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Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial

Elvira O G van Vliet, Tobias A J Nijman, Ewoud Schuit, Karst Y Heida, Brent C Opmeer, Marjolein Kok, Wilfried Gyselaers, Martina M Porath, Mallory Woiski, Caroline J Bax, Kitty W M Bloemenkamp, Hubertina CJ Scheepers, Yves Jaquemyn, Erik van Beek, Johannes J Duvekot, Maureen T M Franssen, Dimitri N Papatsonis, Joke H Kok, Joris A M van der Post, Arie Franx, Ben Willem J Mol, Martijn A Oudijk,

Summary

[A: we have a strict style for summaries. I have edited to stay in line with this. Please let me know any queries]

Background In women with threatened preterm labour, delay of delivery by 48 h allows antenatal corticosteroids to improve neonatal outcomes. For this reason, tocolytics are often given for 48 h; however, there is no consensus about which drug results in the best maternal and neonatal outcomes. In the APOSTEL III trial we aimed to compare the effectiveness and safety of the calcium-channel blocker nifedipine and the oxytocin inhibitor atosiban in women with threatened preterm labour.

Methods We did this multicentre, randomised controlled trial in ten tertiary and nine teaching hospitals in The Netherlands and Belgium. Women with threatened preterm birth (gestational age 25–34 weeks) were randomly assigned (1:1) to either oral nifedipine or intravenous atosiban for 48 h. An independent data manager used a web-based computerised programme to randomly assign women in permuted block sizes of four, with groups stratified by centre [A: correct?]. Clinicians, outcome assessors, and women were not masked to treatment group. The primary outcome was a composite of adverse perinatal outcomes and included all babies with who died or had bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis. Analysis was done in all women and babies with follow-up data. [A: please see statistical analysis section] The study is registered at the Dutch Clinical Trial Registry, number NTR2947.

Findings Between July XX, 2011 and July XX, 2014,[A: please add exact dates] we randomly assigned 254 women to nifedipine and 256 to atosiban. Primary outcome data were available for 248 women and 297 babies in the nifedipine group and 255 women and 294 babies in the atosiban group. The primary outcome was recorded in 42 neonates (14%) in the nifedipine group and in 45 neonates (15%) in the atosiban group (relative risk [RR] 0·91, 95% CI 0·61–1·37). 16 (5%) neonates died in the nifedipine group and seven (2%) died in the atosiban group (RR 2·20, 95% CI 0·91–5·33); all deaths were deemed unlikely to be related to the study drug. Maternal adverse events did not differ between groups.

Interpretation In women with threatened preterm birth, 48 h of tocolysis with nifedipine or atosiban results in similar perinatal outcomes. [A: please add sentence about future clinical and research directions from these findings]

Funding ZonMw (the Netherlands Organisation for Health Research and Development). [A: OK – for consistency with past trials]

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[A: please check details given here, especially qualifications and full professors. We list one preferred qualification per author at first mention of them in the list] **Department of Obstetrics, Wilhelmina Hospital Birth Centre, Division Woman & Baby, University Medical Centre Utrecht, Utrecht, The Netherlands** (E O G van Vliet MD, T A J Nijman MD, K Y Heida MD, Prof K W M Bloemenkamp MD, Prof A Franx PhD, M A Oudijk MD); **Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands** (E Schuit PhD); **Stanford Prevention Research Center, Stanford University, Stanford, CA, USA** (E Schuit); **Clinical Research Unit** (B C Opmeer PhD) **and Department of Obstetrics and Gynecology** (M Kok MD, Prof J A M van der Post PhD, M A Oudijk), **and Department of Neonatology** (Prof J H Kok PhD), **Academic Medical Centre, Amsterdam, Netherlands; Department of Obstetrics and Gynecology, Ziekenhuis Oost-Limburg, Genk, Belgium** (W Gyselaers MD); **Department of Physiology, Hasselt University, Diepenbeek, Belgium** (W Gyselaers); **Department of Obstetrics and Gynaecology, Maxima Medical Centre, Veldhoven, Netherlands** (M M Porath MD); **Department of Obstetrics and Gynaecology, University Medical Centre Nijmegen, Nijmegen, Netherlands** (M Woiski MD); **Department of Obstetrics and Gynaecology, Vrije University Medical Centre, Amsterdam, Netherlands** (C J Bax MD); **Department of Obstetrics, Leiden University Medical Centre, Leiden, Netherlands** (Prof K W M Bloemenkamp);

Introduction

Preterm birth is associated with 50% of neonatal morbidity and 50–75% of neonatal mortality worldwide,[1–5] and affects 5–13% of all pregnancies in high-income countries.[2–5] Additionally, preterm birth can cause long-term physical and developmental impairment and thereby has a substantial impact on infant, parents, families, and health-care costs.[1,2] To improve outcomes in preterm infants, women in labour before 34 weeks of gestation receive antenatal corticosteroids to enhance fetal lung maturation.[6] To allow optimal effect of maternal steroid administration, most perinatal centres attempt to delay birth by administrating tocolytic drugs for 48 h.[7] Previous meta-analyses have shown that tocolytic drugs are effective in delaying delivery by 48 h and 7 days.[8,9] Several types of tocolytic drugs are used as treatment in preterm labour, including b adrenoceptor agonists, cyclooxygenase inhibitors, magnesium sulphate, calcium-channel blockers and oxytocin receptor antagonists. Uncertainty remains over which tocolytic should be drug of choice.

Studies of b adrenoceptor agonists have shown contradictory results for its ability to postpone delivery and decrease neonatal mortality compared with placebo,[9,10] and their use has been largely abandoned in clinical practice due to a substantial side-effect profile. For COX inhibitors, no effect on perinatal mortality and morbidity have been reported and some concerns exist about potential adverse effects on neonatal outcomes; a recent meta-analysis found an increase in intraventricular haemorrhage, necrotising enterocolitis, and periventricular leukomalacia with COX inhibitors versus placebo.[11,12] For initial tocolysis, calcium-channel blockers or oxytocin antagonists for 48 h are

Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, Netherlands. (H C J Scheepers MD); **Department of Gynecology and Obstetrics, Antwerp University Hospital, Antwerp, Belgium** (Prof Y Jaquemyn PhD); **Department of Obstetrics and Gynaecology, St Antonius Hospital, Nieuwegein, Netherlands** (E van Beek MD); **Department of Obstetrics and Gynecology, Erasmus University Medical Centre, Rotterdam, Netherlands** (J J Duvekot MD); **Department of Obstetrics, University Medical Centre, University of Groningen, Groningen, Netherlands** (M T M Franssen MD); **Department of Obstetrics and Gynecology, Amphia Hospital, Breda, Netherlands** (D N Papatsonis MD); **The Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia** (Prof B W J Mol PhD); **and South Australian Health and Medical Research Institute, Adelaide, SA, Australia** (Prof B W J Mol)

Correspondence to:
[A: details correct?]
Dr Tobias AJ Nijman, Department of Obstetrics, Wilhelmina Hospital Birth Centre, Division Woman & Baby, University Medical Centre Utrecht, Utrecht 3508, The Netherlands
t.a.j.nijman@umcutrecht.nl

For the **Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology** see www.studies-obsgyn.nl

Research in context

Evidence before this study

We searched Medline, Embase, and the Cochrane Library from inception until Nov 24, 2015, without language limitation. We used the following search strategy "atosiban AND nifedipi* AND tocoly*" and included randomised clinical trials comparing nifedipine and atosiban as tocolytic therapy in women with threatened preterm birth. We excluded quasi-randomised trials. We found 223 records—48 articles in Medline, 162 articles in Embase, and 13 in the Cochrane Library. After reviewing manuscripts we found two trials meeting our inclusion criteria (Al-Omari and colleagues, 2006; and Kashanian and colleagues, 2005). Both studies had a low risk of bias according to the Cochrane Collaboration's risk of bias tool. Outcome measures in the meta-analysis were neonatal mortality, prolongation of pregnancy in days, and prolongation of pregnancy by more than 48 h. No pooled estimate could be calculated for neonatal mortality because no children died in the study by Al-Omari and colleagues and Kashanian and colleagues did not report this outcome. In the two studies, prolongation of pregnancy (days) was similar between nifedipine and atosiban groups (pooled **[A: correct?]** mean difference –0·25 days, 95% CI –11·89 to 11·39; 225 women). Prolongation of pregnancy by more than 48 h was also did not differ between nifedipine and atosiban groups (pooled relative risk [RR] 1·02, 95% CI 0·87–1·19; 225 women).

Added value of this study

Our study is the largest randomised trial to compare nifedipine and atosiban. Our primary outcome was a composite of adverse perinatal outcomes, which we believe is the most important outcome measure because improving neonatal outcome is the ultimate goal of tocolysis. Randomised trials published so far were not powered to detect differences in neonatal outcomes. We report similar adverse perinatal outcome rates in nifedipine and atosiban, as well as comparable delays in delivery for 48 h. Inclusion of our study data in meta-analysis with findings from Al-Omari and colleagues showed a non-significant increase in neonatal death between nifedipine and atosiban treatment groups (pooled RR 2·12; 95% CI 0·88–5·13; two studies, 780 children). In a meta-analysis including data from all three studies, prolongation of pregnancy in days remained similar between nifedipine and atosiban groups (pooled **[A: correct?]** mean difference 0·54 days; 95% CI –5·67 to 6·76; 727 women), as did prolongation of pregnancy of more than 48 h (risk ratio 1·03; 95% CI 0·94–1·12; three studies, 727 women).

Implications of all the available evidence

Our study findings showed that tocolysis for 48 h with nifedipine or atosiban results in similar adverse perinatal outcome rates and prolongation of pregnancy. The choice between nifedipine and atosiban must be based on the effectiveness, safety, adverse effects, and costs of these tocolytic drugs. Further large randomised trials are needed to assess tocolysis drugs. **[A: conclusion ok?]**

recommended because they have the best efficacy to side-effect ratio; however it has not yet been established which drug leads to the best outcomes.[13–15] **[A: cut some text for redundancy here]** Three small randomised trials comparing the calcium-channel blocker nifedipine with the oxytocin antagonist atosiban have shown contradictory results.[16–18] One study (n=145) found a lower proportion of women assigned to nifedipine delivered a baby within 7 days than in those assigned to atosiban, but more in this group delivered within 48 of administration.[17] The two other trials (n=80 and n=63) did not find a significant difference in the ability of either drug to delay delivery for 48 h.[16,17] Salim and colleagues[18] showed a shorter length of stay at the neonatal intensive care unit for babies from women in the nifedipine group as compared with those from women in the atosiban group. The two trials that reported on neonatal outcome did not show a significant difference, but were underpowered.[17,18]

In view of this uncertainty, we started the Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour (APOSTEL-III) study, a multicentre randomised clinical trial in which we aimed to compare calcium-channel blocker nifedipine with the oxytocin antagonist atosiban in women with threatened preterm birth.

Methods

Study design and participants

[A: I have edited text order and subheadings to preserve our standard sections for clinical trials, see http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf for more details]

We did this multicentre, randomised controlled trial in 19 centres (10 tertiary care centres with a neonatal intensive care unit facility and 9 secondary centres) in **XX [A: please add]** cities in The Netherlands and Belgium that collaborate in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. The protocol has been published previously.[19] Women were eligible if they were aged 18 years or older and had threatened preterm birth at a gestational age between $25^{0/7}$ weeks and $34^{0/7}$ weeks. Threatened preterm birth was defined as at least three uterine contractions per 30 min and presence of one of the following: cervical length of 10 mm or less, both a cervical length of 11–30 mm and a positive fetal fibronectin test, or presence of ruptured amniotic membranes **[A: should this be PPROM?]**. Women with singleton or multiple pregnancies were eligible. Exclusion criteria were a contraindication for tocolysis (severe vaginal bleeding or signs of intrauterine infection), hypertension or **[A:**

current use, or history of?] use of antihypertensive drugs, history of myocardial infarction or angina pectoris, cerclage, cervical dilatation greater than 5 cm, tocolytic treatment for more than 6 h before arrival in a participating centre, or a previous episode of tocolytic treatment [A: previous tocolytis is not indicated in the protocol, please confirm this was an exclusion criteria]. Women with a fetus showing signs of fetal distress or a fetus suspected of chromosomal or structural anomalies were not included. Eligible women were identified [A: how? And by who?] and counselled by the local staff or research coordinators. This study was approved by the ethics committee of the Academic Medical Centre Amsterdam (reference number MEC AMC 09/258) and the boards of management of all participating hospitals. All women provided written informed consent.

Randomisation and masking

[A: edited to active tense. Please check details] An independent data manager used a web-based computerised program to randomly assign women to nifedipine or atosiban in a 1:1 ratio, with assignment done in permuted blocks of four and stratified [A: stratified ok? Previously said "per centre"] by centre. Because of the nature of the interventions, oral medication, and intravenous medication, clinical staff or women were not masked.

Procedures

[A: we have added details from appendix here – I think it's quite essential for the reader] In the nifedipine group, the initial dose was 20 mg nifedipine (two 10 mg capsules) orally in the first hour, followed by 20 mg slow-release nifedipine per 6 h for the next 47 h (appendix). In the first hour after the start of nifedipine administration, blood pressure and heart rate were measured every 15 mins. If blood pressure remained within the normal limits, treatment continued with blood pressure and heart rate measured four times every 24 h. In the atosiban group, women received a bolus injection of 6·75 mg intravenous in 1 min, followed by 18 mg/h for 3 h, followed by a maintenance dosage of 6 mg/h for 45 h. Antenatal corticosteroids were administered according to national guidelines [A: reference?] for management of preterm birth, which advise antenatal corticosteroids to women in preterm labour of babies younger than 34 weeks of gestation. We gave magnesium sulphate for neuroprotection in case of expected preterm birth of babies younger than 32 weeks of gestation, according to the national guideline. [A: reference?] The provision of prophylactic antibiotics was at the discretion of the attending physician.

Trained research staff documented demographic characteristics, obstetric and medical history, and data for pregnancy and delivery until the day of discharge from hospital [A: OK? Or from a specific unit?] of both mother and baby. [A: any prespecified follow-up visits?] Data were entered in an online electronic case report form by research nurses and midwives (Oracle Clinical version 4·5.3; Redwood City, CA, USA).

For more on the **Oracle system** see www.oracle.com

Bronchopulmonary dysplasia was diagnosed according to the international consensus guideline as described by Jobe and Bancalari at time of discharge home or at 36 weeks of corrected gestational age.[20] Culture-proven sepsis was diagnosed based on clinical signs and a positive culture in blood sample. Intraventricular haemorrhage of grade 2 or higher and periventricular leukomalacia of grade 1 or higher were diagnosed by repeated neonatal cranial ultrasound by the neonatologist according to the guidelines on neuroimaging described by de Vries and colleagues.[21,22] Necrotising enterocolitis was staged by methods reported by Bell.[23]

[A: I've moved this here because not technically an outcome] All perinatal deaths were assessed by a panel of two neonatologists and two consultant obstetricians who were not involved in the trial. The members individually reviewed all cases of perinatal death while remaining blinded to the administered study drug. They assessed whether the perinatal deaths could be causally related to the study drug using WHO categories of: certain, probable, possible, unlikely, conditional, and non-assessable.[24] When more than a 75% consensus was reached the conclusion was considered valid.

Outcomes

[A: We have edited so this section contains only information on outcomes. Please check this is a complete list of all prespecified outcomes. Post-hoc outcomes should be flagged and we will move into the findings. Why were some outcomes highlighted in the protocol provided – were these added later?]

See **Online** for appendix

The primary outcome measure was a composite of adverse perinatal outcome composed of perinatal in-hospital deaths and the following severe perinatal morbidities: bronchopulmonary dysplasia, culture-proven sepsis, intraventricular haemorrhage of grade 2 or higher, periventricular leukomalacia of grade 1 or higher, and necrotising enterocolitis of Bell's stage 1 or higher. All children with one or more of these outcomes were deemed to have met the primary outcome criteria. [A: Correct that this is how this composite was calculated. Was there a cut off limit for time to these outcomes?] Prespecified secondary outcome measures on the maternal level were gestational age at delivery; time from randomisation to delivery (prolongation of pregnancy); [A: OK? This is how this was listed in protocol rather than prolongation of delivery so I think it would be good to be consistent here] and rates of maternal death and side-effects leading to discontinuation of study drug. Secondary outcomes on the neonatal level were the individual components of the composite perinatal outcome ([A: these were not prespecified as individual outcomes in the protocol]bronchopulmonary dysplasia, culture-proven sepsis, intraventricular haemorrhage of grade 2 or higher, periventricular leukomalacia of grade 1

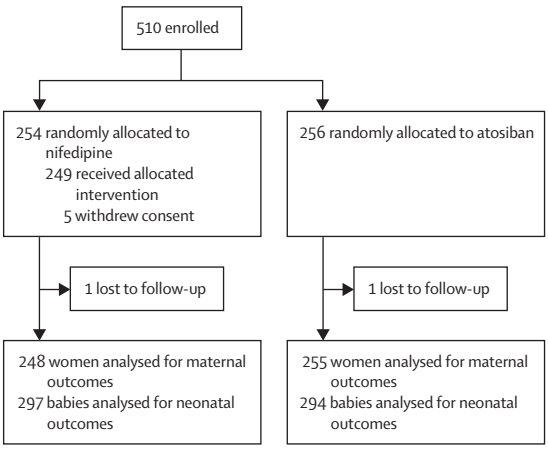

Figure 1: **Study profile**

	Nifedipine group (n=249)	Atosiban group (n=256)
Age (years)	30·7 (26·2–34·0)	30·2 (27·2–33·0)
Body-mass index (kg/m²)*	23·1 (20·8–25·8)	22·8 (20·6–25·6)
White race	180/220 (82%)	184/227 (81%)
Nulliparous	160 (64%)[A1]	170 (68%)[A1]
Previous preterm birth	33 (13%)	30 (12%)
Gestational age at study entry (weeks)	30·3 (28·4–32·1)	30·3 (28·1–31·7)
Multiple pregnancy		
Twin	49 (20%)	37 (14)
Triplet	0	1 (<1%)
PPROM at study entry	85/248 (34%)	88/255 (39%) [A1]
Previous tocolytic treatment	47/244 (21%)[A1]	61/255 (27%)
Vaginal examination at study entry	114/245 (47%)	122/256 (48%)
Dilatation (cm)†	1 (1–2)	1 (1–2)
Cervical length (mm)‡	15 (9–22)	14 (8–23)

Data are median (IQR), n (%), or n/N (%).PPROM= preterm premature rupture of membranes. *n=198 for nifedipine group and n=207 for atosiban group. †n=112 for nifedipine group and n=121 for atosiban group. ‡n=159 for nifedipine group and n=153 for atosiban group. **[A: We round all percentages of people to one decimal place. Some (marked [A1]) have been corrected from original. Please check numbers and denominators and correct as appropriate]**

Table 1: **Baseline characteristics**

or higher, and necrotising enterocolitis); days of stay in a neonatal intensive-care unit (NICU) after birth; days of ventilation support after birth; total days in hospital until corrected age 3 months; number of babies with apnoea; number of babies with asphyxia; number of babies with proven meningitis; and number of babies with pneumothorax **[A: convulsions were also listed as a prespecified secondary endpoint. Please include here and report data. Was there a time range for apnoea, asphyxia, meningitis, and pneumothorax?]**

Statistical analysis

We designed the trial to detect a reduction in the prevalence of the primary outcome from 25% to 15%. We calculated that we would need to enrol 500 women (250 in each group) to provide a power of 80% at a two-sided significance level of 0·05.

Primary and secondary outcomes were analysed in the modified intention to treat population; all women and babies with follow-up data were included. **[A: Because women who withdrew informed consent or were lost to follow-up were excluded (as opposed to data being imputed) this is more accurately described as a modified intention to treat]** We assessed the primary outcome on a neonatal level with a generalised estimating equations model (GEEs) for binomial data with a log-link function and using an unstructured correlation matrix, resulting in a calculated relative risk (RR) and 95% CI. We accounted for interdependence between outcomes in multiple pregnancies by considering the mother as a cluster variable.[25] Secondary outcomes on the neonatal level were calculated in a similar way as the primary outcome. Continuous outcomes on the neonatal level were assessed with linear quantile mixed models with mother as the grouping variable, resulting in a median difference with 95% CI. Prolongation of pregnancy and gestational age at delivery were evaluated by Cox proportional hazards regression and Kaplan-Meier estimates, accounting for differing gestational age at entry, and tested with the Log rank test. Gestational age at delivery was censored at 37 weeks of gestation because the interest of the effectiveness of tocolytic therapy is mainly focused on preterm birth and not necessarily on overall gestational age at delivery. The proportional hazards assumption was verified by plotting Schoenfeld residuals over time.[26] Outcomes on the maternal level were assessed by a binomial regression model with log-link function.

Pre-specified subgroup analyses were calculated for the following subgroups: PPROM status (PPROM *vs* intact membranes), gestational age at randomisation (<30 weeks vs ≥30 weeks), number of fetuses (multiple *vs* singleton pregnancies), and history of preterm birth (yes vs no), women with a positive fibronectin test (yes *vs* no), and cervical length (<10 mm *vs* ≥10 mm). Subgroup effects were investigated for adverse perinatal outcome and prolongation of pregnancy. Subgroup effects were assessed by including an interaction term between the subgrouping variable and treatment allocation as covariate to the regression model. When the interaction term was statistically significant ($p_{interaction}$<0·05) a stratified subgroup analysis was done to study the effect of treatment in different strata of the subgroups.

We did a planned interim analysis based on the outcomes of 145 women, at which the data safety monitoring committee noted no conditions to stop the trial. All analyses were adjusted for the interim analyses with the O'Brien-Fleming α spending function. As a result, we deemed a nominal p value of less than 0·049 as indicative of statistical significance. **[A: Does this affect the significance of a value with an upper 95% CI of 0.99. Please check, especially for PPROM subgroup analysis**

	Nifedipine group	Atosiban group	RR, HR, or median difference (95% CI)
Perinatal outcomes			
Number of babies analysed	297	294	..
Adverse perinatal composite outcome (primary analysis)	42 (14%)	45 (15%)	RR 0·91 (0·61–1·37)
Perinatal deaths	16 (5%)	7 (2%)	RR 2·20 (0·91–5·33)
Bronchopulmonary dysplasia	11 (4%)	21 (7%)	RR 0·55 (0·27–1·15)
Culture-proven sepsis	25 (8%)	25 (9%)	RR 0·97 (0·55–1·70)
Intraventricular haemorrhage	5 (2%)	2 (1%)	RR 2·47 (0·48–12·75)
Periventricular leukomalacia	1 (<1%)	2 (1%)	RR 0·49 (0·05–5·46)
Necrotising enterocolitis	7 (2%)	4 (1%)	RR 1·72 (0·51–5·83)
NICU admittance	155 (52·2)	182 (61·9)	RR 0·85 (0·73–0·99)
Length of admission at NICU (days)	17 (7·0–43·0)	17 (7·0–39·8)	Median difference –1 (–5·52 to 3·52)
Ventilation support*	42 (14%)	53 (19%)	RR 0·76 (0·51–1·12)
Time on ventilation support (days)*	3 (1·3–9·5)	3 (1·0–8·0)	Median difference –0·33 (–2·82 to 2·16)
Total days in hospital until 3 months corrected age	24 (5·0–46·0)	28 (9·0–52·0)	Median difference –2·88 (–8·37 to 2·61)
Apnoea	20 (7%) [A1]	25 (9%)	RR 0·73 (0·41–1·32)
Asphyxia	2 (1%)	2 (1%)	RR 0·99 (0·14–7·06)
Proven meningitis	5 (2%)	2 (1%)	RR 2·44 (0·48–12·49)
Pneumothorax	2 (1%)	5 (2%)	RR 0·40 (0·08–2·04)
Maternal outcomes			
Number of women analysed	248	255	..
Gestational age at delivery (weeks)	33·1 (30·5–37·0)	32·4 (30·1–35·8)	XX 0·86 (0·70–1·05)
Prolongation of pregnancy			
Continuous (days)	7 (1·0–40·0)	4 (1·0–38·0)	HR 0·88 (0·72–1·07)
≥48 h	169 (68%)	168 (66%)	XX 1·04 (0·92–1·17)
≥7 days	127 (51%)	116 (45%)	XX 1·13 (0·94–1·36)
Maternal deaths	0	0	..
Discontinuation of study drug	74 (30%)	75 (29%)	XX 1·01 (0·77–1·32)
Due to progression to labour†	66 (26%)[A2]	70 (27%)[A2]	XX 0·97 (0·73–1·30)
Due to side-effects†	15 (6%)[A2]	7 (3%)[A2]	XX 2·20 (0·91–5·33)
Unknown†	2 (1%)[A2]	2 (1%)[A2]	..

Outcome data are n (%) or median (IQR). RR=relative risk. HR=hazard ratio. [A: please add whether data are HR or RR in the latter part of the table - XX] NICU=neonatal intensive care unit. *n=292 for nifedipine and n=286 for atosiban. †Study drug could be discontinued for more than one reason. [A2: corrected percentages to that for the whole study group]

***Table* 2: Perinatal outcomes**

and NICU stay] Serious adverse events (perinatal death, maternal mortality or severe maternal morbidity including intensive care admission) were reported to the central committee on research involving human subjects and to the ethics committee of the Academic Medical Centre, Amsterdam. We analysed data with R, version 3·1·1; specifically, we did GEE using the gee library and did linear quantile mixed models using the lqmm library. We used a data safety and monitoring committee composed of XXX [A: Independent academics?] from XX [A: please provide location of this committee]. The study is registered at the Dutch Clinical Trial Registry, number NTR2947.

Role of the funding source

The funder of the study, ZonMW, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

[A: we do not use subheadings in our results section. Non-primary data in tables and figures have been removed from the text for redundancy; the written interpretation remains]

Between July XX, 2011, and July XX, 2014 [A: please add exact dates, including last measure of outcomes for those enrolled], we enrolled 510 women. We randomly assigned 254 women to the nifedipine group and 256 to the atosiban group (figure 1, table 1). Outcome data were available for 248 women in the nifedipine group and 255 in the atosiban group, corresponding to 297 and 294 babies, respectively (figure 1). [A: deleted some information here covered in figure 1 and table 1]

In the primary analysis, 42 (14%) of 297 babies in the nifedipine group and 45 (15%) of 294 in the atosiban group had the adverse perinatal outcome (RR 0·91, 95% CI 0·61–1·37; table 2). Gestational age at delivery was similar between the groups (table 2). Median

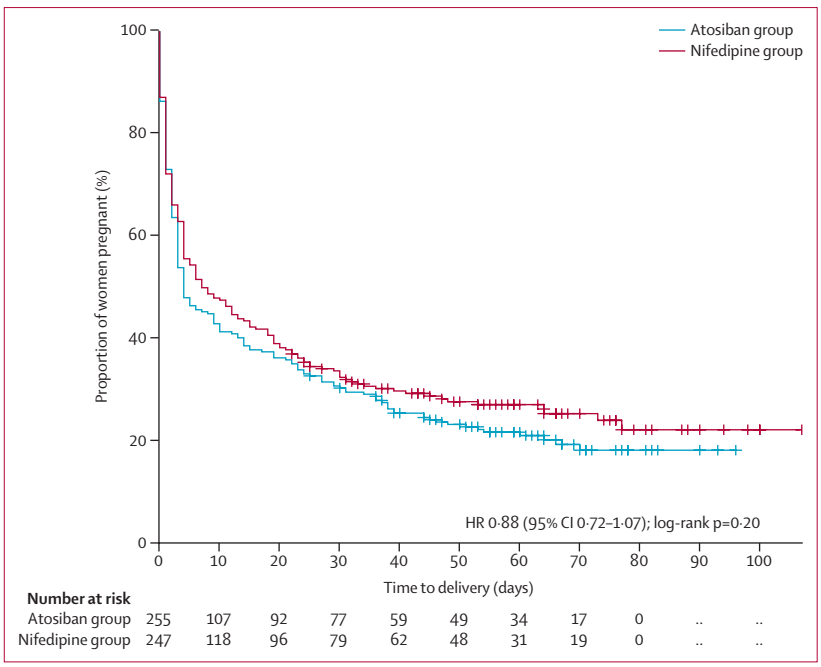

Figure 2: **Time to delivery**
HR=hazard ratio.

prolongation of pregnancy was 7 days (IQR 1·0–40·0) for women in the nifedipine group and 4 days (1·0–38·0) for those the atosiban group, with the Kaplan-Meier curve of time to pregnancy showing no significant difference (figure 2). The Schoenfeld residuals for gestational age at delivery and prolongation of pregnancy showed a random pattern with time, indicating the proportional hazards assumption is realistic **[A: are these data shown anywhere?]**.

The individual rates of bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis were similar between groups (table 2). In the nifedipine group, 155 (52%) infants were admitted to the NICU, compared with 182 (62%) in the atosiban group (RR 0·85, 95% CI 0·73–0·99, table 2). 42 (14%) of the infants in the nifedipine group needed ventilation support, compared to 53 (19%) infants in the atosiban group (RR 0·76, 95% CI 0·51–1·12). Time on ventilation, time in hospital, and rates of apnoea, asphyxia, meningitis, and pneumothorax in babies also did not differ (table 2). 16 (5%) children died in the nifedipine group and in seven (2%) children died in the atosiban group (RR 2·20, 95% CI 0·91–5·33). A panel of experts independently assessed these deaths and classified all as unlikely to be caused directly by the study drug (appendix).

No women died. 74 women (30%) in the nifedipine group and 75 (29%) in the atosiban group withdrew from the study drug (RR 1·01, 95% CI 0·77–1·32), with withdrawals mainly due to progression into labour (table 2). Side-effects leading to discontinuation of study drug were reported in 15 (6%) women in the nifedipine group and 7 (3%) in the atosiban group (table 2). Side-effects and adverse events in women were similar between group assignments and are listed in table 3 **[A: to be in line with CONSORT I have added the adverse event table. Please check]**.

[A: Findings shown in the subgroup analysis table are quite supplemental to the findings and are largely non-significant. To save space and to ensure all non-text items can fit near the results section we suggest adding into the appendix. This can be discussed if you disagree] In women without PPROM at study entry, time to delivery was longer in women assigned to treatment with nifedipine (median 24 days, IQR 4·0–54·8) than for those assigned to atosiban (14 days, 2·0–51·5 **[A: the 95% CI goes up to 0·99, this is barely significant, and I have worded to clarify. Please add the p value into figure 3]** (figure 3, appendix). Adverse perinatal outcome rates did not differ between group assignments in women with and without PPROM (RR 0·90, 95% CI 0·56–1·43). **[A: why aren't these data listed in the subgroup analysis table]**No significant interactions were found between drug allocation and the adverse perinatal outcomes or prolongation of pregnancy for the subgroups (appendix); hence no effect sizes were calculated in different strata of

	Nifedipine group (n=248)	Atosiban group (n=255)
Side-effects leading to discontinuation of study drug		
Signs of fetal asphyxia	1 (<1%)	2 (1%)
Fetal death	0	0
Suspected intrauterine infection	6 (2%)	1 (<1%)
Maternal dyspnoea	0	0
Maternal hypotension	0	0
Maternal liver disease	1 (<1%)	0
Maternal pulmonary oedema	0	0
Maternal myocardial infarction	0	0
Maternal ICU admission	0	0
Other	11 (4%)	4 (2%)
Progression into labour	66 (27%)	70 (27%)
Maternal shock	0	0
Withdrawal **[A: OK?]**	0	0
Complications after randomisation		
Pneumonia	0	0
Hypotension	0	1 (<1%)
Hypertension	8 (3%)	8 (3%)
PE/HELLP	3 (1%)	2 (1%)
Eclampsia	0	1 (<1%)
Thromboembolic event	0	0
Pregnancy diabetes	1 (<1%)	3 (1%)
IUGR	2 (2%)	5 (2%)

Data are n (%). **[A: please check inserted percentages. Is there a need to list adverse events experienced by no one?]** ICU=intensive care unit. PE=pre-eclampsia. HELLP=haemolysis elevated liver enzymes and low platelets. IUGR=intrauterine growth restriction.

Table 3: **Adverse events in women**

the subgroups. No significant effects of treatment assignment were found in women with a positive fibronectin test or a cervical length smaller than 10 mm (appendix).

Discussion

In this multicentre, randomised controlled trial we show that 48 h of tocolysis with nifedipine and atosiban resulted in similar rates of adverse perinatal outcomes in babies born to women with threatened preterm birth. Almost all neonatal and maternal secondary outcomes were similar; however, NICU admittance rates were lower in the nifedipine group (52%) than in the atosiban group (62%; RR 0·85, 95% CI 0·73–0·99). **[A: incorporated sentence about deaths to the fourth paragraph to reduce redundancy]**

Our study has several strengths. First, our primary outcome measure reflects the main goal of tocolysis, which is to improve neonatal outcome and not prolongation of pregnancy in itself. Previous trials on this topic were not sufficiently powered to examine neonatal outcomes.[16–18] Second, to our knowledge this is the largest randomised controlled trial to directly compare the effectiveness and safety of the widely used tocolytic drugs nifedipine and atosiban in a multicentre setting. Third, we aimed to include women at high risk of preterm delivery. Indeed, more than half of the women in our study delivered within 7 days after inclusion, and more than 75% delivered preterm, a contrast with previous trials in which most women did not deliver shortly after randomisation.[17,18]

Our study also has some limitations. Because of the different administration routes of the interventions (oral *vs* intravenous), our study was not masked. This factor might have caused bias, although it is unlikely to have an impact on the main outcomes of the study since all women received an active drug and since our outcome measures could be objectively assessed. Second, perinatal death was part of our composite outcome measure. Although the use of a composite outcome is common practice and can help to make statistically reliable comparisons with a smaller population, it also has a limitation since it ignores clinical differences in the components of the composite outcome, and considers more severe (eg, death) and less severe outcomes (eg, bronchopulmonary dysplasia) as equal. Also, certain mechanisms can have different effects on parts of the composite outcome; for example, prolongation of pregnancy could improve respiratory perinatal outcome but lead to more fetal deaths due to circulatory instability. Our study was not powered to reliably assess the treatment effect on the level of the individual components of the composite outcome.

Subgroup analyses showed a longer duration of pregnancy in women without ruptured membranes who were treated with nifedipine (appendix). However, this prolongation of pregnancy did not improve perinatal outcomes. A statistically non-significant, but possibly clinically relevant, increase in neonatal death was noted in the nifedipine group, although the expert panel could not find a direct causal association between the drugs and mortality (table 2; appendix). It could be postulated 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. Animal studies have described changes in uterine blood flow and occurrence of fetal acidaemia, but studies in humans showed no adverse effects on umbilical artery blood flow or fetal movements.[28–35] Investigators have reported fetal death after tocolysis with nifedipine, most likely due to maternal hypotension.[36] A prospective cohort study from the Netherlands and Belgium concluded that maternal adverse events, mainly hypotension and tachycardia, were more frequent with the use of nifedipine.[37] In our study, no severe maternal side-effects were observed and review of the charts of the perinatal deaths did not reveal any deaths in which mothers had severe hypotension (appendix). However, the safety of nifedipine in pregnancy has not been studied extensively, and nifedipine is not registered for use in pregnancy **[A: worldwide? Or in the Netherlands?]**.[38] This fact is of concern, especially since nifedipine is recommended as a first-line tocolytical drug in international guidelines.[39,40] Since our expert panel could not find a direct causal association between the drug and deaths, we could not find evidence in our study for a clinical effect of the proposed pathophysiological mechanism.

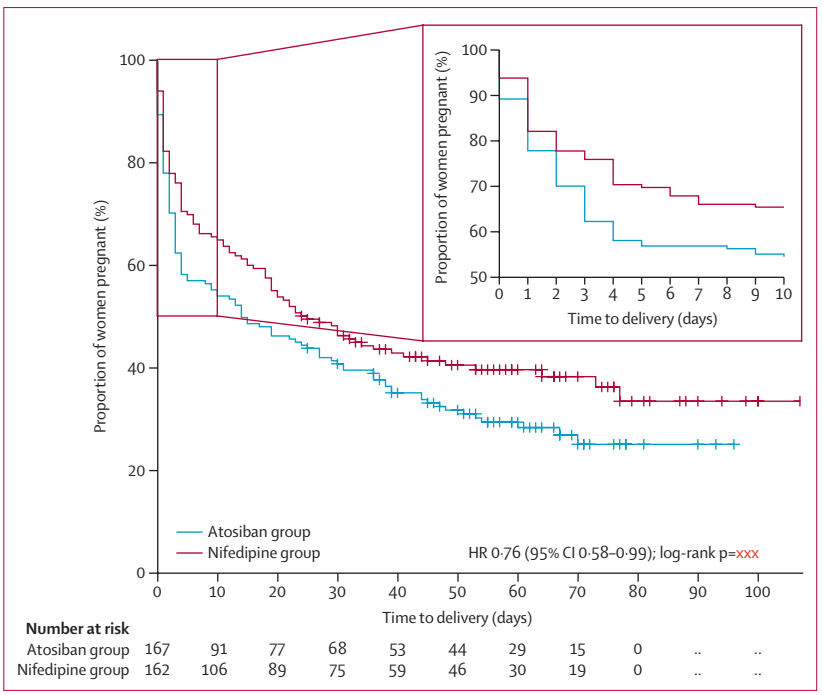

***Figure 3*: Time to delivery in women without PPROM**
PPROM=preterm premature rupture of membranes. HR=hazard ratio. **[A: please check data and confirm p value]**

Atosiban has a favourable adverse event profile [A: reported profile? I ask because they seem similar in table 3? Please clarify] and is registered for the use in pregnancy in many countries; however, it is not readily available throughout the world. The costs of atosiban also exceed the costs of other tocolytic drugs such as nifedipine. Most importantly, the debate about the effectiveness and safety of tocolysis in general is inconclusive. There is little [A: OK instead of lack, which we find quite vague] proof that tocolysis, and thereby prolongation of pregnancy in preterm labour in general, improves perinatal outcome and it might even be harmful.[13,41] This dearth was recognised by an international panel of experts who advised in the new WHO guidelines against the use of any tocolytics other than to facilitate intra-uterine transfer.[42] We therefore recommend the initiation of large placebo-controlled trials to assess treatment of preterm labour, with adverse perinatal outcome being the primary outcome. Trials should be specifically powered to assess the treatment effect in women without PPROM.

Contributors

MAO, BWJM, BCO and JHK conceived of and designed the study. MAO, BWJM, TAJN, ES and EOGvV drafted the manuscript and analysed and interpreted the data. All authors are members of the Apostel-III study group or collaborators, were local investigators at the participating centres, and participated in the design of the study during several meetings. All authors edited the manuscript and read and approved the final draft.

Declaration of interest

We declare no competing interests. [A: please ensure this statement matches that given in your submitted ICMJE forms]

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