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Maintenance tocolysis with nifedipine in threatened preterm labour: 2-year follow up of the offspring in the APOSTEL II trial

EOG van Vliet,[a] L Seinen,[b] C Roos,[b] E Schuit,[c,d] HCJ Scheepers,[e] KWM Bloemenkamp,[f] JJ Duvekot,[g] J van Eyck,[h] JH Kok,[i] FK Lotgering,[b] A van Baar,[j] AG van Wassenaer-Leemhuis,[i] MT Franssen,[k] MM Porath,[l] JAM van der Post,[m] A Franx,[a] BWJ Mol,[n] MA Oudijk[a,m]

[a] Department of Obstetrics and Gynaecology, University Medical Centre Utrecht, Utrecht, the Netherlands [b] Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands [c] Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands [d] Stanford Prevention Research Centre, Department of Medicine, Stanford University, Stanford, CA, USA [e] Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, the Netherlands [f] Department of Obstetrics and Gynaecology, Leiden University Medical Centre, Leiden, the Netherlands [g] Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, the Netherlands [h] Department of Obstetrics and Gynaecology, Isala Clinics, Zwolle, the Netherlands [i] Department of Neonatology, Academic Medical Centre, Amsterdam, the Netherlands [j] Utrecht Centre for Child and Adolescent Studies, Utrecht University, Utrecht, the Netherlands [k] Department of Obstetrics, University Medical Centre, University of Groningen, Groningen, the Netherlands [l] Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven, the Netherlands [m] Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam, the Netherlands [n] The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia

Correspondence: MA Oudijk, Department of Obstetrics, Academisch Medisch Centrum, Postbus 22660, room H4-275, 1100 DD Amsterdam, the Netherlands. Email m.a.oudijk@amc.nl

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Objective To evaluate long-term effects of maintenance tocolysis with nifedipine on neurodevelopmental outcome of the infant.

Design, Setting and Population Follow up of infants of women who participated in a multicentre randomised controlled trial on maintenance tocolysis with nifedipine versus placebo.

Methods Two years after the APOSTEL II trial on maintenance tocolysis with nifedipine versus placebo, we asked participants to complete the Ages and Stages Questionnaire.

Main outcome measures Infant development was measured in five domains. Developmental delay was defined as a score of ≤1 SD in one or more developmental domains. We performed exploratory subgroup analysis in women with preterm prolonged rupture of the membranes, and in women with a cervical length <10 mm at study entry.

Results Of the 276 women eligible for follow up, 135 (52.5%) returned the questionnaire, encompassing data of 170 infants. At 2 years of age, infants of women with nifedipine maintenance tocolysis compared with placebo had a higher overall incidence of fine motor problems (22.2 versus 7.6%, OR 3.43, 95% CI 1.29–9.14, $P = 0.01$), and a lower incidence of poor problem-solving (21.1 versus 29.1%, OR 0.27, 95% CI 0.08-0.95, $P = 0.04$).

Conclusions This follow-up study revealed no clear benefit of nifedipine maintenance tocolysis at 2 years of age. As short-term adverse perinatal outcome was not reduced in the original APOSTEL II trial, we conclude that maintenance tocolysis does not appear to be beneficial at this time.

Keywords Maintenance tocolysis, nifedipine, outcome, preterm birth.

Tweetable abstract No clear benefit of nifedipine maintenance tocolysis in preterm labour on 2-year infant outcome.

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Introduction

Early preterm birth is a major health care problem. In very premature infants it may cause long-term physical and developmental impairment and has a substantial impact on parents and families.[1,2] Perinatal morbidity and mortality is strongly inversely related to gestational age.[3]

In threatened preterm labour before 34 weeks of gestation, antenatal corticosteroids enhance fetal lung maturation and thereby improve outcome in these infants.[4] To allow optimal effect of maternal steroid administration, the simultaneous use of tocolytic drugs for 48 hours is common practice in most perinatal centres. As perinatal morbidity and mortality are strongly related to gestational age,[3] further postponement of delivery through maintenance tocolysis was long thought to improve neonatal outcome. However, recent randomised controlled trials have failed to show any effect of nifedipine maintenance tocolysis on prolongation of pregnancy and perinatal outcome.[5–8] Although, nifedipine maintenance tocolysis does not have an effect on short-term outcome, it might have an effect on long-term infant outcome. Nifedipine crosses the placenta easily,[9,10] thereby exposing the fetus to medication with unknown effects on fetal brain development. Previous studies have shown a decline in uterine artery and middle cerebral artery flow[11] and resistance[12] after nifedipine tocolysis, but other studies did not find such an effect.[13] *In vitro* studies have shown a potential neuroprotective effect of nifedipine.[14,15] In light of potential effects on fetal brain development, it is important to determine the effect of nifedipine maintenance tocolysis on long-term infant outcome.

The APOSTEL II (Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour) trial[7] included women with threatened preterm labour between $26^{+0/7}$ weeks and $32^{+2/7}$ weeks of gestation who had not delivered after 48 hours of tocolysis and a completed course of corticosteroids. Women were randomly assigned to maintenance tocolysis with nifedipine or placebo for a maximum of 12 days. The objective of the current study was to determine the extent to which maintenance tocolysis with nifedipine was associated with long-term neurodevelopmental outcome, assessed at 2 years of age in infants of women who participated in the APOSTEL II trial. We analysed neurodevelopmental outcome for the group as a whole, and for subgroups with and without preterm prolonged rupture of the membranes (PPROM), and with and without a cervical length <10 mm at study entry.

Methods

The APOSTEL II trial is a double-blind placebo controlled trial conducted in all 10 perinatal centres and one large teaching hospital in the Netherlands. The study protocol and the main results of the APOSTEL II trial have been published elsewhere.[7,16] In all, 406 women participated in the APOSTEL II trial between June 2008 and February 2010. Women with threatened preterm labour and a gestational age between $26^{+0/7}$ and $32^{+2/7}$ weeks who had not delivered after a completed 48-hour course of tocolytics and corticosteroids, were allocated to maintenance tocolysis with nifedipine ($n = 201$) or placebo ($n = 205$). Study medication was 20 mg nifedipine slow-release tablets every 6 hours, or placebo tablets. The APOSTEL II trial included women with singleton and multiple pregnancies with and without ruptured membranes.

The intention to follow up the children was described in the study protocol.[16] The follow-up study was approved by the institutional review board of all the participating centres as part of the APOSTEL II trial.

Participants

The follow up of the APOSTEL II study started in 2009 and sought information about infants born to the 406 women who were randomised in the APOSTEL II trial. Figure 1 shows that after exclusion of 130 women (not eligible because infants died, who were not traceable or whose infants were older than 24 months at start of follow up), follow-up data were available on 170 infants of 145 women, a response rate of 52.5% (145/276 women). One infant had West syndrome and was excluded from analysis. Parents were contacted by mail, and if there was no response, trained research midwifes sought contact by phone. Data on demographic and clinical characteristics were collected as described in the original trial.[16]

Follow-up measures

Parents were contacted and asked to fill out the Dutch translation of the parent-rated Ages and Stages Questionnaire (ASQ) at the corrected age of 24 months. The ASQ consists of five subscales, each with six items, on communication, gross motor performance, fine motor performance, problem-solving and personal–social functioning. Parents indicated whether their child did, did not or sometimes/a little showed the behaviour as described in an item. Poor outcome on a subscale was defined as a score lower than 1 standard deviation below the mean of the norm group.[17] Developmental delay was defined as a score of ≤1 SD in one or more developmental domains. A score ≤1 SD indicates that this infant is at risk of poor outcome, and warrants targeted interventions and close follow up of the infant. The ASQ is a valuable screening instrument for the study of developmental delay in ex-premature infants,[18] and outcome is not influenced by the socio-economic status of the parents.[19] Parents were unaware of the treatment allocation at the time of follow up.

Statistical analysis

The size and power of the study was limited by the number of participants in the APOSTEL II trial. To determine how representative our sample was, we tested for differences in demographic and clinical data between participants and non-participants in the follow-up trial.

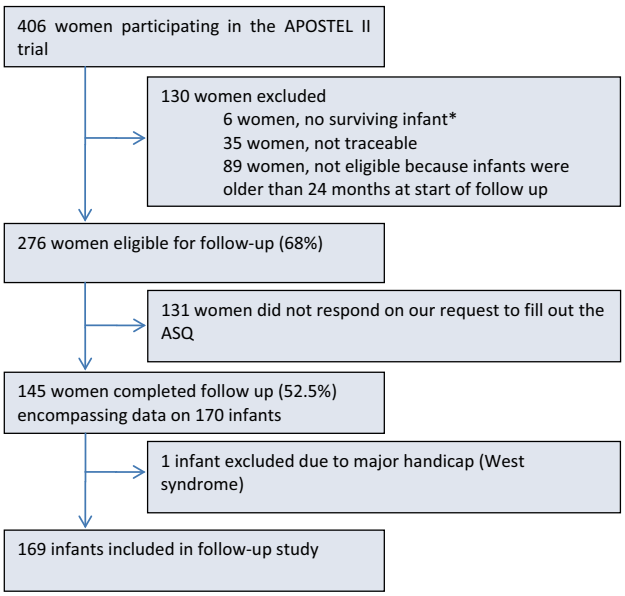

Figure 1. Flow chart. *9 infants died in the APOSTEL II trial. However, three of them had a surviving twin sibling.

Furthermore, we tested for differences in baseline characteristics between the nifedipine group and the placebo group. Baseline characteristics were compared using ANOVA for continuous data, chi-square tests for dichotomous data and Mann–Whitney *U*-tests for non-normal distributed data. For outcome at infant level, we used a generalised estimated equation model to test for differences in outcome between infants exposed to nifedipine maintenance tocolysis compared with placebo, accounting for interdependence of scores in siblings. Odds ratios (OR) and 95% CI are reported. We tested for possible subgroup effects for women with and without PPROM, and women with a cervical length <10 and ≥10 mm at study entry. Subgroup effects were studied using an interaction term between the subgroup and treatment, corrected for gestational age at delivery. When the interaction was found to be statistically significant ($P < 0.05$), we performed stratified analysis to investigate the effect of treatment in the different subgroups.

In a cohort of preterm infants, there is a risk for bias because deceased and very disabled infants are not able to participate in follow up. We therefore performed *post hoc* sensitivity analyses using a composite of death ($n = 9$), severe disabilities ($n = 1$) or ASQ score <1 SD. Because not all parents filled out the questionnaire within the preferred time frame (24 months corrected age ±1 month), we compared the incidence of poor outcome between infants that were assessed too early, on time or too late, and we performed sensitivity analysis excluding these cases if there were any differential effects.

Results

Study population

Baseline characteristics of the mothers in the placebo group ($n = 66$), nifedipine group ($n = 78$) and the non-participants ($n = 262$) are displayed in Table 1. There was a higher percentage of white Europeans in the group who participated in the follow-up study than in the non-participants ($P < 0.01$) and a lower percentage of lower maternal education ($P < 0.01$). These characteristics did not differ between the nifedipine group and the placebo group. Other baseline characteristics were comparable between the participants and nonparticipants, and between the nifedipine group and the placebo group. Median corrected age (range; interquartile range, IQR) at time of completion of the questionnaire was 22.9 (range 21.3–29.1; IQR 22.1–24.0) for the nifedipine group and 22.7 (range 21.1–30.2; IQR 22.2–23.7) for the placebo group ($P = 0.52$).

Main outcome

Developmental outcome as measured by ASQ at 2 years of age is shown in Table 2. Overall, infants of women who received nifedipine maintenance tocolysis had a higher incidence of poor outcome on the fine motor scale (22.2 versus 7.6%, OR 3.43, 95% CI 1.29–9.14, $P = 0.01$) but did better on the problem-solving scale (21.1 versus 29.1%, OR 0.27, 95% CI 0.08–0.95, $P = 0.04$).

Subgroup analysis

The subgroup analysis for possible interaction between the intervention and PPROM at inclusion, corrected for differences in gestational age at delivery (mean gestational age 32.4 weeks for PPROM versus 34.5 without PPROM, $P = 0.002$) showed that there was a significant interaction effect for gross motor performance ($P = 0.02$) and developmental delay ($P = 0.02$; Table 3).

Infants with PPROM born after nifedipine maintenance tocolysis had a non-significant higher incidence of poor gross motor outcomes than those on placebo (44.4 versus 28.6%, OR 2.34, 95% CI 0.64–8.59). Poor gross motor outcomes were less common in infants exposed to nifedipine maintenance compared with placebo in the absence of PPROM (31.9 versus 43.1%, OR 0.23, 95% CI 0.07–0.79).

Infants with PPROM born after nifedipine maintenance tocolysis more often had developmental delay compared with those on placebo (77.8 versus 57.1%, OR 2.67, 95% CI 0.66–10.82), although this difference was not significant. Developmental delay was less common in infants without PPROM and nifedipine maintenance tocolysis than those on placebo (54.2 versus 68.6%, OR 0.31, 95% CI 0.13–0.74). There was no significant interaction effect between treatment group and time interval to delivery (data not

Table 1. Baseline demographics and clinical characteristics

Number of women	Placebo (n = 66)	Nifedipine (n = 78)	No follow-up (n = 262)
At entry to APOSTEL II			
Age, years	30.9 (4.6)	30.9 (4.6)	29.8 (5.3)
Body mass index*	22.4 (3.2)	24.1 (5.7)	23.3 (4.3)
White European	59 (92.2)	74 (98.7)	188 (74.6)**
Lower maternal education	5 (12.2)	3 (7.1)	40 (26.1)***
Nulliparous	32 (48.5)	32 (41.0)	111 (42.4)
Prior preterm birth	16 (24.2)	17 (21.8)	60 (22.9)
Gestational age, week	29.1 (1.8)	29.1 (1.7)	29.3 (1.7)
Multiple gestation			
Twins	12 (18.1)	12 (15.4)	58 (22.1)
Triplets	1 (1.5)	0 (0)	5 (1.9)
PPROM	21 (31.8)	17 (21.8)	63 (24.1)
Cervix <10 mm****	8 (21.6)	7 (13.0)	22 (12.6)
Short-term outcomes of APOSTEL II			
Adverse perinatal outcome*****	10 (15.2)	10 (12.8)	32 (12.2)
Perinatal death	1 (1.5)	0 (0.0)	8 (3.1)

Number of infants	Placebo (n = 79)	Nifedipine (n = 90)	No follow up (n = 333)
Birthweight, g	2152.7 (100.3)	2304.2 (98.0)	2251.6 (50.4)
NICU admittance	36 (45.6)	37 (41.1)	129 (38.7)
Ventilation support	7 (8.9)	16 (17.8)	69 (13.7)

Data are in mean (SD) or n (%). None of the other characteristics differed between placebo and nifedipine group, or between the follow-up and no follow-up group.
*Body mass index is calculated as weight in kilograms divided by height in meters squared.
**$P < 0.01$ compared with women who participated in follow up.
***Based on n = 236 due to missing data on maternal education.
****Based on n = 266 women who had cervical length measurement.
*****Adverse perinatal outcome is a composite of perinatal death, chronic lung disease, neonatal sepsis, IVH > grade 2, PVL > grade 1, and necrotising enterocolitis, measured per pregnancy.

shown, $P = 0.99$), i.e. there was no difference in the effect of nifedipine maintenance therapy on time interval to delivery between women with and without PPROM.

Interaction tests of the intervention and cervical length <10 mm at randomisation were based on limited numbers (n = 63 for nifedipine and n = 46 for placebo) because cervical length measurement was not performed in all women. We observed a significant interaction effect on the problem-solving scale ($P = 0.03$, Table 4). In both the group of women with a cervix <10 mm and those with a cervix ≥10 mm at study entry, infants of the nifedipine group had a lower incidence of poor problem-solving compared with infants of the placebo group, but this difference was not significant (22.2 versus 50%, OR 0.05, 95% CI 0.00–0.58 18.5 versus 27.8%, OR 0.66, 95% CI 0.22–1.96, respectively).

Sensitivity analysis

Sensitivity analysis using a composite of poor outcome and perinatal death revealed comparable results, except that the lower incidence of poor outcome on the problem-solving scale in the nifedipine group was no longer significant (OR 0.33, 95% CI 0.11–1.02, $P = 0.06$).

Not all parents filled out the questionnaires within the preferred timeframe, therefore we performed additional analyses to test to what extent this might have influenced our results. For fine motor problems, there was a significantly lower incidence of delay in the infants who were tested too late than in those who were tested within the correct time frame (0.0% versus 18%). After exclusion of these infants (n = 11), the effect of the intervention on fine motor problems remained comparable (OR 3.23, 95% CI 1.21–9.09, $P = 0.02$). For all other outcome measures there was no significant difference in the incidence of poor outcome between infants that were assessed too early, on time or too late.

Discussion

Main findings

To the best of our knowledge, this is the first study to examine the long-term outcome of infants exposed to nifedipine maintenance tocolysis compared with a placebo group. We observed that at 2 years of age these infants have a higher incidence of fine motor problems but a lower incidence of poor problem-solving. In a specific subgroup of women without PPROM, there was a lower incidence of gross motor problems and developmental delay in infants of the treatment group than the placebo group.

Strengths and limitations

Several methodological issues deserve discussion. First, this study used questionnaire data to measure developmental outcome. Although questionnaire data have their inherent limitations, the ASQ is regarded as a validated screening tool for developmental problems.[19] There is some evidence to suggest that the ASQ underestimates the incidence of motor delay in premature infants;[20] however, it is independent of socio-economic status or maternal education.[19] The ASQ has excellent psychometric properties for use as a screening instrument for abnormal development.[18,19] However, the ASQ is not a diagnostic test and abnormal scores require further examination. In addition, the ASQ does not substitute for clinical examination and sensory screening.[18]

Secondly, selection bias cannot be excluded. Of the 406 women enrolled in the APOSTEL II trial, infants of 145

Table 2. Follow up at age 2

	Nifedipine (n = 90)	Placebo (n = 79)	OR	95% CI	P-value
Communication scale	14 (15.6)	20 (25.3)	0.56	0.25–1.26	0.16
Gross motor scale	31 (34.4)	30 (38.0)	0.41	0.15–1.14	0.09
Fine motor scale	20 (22.2)	6 (7.6)	3.43	1.29–9.14	0.01
Problem solving scale	19 (21.1)	23 (29.1)	0.27	0.08–0.95	0.04
Personal social scale	25 (27.8)	26 (32.9)	0.88	0.43–1.78	0.72
Developmental delay	53 (58.9)	51 (64.6)	0.50	0.22–1.13	0.10

CI, confidence interval; OR, odds ratio.
Delayed development is defined as performance <1 SD below the mean score. Developmental delay is defined as performance <1 SD below the mean score at 1 or more subscales. Data presented as n (%).

Table 3. Developmental outcome, interaction with PPROM

				Subgroup effect	
	Nifedipine (n = 90)	Placebo (n = 79)	OR	95% CI	P-value for interaction
Communication scale					
PPROM	4/18 (22.2)	8/28 (28.6)			0.60
No PPROM	10/72 (13.9)	12/51 (23.5)			
Gross motor scale					
PPROM	8/18 (44.4)	8/28 (28.6)	2.34	0.64– 8.59	0.02
No PPROM	23/27 (31.9)	22/51 (43.1)	0.23	0.07–0.79	
Fine motor scale					
PPROM	7/18 (38.9)	3/28 (10.7)			0.70
No PPROM	13/72 (18.1)	3/51 (5.9)			
Problem-solving scale					
PPROM	4/18 (22.2)	7/28 (25.0)			0.22
No PPROM	15/72 (20.8)	16/51 (31.4)			
Personal social scale					
PPROM	10/18 (55.6)	11/28 (39.3)			0.10
No PPROM	15/72 (20.8)	15/51 (29.4)			
Developmental delay					
PPROM	14/18 (77.8)	16/28 (57.1)	2.67	0.66–10.82	0.02
No PPROM	39/72 (54.2)	35/51 (68.6)	0.31	0.13–0.74	

Data presented as (n performing –1 SD)/total (%), corrected for gestational age.

women could be included in this follow-up study. This may have caused unknown effects. Women participating in the follow-up study more often were white Europeans and less often had a low educational level compared with women who did not participate in the follow-up study. Yet, there was no difference between these baseline characteristics between the nifedipine and placebo groups, and a previous study has shown that the ASQ scores are not significantly associated with socio-economic status or maternal education.[19] Furthermore, other baseline characteristics were comparable between the participants and non-participants of this follow-up study. Therefore, we feel that selection bias may not have greatly affected the results.

Nine infants in this cohort died and one was too disabled to participate in the follow-up study. As this could lead to bias, we re-ran all analyses including deceased and severely disabled infants in the poor outcome group. The results were still comparable.

Thirdly, some of the parents participating in this follow-up study did not fill out the questionnaire within the correct time frame; however, follow-up time was equal in both treatment groups and it is therefore unlikely that this ad a great influence on the results. Besides, sensitivity analyses revealed comparable results after exclusion of infants who were assessed too late.

The subgroup analyses should be interpreted with caution because the study was not powered to conduct long-term

Table 4. Developmental outcome, interaction with cervical length <10 mm at inclusion

				Subgroup effect	
	Nifedipine (n = 63)	Placebo (n = 46)	OR	95% CI	P-value for interaction
Communication scale					
Cervix <10 mm	2/9 (22.2)	2/10 (20.0)			0.36
Cervix ≥10 mm	9/54 (16.7)	10/36 (27.8)			
Gross motor scale					
Cervix <10 mm	5/9 (55.6)	2/10 (20.0)			0.43
Cervix ≥10 mm	17/54 (31.5)	15/36 (27.8)			
Fine motor scale					
Cervix <10 mm	0/9 (0.0)	0/10 (0.0)			NA
Cervix ≥10 mm	11/54 (20.4)	2/36 (5.6)			
Problem-solving scale					
Cervix <10 mm	2/9 (22.2)	5/10 (50.0)	0.05	0.00–0.58	0.03
Cervix ≥10 mm	10/54 (18.5)	10/36 (27.8)	0.66	0.22–1.96	
Personal social scale					
Cervix <10 mm	1/9 (11.1)	1/10 (10.0)			0.98
Cervix ≥10 mm	16/54 (29.6)	12/36 (33.3)			
Developmental delay					
Cervix <10 mm	7/9 (77.8)	6/10 (60.0)			0.86
Cervix ≥10 mm	27/54 (50.0)	22/36 (61.1)			

NA, not applicable.
Data presented as (n performing −1 SD)/total (%), corrected for gestational age. Analysis based on n = 46 for placebo and n = 63 for nifedipine because cervical length measurement was not performed in all women.

follow up within subgroups. Especially the number of women with a cervical length ≤10 mm (n = 19) is small. Nonetheless, the results of our subgroup analyses underscore the fact that prematurity is heterogeneous in origin and interventions may well elicit differential effects in subgroups, which should be taken into account when evaluating neonatal outcome.

Interpretation

To the best of our knowledge, no previous trials have studied the effect of nifedipine maintenance tocolysis on neurodevelopmental outcome compared with placebo. A previous randomised controlled trial[21] on maintenance tocolysis with nifedipine versus ritodrine found no differences in long-term behaviour–emotional outcome or motor functioning between the groups.[22] Despite the lack of effect on short-term outcome, as found in the APOSTEL II trial,[7] maintenance tocolysis may have an effect on long-term development. We found a higher incidence of fine motor problems but better problem-solving abilities in infants in the nifedipine group. A possible explanation for the differential effect on motor skills and problem-solving skills might be that structures that play important roles in motor functioning may be more vulnerable to injury. For example, the cerebellum undergoes the most rapid growth in the third trimester[23] and might therefore be more vulnerable to adverse effects of medication. Besides, disturbance of the myelination process is one of the hallmarks of hypoxic–ischaemic brain injury,[24] and contributes to poorer corticospinal tract functioning and motor development. Some studies have shown that nifedipine is associated with a decline in uterine artery and middle cerebral artery flow,[11] leading to the speculation that nifedipine may contribute to poor motor functioning.

Nifedipine maintenance therapy has a differential effect on infants with and without PPROM. We observed that infants of women with PPROM receiving maintenance tocolysis had a non-significant higher incidence of poor gross motor development and developmental delay compared with the placebo group, whereas infants of women with nifedipine maintenance without PPROM had a lower incidence of poor gross motor development and developmental delay. This did not result from a difference in prolongation of pregnancy or in time interval to delivery. One may speculate that nifedipine maintenance therapy in women with PPROM may actually have an adverse effect through an association with subclinical infection. A possible explanation of the specific effects on motor development might be that the white matter myelination process, which is essential for corticospinal tract functioning and motor development might be the most vulnerable to adverse effect of medication or perinatal inflammation.[25,26] There is on-going debate whether any tocolysis should be administered in PPROM. A Cochrane review indicates that tocolysis in women with PPROM before 34 weeks'

gestation is associated with a higher risk of chorioamnionitis, which is in turn associated with poor neonatal and neurodevelopmental outcome.[27] Although we observed fewer gross motor problems and developmental delay in infants after nifedipine maintenance in the absence of PPROM, given the limited number of women in this study, the loss to follow up, the resultant low power and the lack of short-term neonatal benefit, we feel that the results of the study should not be used as a basis for maintenance tocolysis in women with threatened preterm labour without PPROM.

Conclusion

Our 2-year follow-up study of the APOSTEL II trial showed that maintenance tocolysis with nifedipine is associated with a higher incidence of fine motor problems and a lower incidence of poor problem-solving. These findings stress the importance of long-term follow up of intervention studies designed to optimise outcome in preterm infants. As stated by the authors of the follow-up study of ORACLE II trial on antibiotics in spontaneous preterm labour,[28] the current study underscores the need for caution with interfering in systems that are poorly understood without clear evidence of the benefit of our intervention in the short- and long-term. Therefore, long-term follow-up studies of clinical interventions remain of utmost importance.

As the APOSTEL II trial found no reduction in adverse perinatal outcome, and this follow-up study revealed no clear benefit of nifedipine maintenance tocolysis at age 2, we maintain our conclusion that its use does not appear beneficial.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

EOGvV and ES had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MAO,BWJM, CR, ES. Acquisition, analysis or interpretation of the data: EOGvV, LS, ES, MAO,BWJM, FKL, CR. Drafting of the manuscript: EOGvV, MAO. Critical revision of the manuscript for important intellectual content: LS, CR, ES, HCJS, KWMBD, JvE, JHK, FKL, AvB, AGvW, MTF, MMP, JAMvP, AF, BWJ, MAO. Statistical analysis: EOGvV, ES. Study supervision: MAO, BWJM.

Details of ethics approval

The follow-up study was approved by the institutional review board of all participating centres as part of the approval of the APOSTEL II trial.

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References

1 Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10(Suppl 1):S2.
2 Treyvaud K, Lee KJ, Doyle LW, Anderson PJ. Very preterm birth influences parental mental health and family outcomes seven years after birth. *J Pediatr* 2014;164:515–21.
3 Bolisetty S, Bajuk B, Abdel-Latif ME, Vincent T, Sutton L, Lui K. Preterm outcome table (POT): a simple tool to aid counselling parents of very preterm infants. *Aust N Z J Obstet Gynaecol* 2006;46:189–92.
4 Keirse MJ. The history of tocolysis. *BJOG* 2003;110(Suppl 20):94–7.
5 Naik GN, Raman P, Bain E, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. *Cochrane Database Syst Rev* 2013;(10):CD004071.
6 Parry E, Roos C, Stone P, Hayward L, Mol BW, McCowan L. The NIFTY study: a multicentre randomized double-blind placebo-controlled trial of nifedipine maintenance tocolysis in fetal fibronectin-positive women in threatened preterm labour. *Aust N Z J Obstet Gynaecol* 2014;54:231–6.
7 Roos C, Spaanderman ME, Schuit E, Bloemenkamp KW, Bolte AC, Cornette J, et al. Effect of maintenance tocolysis with nifedipine in threatened preterm labour on perinatal outcomes. A randomized controlled trial. *JAMA* 2013;309:41–7.
8 Lyell DJ, Pullen KM, Mannan J, Chitkara U, Druzin ML, Caughey AB, et al. Maintenance nifedipine tocolysis compared with placebo: a randomized controlled trial. *Obstet Gynecol* 2008;112:1221–6.
9 Silberschmidt AL, Ku WN, Velten HN, Juon AM, Zimmermann R, von Mandacha U. Nifedipine concentration in maternal and umbilical cord blood after nifedipine gastrointestinal therapeutic system for tocolysis. *BJOG* 2008;115:480–5.
10 Ferguson JE, Schutz T, Pershe R, Stevenson DK, Blaschke T. Nifedipine pharmacokinetics during preterm labour tocolysis. *Am J Obstet Gynecol* 1989;161:1485–90.
11 Guclu S, Gol M, Saygili U, Demir N, Sezer O, Baschat AA. Nifedipine therapy for preterm labour: effects on placental, fetal cerebral and atrioventricular Doppler parameters in the first 48 hours. *Ultrasound Obstet Gynecol* 2006;27:403–8.
12 de S Lima MM, Souza ASR, Diniz C, Porto AMF, Amorim MMR, Moron AF. Doppler velocimetry of the uterine, umbilical and fetal middle cerebral arteries in pregnant women undergoing tocolysis with oral nifedipine. *Ultrasound Obstet Gynecol* 2009;34:311–5.

13 de Heus R, Mulder EJH, Derks JB, Visser GHA. The effects of the tocolytics atosiban and nifedipine on fetal movements, heart rate and blood flow. *J Matern Fetal Neonatal Med* 2009;22:485–90.

14 Sribnick EA, Del Re AM, Ray SK, Woodward JJ, Banik NL. Estrogen attenuates glutamate-induced cell death by inhibiting $Ca2^{+}$ influx through L-type voltage-gated $Ca2^{+}$ channels. *Brain Res* 2009;1276:159–70.

15 Berger R, Garnier Y, Jensen A. Perinatal brain damage: underlying mechanisms and neuroprotective strategies. *J Soc Gynecol Invest.* 2002;9:319–28.

16 Roos C, Scheepers LH, Bloemenkamp KW, Bolte A, Cornette J, Derks JB, et al. Assessment of perinatal outcome after sustained tocolysis in early labour (APOSTEL-II trial). *BMC Pregnancy Childbirth* 2009;9:42.

17 Squires J, Twombly E, Bricker D, Potter L. The ASQ-3 user's Guide, 3rd edn. Baltimore: Brookes.

18 Skellern CY, Rogers Y, O'Callaghan MJ. A parent-completed developmental questionnaire: follow-up of ex-premature infants. *J Paediatr Child Health* 2001;37:125–9.

19 Flamant C, Branger B, Nguyen The Tich S, de la Rochebrochard E, Savagner C, Berlie I, et al. Parent-completed developmental screening in premature children: a valid tool for follow-up programs. *PLoS ONE* 2011;6:e20004.

20 Simard MN, Luu TM. Gosselin J Concurrent validity of ages and stages questionnaires in preterm infants. *Pediatrics* 2012;130: e108–14.

21 Papatsonis DN, Van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labour: a randomized multicenter trial. *Obstet Gynecol* 1997;90:230–4.

22 Houtzager BA, Hogendoorn SM, Papatsonis DN, Samsom JF, van Geijn HP, Bleker OP, et al. Long-term follow-up of children exposed in utero to nifedipine or ritodrine for the management of preterm labour. *BJOG* 2006;113:324–31.

23 Brossard-Racine M, du Plessis AJ, Limperopoulos C. Developmental cerebellar cognitive affective syndrome in ex-preterm survivors following cerebellar injury. *Cerebellum* 2015;14:151–64.

24 Back SA. Cerebral white and gray matter injury in newborns: new insights into pathophysiology and management. *Clin Perinatol* 2014;41:1–24.

25 Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009;8:110–24.

26 van Vliet EO, de Kieviet JF, Oosterlaan J, van Elburg RM. Perinatal infections and neurodevelopmental outcome in very preterm and very low-birth-weight infants: a meta-analysis. *JAMA Pediatr* 2013;167:662–8.

27 Soraisham AS, Trevenen C, Wood S, Singhal N, Sauve R. Histological chorioamnionitis and neurodevelopmental outcome in preterm infants. *J Perinatol* 2013;3:70–5.

28 Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;372:1319–27.