Study protocol

Assessment of perinatal outcome after sustained tocolysis in early labour (APOSTEL-II trial)

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Abstract

Background: Preterm labour is the main cause of perinatal morbidity and mortality in the Western world. At present, there is evidence that tocolysis for 48 hours is useful in women with threatened preterm labour at least before 32 weeks. This allows transfer of the patient to a perinatal centre, and maximizes the effect of corticosteroids for improved neonatal survival. It is questionable whether treatment with tocolytics should be maintained after 48 hours.

Methods/Design: The APOSTEL II trial is a multicentre placebo-controlled study. Pregnant women admitted for threatened preterm labour who have been treated with 48 hours corticosteroids and tocolysis will be eligible to participate in the trial between 26+0 and 32+4 weeks.
gestational age. They will be randomly allocated to nifedipine (intervention) or placebo (control) for twelve days or until delivery, whatever comes first.

Primary outcome is a composite of perinatal death, and severe neonatal morbidity up to evaluation at 6 months after birth. Secondary outcomes are gestational age at delivery, number of days in neonatal intensive care and total days of the first 6 months out of hospital. In addition a cost-effectiveness analysis will be performed. Analysis will be by intention to treat. The power calculation is based on an expected 11% difference in adverse neonatal outcome. This implies that 406 women have to be randomised (two sided test, β 0.2 at alpha 0.05).

Discussion: This trial will provide evidence as to whether maintenance tocolysis reduces severe perinatal morbidity and mortality in women with threatened preterm labour before 32 weeks.

Trial Registration: Clinical trial registration: http://www.trialregister.nl, NTR 1336, date of registration: June 3rd 2008.

Background

Preterm birth is the most common cause of neonatal morbidity and death worldwide [1]. Two thirds of the preterm births occur as a result of spontaneous labour beginning with spontaneous contractions or with preterm rupture of membranes. Preterm birth accounts for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities [2]. Moreover, it is associated with high immediate and long-term costs after discharge from the hospital [3]. These include costs for special education services and institutionalised care for physically and mentally disabled infants [4]. The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery and declines from 77% at 24-27 weeks to less then 2% at 34 weeks and beyond [5]. Perinatal death and morbidity are not only strongly related to early gestational age but also to whether or not antenatal corticosteroids are administered [6] and whether a preterm infant is transferred to a tertiary care centre before or after birth. Postponing delivery for 48 hours with tocolytics in order to allow maximal effect of maternal parenteral steroid administration and transfer of the mother to a centre with Neonatal Intensive Care Unit (NICU) facilities is therefore standard treatment in women with the diagnosis of threatened preterm labour before 32 weeks gestational age [7].

Approximately 75% of women with a diagnosis of threatened preterm labour have not delivered after the first 48 hours of tocolytic therapy with nifedipine. After this 48 hour period the risk of preterm delivery persists. Two weeks after treatment for threatened preterm labour with nifedipine 65% of women are still pregnant [8].

Fetal fibronectin can be helpful in selecting women at risk for preterm delivery. Management based on knowledge of fetal fibronectin results significantly reduces preterm delivery less than 37 weeks compared to management without knowledge of these results (RR 0.54, 95% confidence interval 0.34 to 0.87). However the incidence of preterm delivery less than 34, 32 and 28 weeks were similar in both groups [9].

In national and international guidelines, a uniform treatment of threatened preterm delivery after 48 hours of tocolytic therapy has not yet been developed. Some obstetricians maintain tocolytic therapy until term, 37 weeks gestational age, whereas others stop tocolytics after 48 hours irrespective of gestational age or continue until for example 28 weeks gestational age. Maintenance treatment with several tocolytic agents has been being carried out in daily practice and include betamimetics [10,11], magnesium sulphate, indomethacin and calcium channel blockers [12] in order to achieve further prolongation of pregnancy and improvement of neonatal outcome. At present, no beneficial effect on perinatal outcome of such prolonged treatment has been established [13]. On one hand, tocolytic maintenance therapy with calcium channel blockers might be beneficial due to a positive effect on gestational age and possibly on neonatal outcome. On the other hand, use of tocolytics is associated with rare but severe side effects on mother and child [14,15], and may increase the risk of some perinatal complications - including intra-uterine infection.

Two systematic reviews included in DARE [16,17] and the Cochrane systematic review on maintenance tocolysis with nifedipine [12] reported only a few studies on the subject, and no reliable statement on the effectiveness of tocolytic maintenance therapy (TMT) on neonatal outcome. Although nifedipine maintenance therapy may increase gestational age at delivery, there has been no improvement in neonatal or maternal outcome [18-20].

In summary, preterm delivery is an important health care problem. Whereas it is evident that tocolysis with administration of corticosteroids for 48 hours is effective, there is insufficient evidence for a uniform policy after these 48
hours. In this randomised clinical trial we will investigate
the effectiveness of maintenance therapy with nifedipine
compared to placebo therapy in women with a gestational
age below 32 weeks. Additional data will be collected for
post-hoc evaluation of the clinical relevance of cervical
length measurement and the presence of fibronectin in
cervical mucus prior to maintenance tocolytic therapy.

This study is conducted within the Dutch Obstetric Con­
sortium, a collaborative effort of obstetric clinics in The
Netherlands to perform clinical trials. All ten Dutch peri­
natal centres with NICU facilities will participate in this
trial.

Methods/Design

Aims
The aim of this study is to evaluate the effectiveness of toc­
olytic maintenance therapy on perinatal outcome after
initial standard 48-hours’ tocolytic therapy in women
with threatened preterm birth between 26+0-32+2 weeks
gestational age. The outcome is measured in terms of neo­
natal mortality and composite neonatal morbidity
(chronic lung disease, severe intraventricular haemor­
hage, periventricular leucomalacia, proven sepsis and
necrotising enterocolitis), gestational age at delivery and
costs.

Participants/eligibility criteria
Women with threatened preterm delivery with a gesta­
tional age between 26+0 and 32+2 weeks who have not
delivered after 48 hours of tocolytics and corticosteroids
are eligible for participation in the APOSTEL II-trial.
Women with both singleton and multiple gestations are
included. We chose not to include women with a gesta­
tional age between 24 and 26 weeks to prevent protocol
violation (rescue tocolysis during study medication).

Maternal exclusion criteria are signs of intrauterine infec­
tion, placenta praevia, maternal disease requiring delivery
(i.e. HELLP syndrome or preeclampsia), maternal hyper­
tension and contraindications for the use of nifedipine.
Fetal exclusion criteria are signs of fetal distress (abnormal
-cardiotocogram, abnormal biophysical profile), serious
congenital defects and intrauterine death.

Procedures, recruitment, randomisation and collection of
data
The research nurse and/or the staff of participating hospi­
tals will identify eligible women. After the patient has
given informed consent for participation in the study, she
is randomised using an internet-based procedure. Ran­
domisation is 1:1 for nifedipine or placebo.

At study entry baseline demographics, obstetric and med­
ical history are recorded. For post-hoc analysis on a subset
of women, at study entry cervical length is measured by
transvaginal ultrasound and a vaginal swab is taken for
fibronectin testing. Fibronectin will not be tested in
women with ruptured membranes, more than 3 cm dila­
tation or vaginal bleeding. Fibronectin swabs are stored
and analyzed after the patient has delivered. All data are
collected, coded and processed with adequate precautions
to ensure patient confidentiality.

Interventions
Patients are allocated to nifedipine or placebo for twelve
days. Start of study medication is 48 hours after start of
the initial tocolysis. Initial tocolysis is provided according
to local protocol, usually this will be Nifedipine or Atosiban.
Study medication consists of 20 milligrams nifedipine
every six hours, administered orally, resulting in a total
daily dose of 80 milligrams, or placebo. The medication is
phased out from day 10 (total daily dose 60 milligrams
nifedipine) till day 12 (total daily dose 20 milligrams
nifedipine) and discontinued on day 13.

After randomisation the medication package is stored by
the patient herself. The administration of the study med­i­
cation is noted in a schedule that is kept both by the
patient and in her medical record. Non-compliance is
defined as a delay in administration of study medication
of more than 6 hours.

Follow up of women and infants
All details of delivery, maternal assessments and admis­
sions during pregnancy are recorded in an electronic case
report form (CRF). Details of neonatal admissions are
also recorded. Long-term follow up of children is depend­
ing on future funding.

Outcome measures
The primary outcome measure is neonatal mortality and
a composite of neonatal morbidity. The composite mor­
bidity rate contains chronic lung disease, severe intraven­
tricular haemorrhage more than grade 2, periventricular
leucomalacia more than grade 1, proven sepsis and necr­
otising enterocolitis at six months after birth.

Secondary outcome measures are gestational age at deliv­
ery, birth weight, days on supported ventilation and addi­
tional oxygen, length of admission in neonatal intensive
 care, total days in hospital until three months corrected
age and costs. Moreover, we will compare the number of
days that each neonate surpasses outside the hospital
within the first 6 months after the calculated term date.

Statistical issues
Sample size
The sample size is calculated based on an 11% reduction
in the primary outcome 'composite neonatal morbidity',

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(48 hours from calculated term date). We assume that
9% of neonates will die or have a composite of morbid­
ity and set this as the null hypothesis. With at least 400
women in each arm we have 80% power to detect a
11% difference in the perinatal mortality and morbid­
ity rate.
from 25% to 14%. Using a two-sided test with an alpha of 0.05 and a power of 0.80 we have to randomise 406 patients (203 in each arm).

Data analysis
Data will initially be analysed according to the intention-to-treat method. First, the nifedipine and placebo groups will be compared. Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures.

Planned subgroup analysis will be performed to assess the consistency of a treatment effect among various patient characteristics i.e. cervical fibronectin status, presence of ruptured membranes, multiple pregnancy as well as cervical length at study entry. We will test for interaction between these characteristics and treatment effect.

Interim analysis
An interim analysis will be performed after the follow up data of 100 and 200 women have been obtained. The analyses will be done by an independent Data and Safety Monitoring Committee (DSMC) that is not aware of treatment allocation when they judge the data on effectiveness. In case of patients reporting severe side-effects, the DSMC can order to disclose the label of these patients.

Economic evaluation
General considerations
The aim of the economic evaluation is to compare the optimality, in terms of costs and health effects, of maintenance tocolysis with nifedipine versus placebo. As the clinical study is based on a superiority design (it is hypothesized that nifedipine decreases preterm birth), the proper economic evaluation design is a cost-effectiveness analysis (CEA): the optimal strategy will probably be dominant, i.e. better health outcomes and lower costs. The economic evaluation will be performed from a societal perspective.

Cost analysis
The process of care is divided into three cost stages (antenatal stage, delivery/childbirth, postnatal stage) and three cost categories (direct medical costs, direct non-medical costs and indirect costs). For each stage and each cost category, costs are measured as the volumes of resources used multiplied by appropriate valuations (cost-per-unit estimates, fees, national reference prices).

Volumes of health care resource use are measured prospectively alongside the clinical study in all participating centres as part of the CRF.

Valuations of direct medical resources (unit costs) are estimated comprising "true economic" costs, i.e. including shares of fixed costs and hospital overheads. An analysis based on reimbursement fees is added. Direct medical resources used outside the hospital and direct non-medical volumes are valued using national reference prices. Indirect costs are quantified but remain unvalued. Study-specific costs are excluded from analysis.

Ethical consideration
This study has been approved by the ethics committee of the Academic Medical Centre Amsterdam (Ref. no. MEC 07/286) and by the boards of management of all participating hospitals. The trial is registered in the Dutch Trial Register, NTR 1336, http://www.trialregister.nl, date of registration: June 3rd 2008.

Discussion
Preterm birth is responsible for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities [2]. It is also associated with high immediate and long-term costs after discharge from the hospital [3].

To date, it is not clear whether prolonged treatment with nifedipine is effective in reducing adverse perinatal outcome [12,13]. On the one hand, tocolytic maintenance therapy with calcium channel blockers may be beneficial due to its positive effect on gestational age. On the other hand, use of tocolytics is associated with rare but severe side effects on mother and child [14,15]. Moreover, prolongation of pregnancy may also increase the chance for some perinatal complications such as infection.

As far as we know, there are no similar ongoing studies that will report on the subject. Neither the ISRCTN index of trials (UK), nor IMPACT/PSANZ Perinatal Trials Registry (Australian) or NIH Clinical Trial database (USA) report any trials regarding maintenance tocolysis. There is one ongoing study (NIFTY study) registered that compares oral nifedipine with placebo, in women with singleton pregnancies between 24 and 34 weeks, with intact membranes and a positive fibronectin test, in whom a full course of corticosteroids has been completed. Primary outcome is prolongation of pregnancy for at least seven days. Secondary outcomes are duration and number of NICU admissions, and maternal and neonatal hospital costs. In this study, the sample size needed to detect a difference in neonatal morbidity or mortality between the groups was not calculated.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JAP, FKL and BWJM were involved in conception and design of the study. CR, JAP, FKL, BWJM, MEAS and HCJS drafted the manuscript. All authors mentioned in the
manuscript are members of the APOSTEL II study group. They participated in the design of the study during several meetings and are local investigators in the participating centres. All authors edited the manuscript and read and approved the final draft.

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References

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