European Journal of Obstetrics & Gynecology and Reproductive Biology 205 (2016) 79–84

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

# 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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ARTICLE INFO

*Article history:*
Received 23 February 2016
Received in revised form 18 July 2016
Accepted 1 August 2016

*Keywords:*
Preterm prelabor rupture of membranes
Tocolytics
Nifedipine
Drug safety
Neonatal outcomes
Preterm birth

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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http://dx.doi.org/10.1016/j.ejogrb.2016.08.024

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,