedipine on perinatal outcomes or prolongation of pregnancy in women with PPROM without contractions. Therefore we do not recommend prolonged tocolysis in women with PPROM without contractions. However, since results are based on a small sample size, a difference clinically relevant differences cannot be excluded and conclusions should be drawn with caution.

Conflict of interest

The authors report no conflict of interest.

Trial registration

Clinical trial registration: Dutch Trial Register, http://www.trialregister.nl, register no. 3363, date 20th March 2012.

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This study was not funded.

Authors' contributions

MO and BWM were involved in conception and design of the study. MO, BWM, EvV, CN and TN drafted the manuscript. CN, KOR and TN analyzed and interpreted the data. All authors mentioned in the manuscript are member of the Apostel-IV study group or collaborators. They are local investigators at the participating centers, and participated in the design of the study during several meetings. All authors edited the manuscript and read and approved the final draft of the manuscript.

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