Assessment of Perinatal Outcome after Sustained Tocolysis for Early Labour (APOSTEL)

Summary

AIM/PROBLEM: In the western world, preterm birth is responsible for more than 80% of all neonatal deaths and 50% of childhood neurological disabilities. In women at a gestational age of less than 32 weeks in whom preterm labour is threatening, there is no discussion about the effectiveness of 48 hours of tocolytic treatment and steroid administration in reducing neonatal adverse outcome. When this policy is applied, 75% of the initially treated women remain undelivered after 48 hours. After the initial 48 hours standard tocolytic treatment, these women remain at risk for going into labour prematurely. At present, it is not clear if prolonged tocolytic treatment is effective in postponing delivery and, if so, whether the effects justify the additional costs of this treatment.

DESIGN: Randomized double-blind placebo-controlled trial performed in all 10 perinatal centres in The Netherlands.

PATIENTS: Women with threatened preterm labour between 24 and 34 weeks gestational age who have been treated for 48 hours with tocolytics and steroids.

INTERVENTIONS: Prior to randomization, all patients will undergo measurement of cervical length and, in case of unruptured membranes, measurement of cervical fibronectin and vaginal examination. All women will then be randomly allocated to receive either the calcium antagonist nifedipine (intervention group) or placebo (control group) for a period of 12 days.

OUTCOME: The main outcome measure will be a composite neonatal morbidity status, including perinatal death, chronic lung disease (CLD), intraventricular hemorrhage (IVH) grade 3 and 4, periventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC) at the calculated term date. Secondary outcomes will be gestational age at delivery, number of days in NICU, and total days in hospital and costs.

POWER/DATA ANALYSIS: The analysis will be by intention to treat. Adverse neonatal outcome will be tested for a difference of 10%. We anticipate that the sum of morbidity and mortality rate in the control group will be 25%. To demonstrate that sustained tocolysis will reduce adverse neonatal outcome from 25% to 15%, we need 400 women (200 per arm) to be randomized (two sided test, beta 0.2 at significance level 0.05).

ECONOMICAL EVALUATION: The economical evaluation will be set up as a cost-effectiveness analysis. Calculation of direct health care costs will be based on such cost items as the number of days in obstetric high care, neonatal intensive care, neonatal high care and total hospital care. Calculation of costs associated with persistent infant morbidity will be estimated after modelling, using literature data.

Samenvatting

Dit placebo gecontroleerde dubbel blinde gerandomiseerde onderzoek zal de vraag beantwoorden of het voortzetten van weeënremming, 48 uur na de start van de primaire
behandeling van dreigende vroeggeboorte, de perinatale uitkomst verbetert. In alle tien perinatologische ziekenhuizen in Nederland worden vrouwen (n=400) die de standaard 2-daagse behandeling hebben ondergaan voor dreigende vroeggeboorte tussen 24 en 32 weken zwangerschapsduur gerandomiseerd toegewezen aan verdere toediening van nifedipine (onderzoeksgroep) of van placebo (controlegroep) gedurende 12 dagen. De primaire uitkomst is samengestelde neonatale morbiditeit (chronische longziekte, necrotiserende enterocolitis, intraventriculaire hersenbloedingen graad 3 en 4, en periventriculaire leukomalacie) en mortaliteit. In een “intention to treat” analyse kan na drie jaar studieduur een afname van 25% naar 10% in slechte neonatale uitkomst uitgesloten worden bij een beta van 0,2 en een alpha van 0.05. We zullen ook de directe kosten berekenen, mede op basis van o.a. dagen ziektenhuiszorg. De kosten verbonden aan blijvende kinderlijke morbiditeit worden geschat aan de hand van literatuurgegevens.
Problem

Preterm birth is responsible for over 50% of all neonatal deaths and childhood neurological morbidity (1-5). It is also associated with high immediate and long-term costs after discharge from the hospital (6,7). Two thirds of the preterm births occur as a result of spontaneous labour or preterm rupture of membranes and receive some form of tocolytic therapy. The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery and declines from 77% at 24-27 weeks to less than 2% at 34 weeks and more. It is also related to whether or not steroids are administrated at least 24-48 hours antenatally and whether or not a woman can be transferred to a tertiary care centre (8-10).

Postponing delivery by tocolysis might improve perinatal outcome because adverse perinatal outcome is associated with early gestational age (3,5,9,11). Postponing delivery for 48 hours with tocolytics is the standard treatment of choice in women with a diagnosis of threatened preterm delivery between 24 and 32 weeks gestational age, 24 weeks being considered the limit of viability (10,12). It is not clear if maintenance therapy with tocolytics beyond 48 hours is effective in reducing either perinatal morbidity or mortality (13,14). Data from the Netherlands and Sweden suggest that a reduction of 1 to 3% in neonatal mortality can be found per day increase of gestational age between 23-30 weeks (9,11).

Given these data it is not surprising that 34% of gynaecologists in Australia and New Zealand tend to use tocolytic maintenance therapy (15). A recent survey amongst Dutch gynaecologists showed that 50% of the NICU centres used some form of tocolytic maintenance therapy. The other half is willing in selected high-risk cases to start 48-hours tocolytic therapy repeatedly. However, the positive effects of prolongation of pregnancy might be counterbalanced by maternal and fetal negative side effects associated with tocolytic therapy (16-18). Maintenance therapy with beta mimetics, for example, is associated with an increase in neonatal periventricular leucomalacia (17). In addition, neither the two systematic reviews included in DARE (19,20) nor the Cochrane systematic review on maintenance tocolysis with terbutaline demonstrated a beneficial effect of tocolytic maintenance therapy (21).

The Dutch guideline on tocolytic therapy (2004) considers two types of tocolytics as first line therapy: the calcium antagonist nifedipine and the intravenously administered oxytocin receptor antagonist atosiban; the ß-agonists are now considered second-choice; cyclooxygenase inhibitors have limited use in very early preterm labor (11). At present, one randomized trial evaluating maintenance tocolysis comparing nifedipine with placebo has been published (22). This is the only trial included in the systematic review of the Cochrane database on this subject (23). Besides the fact that this trial only included 74 patients (37 in each arm) and was not able to rule out an effect on prolongation of pregnancy, randomization was started after using magnesium sulfate as initial tocolysis. Since this is an ineffective tocolytic drug (24), a large number of patients who were not at an increased risk for preterm labour will have been selected for this trial on maintenance tocolysis. Indeed only 11 children born after this trial (6 in the nifedipine arm) were admitted to the neonatal intensive care. No difference in the incidence of preterm birth was found (RR 1.00, 95% confidence interval 0.73 to 1.37). The trial did not report stillbirths and neonatal deaths prior to discharge and neurological follow up of the infants was not addressed. Therefore, no conclusions can be drawn from the results of this trial.

Another study concerning nifedipine maintenance tocolysis randomized 73 patients at a mean gestational age of 32.3 weeks, a time when any beneficial effect in term of neonatal outcome
would be expected to be minimal, for treatment with nifedipine, 80 mg/24 hours, or no treatment (25). Initial tocolysis occurred with beta mimetics and time gained from randomization to delivery was 11 days (27 days in the group treated with nifedipine, 16 days in the group with no treatment, p < 0.007). In the patients randomized before 32 weeks the difference was 23 days (p<0.0001). Intravenous rescue therapy with intravenous ritodrine and verapamil occurred in 54% and 61% of the treatment and no-treatment group respectively (ARR 0.05, 95% confidence interval -0.17 – 0.27, NNT 19).

Maintenance tocolysis with atosiban has been evaluated in one trial recruiting 513 patients to allocate to treatment with either atosiban or placebo. This study showed no effect on neonatal mortality in the patients randomized before 32 weeks (n=285, ARR: 0.01, 95% CI: -0.02 – 0.04). However, this study was restricted to patients with intact membranes and it also allowed the use of rescue therapy with atosiban which was used in a total of 23% and 31% of the patients in the atosiban and placebo group respectively. (26).

The Dutch guideline on tocolytic therapy (2004) considers two types of tocolytics as first line therapy: the calcium antagonist nifedipine and the intravenously administered oxytocin receptor antagonist (11). This is because both are considered safe (26-28), and their use is associated with little side-effects, despite a recent report on nifedipine from a single centre (Free University Amsterdam) of 7 cases of temporary pulmonary oedema (18). A Cochrane systematic review of randomised trials shows that calcium antagonists improve neonatal outcome and delay delivery more effectively than β-agonists (28), while Baysian interpretation of several trials comparing beta agonists versus placebo are consistent with tocolytics reducing perinatal mortality and neurological damage (29). Therefore, nifedipine is likely more effective than placebo in reducing neonatal morbidity. In addition, nifedipine (and atosiban) show considerably less side effects than β-agonists (27). Atosiban is the only formally registered tocolytic drug available but is considerably more expensive than nifedipine and can only be given parenterally.

Postnatal follow-up for nifedipine up to the age of 6 years has shown no negative effect (30), while for atosiban there are no long-term follow up data in children.

Approximately 75% of 1,200 women annually treated in the Netherlands with a diagnosis of threatened preterm labour are still pregnant after the first 48 hours of tocolytic therapy (11,26). These 900 women are eligible for the proposed study. In current daily obstetrical practice, including all patients treated with some form of maintenance tocolysis, two weeks after treatment for preterm labour, approximately 60% of women (~800) will have been delivered (11,26).

In summary, in national and international obstetrical guidelines, no uniform treatment of threatened preterm birth following the generally accepted 48 hours of tocolytic therapy can be found (11, see also 13). On the one hand, tocolytic maintenance therapy with either a calcium channel blocker (nifedipine) or an oxytocin receptor blocker (atosiban) might be beneficial due to prolongation of gestational age, and thereby save costs. On the other hand, use of tocolytics is related to severe side effects for mother and child, and it generates costs (16-18). Maintenance treatment in daily practice has been performed with several different tocolytic agents including betamimetics (21) and calcium channel blockers. Maintenance therapy with atosiban has, thus far, only been applied in trials (26), probably because of the prohibitive costs of such treatment. Until now, the possible beneficial effect of prolonged tocolysis has only been studied to a very limited extent and does not allow any conclusion on effectiveness
in terms of neonatal outcome (13,14). There exists, therefore a large policy problem in women with threatened early preterm labour who have been treated with tocolytics for 48 hours. There is no evidence for the effectiveness of prolonged treatment, but (long-term) childhood consequences after early preterm birth are enormous. As a consequence, about half of the Dutch perinatologists will consider prolonged tocolysis, whereas the other 50% does not. In view of this dilemma, we propose a randomized clinical trial on the possible health benefit of prolonged tocolysis in threatened early preterm labour, as well as an economic analysis.

Relevance
The study will document the additional benefit of tocolytic maintenance therapy over placebo in terms of clinical outcome and costs, i.e. whether its use will reduce perinatal death and/or morbidity and whether the associated costs are in reasonable balance to health gains. Several authors have stressed the urgent need for the proposed study (13, 14). If effective, it might considerably reduce the enormous health care costs associated with early preterm birth and its associated neurological morbidity (6,7). If no effect can be demonstrated the practise of sustained tocolysis can be halted, with consequent reduction of unwanted side-effects and costs (16-18).

The largest effect on child health will be found if there is a reduction in perinatal mortality and serious morbidity. Neonatal morbidity includes severe respiratory distress syndrome (RDS), broncho pulmonal dysplasia (BPD) both associated with chronic lung disease (CLD), intraventricular haemorrhage II B or worse (IVH), periventricular leucomalacia (PVL), necrotizing entercolitis (NEC), sepsis and death before discharge. The prevalence of this composite neonatal outcome is 77%, 35% and 12% in children born after early preterm delivery between 24-27, 28-32 and 32-34 weeks, respectively (Landelijke Neonatale Registratie 2003. Dutch Neonatal Database 2002. Prismant 2002.). After 32 weeks, the incidence sharply declines to less than 2% at term.

As far as we know, there are no similar studies underway that will report on the subject. Neither the ISRCTCN index of trials (UK), nor IMPACT/PSANZ Perinatal Trials Registry (Australiasian) or NIH Clinical Trials database (USA) report any trials regarding this topic. The BORN trial in Australia is recruiting for nifedipine versus nifedipine with the COX2 inhibitor rofecoxib. There is one ongoing study (Nifty study) registered that compares oral nifedipine with placebo. In this study, 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, are randomized to either nifedipine or placebo. The primary aim of this study is to prolong pregnancy for at least seven days compared with placebo. Secondary outcomes are duration and number of NICU admissions, and maternal and neonatal hospital costs. In this study, the sample size is not calculated to detect a difference in neonatal morbidity or mortality between the groups, but only to have a difference in prolongation of pregnancy for at least seven days. For this purpose 100 women need to be randomized.

Approximately 1800 children are born annually between 24 and 32 weeks gestational age in the Netherlands (Dutch perinatal registry). In about 1,200 of these women premature birth occurs after spontaneous labour. After 48 hour treatment with tocolytics, about 75% of these women remain undelivered. Thus, the present study affects 900 patients per year in The Netherlands.
The guideline of the Dutch Society of Obstetrics and Gynaecology on treatment of preterm labour (7) recommends the use of tocolytic therapy but states that no evidence exists for continuation of tocolytics after 48 hours. Thus, the results of the study will provide an answer to the question if the use of tocolytic maintenance therapy in threatened preterm labour will reduce serious perinatal morbidity by 10% or more, and provide a clear fundament to the statement in the national guideline or the rejection of it.

The largest cost difference will be found if tocolytic maintenance therapy indeed reduces serious perinatal morbidity. US data from 1990 show that one week increase in pregnancy duration will spare $10,000, and long-term costs and/or custodial care can easily be over $500,000 per case (7).

If no difference is found, effects on cost are associated with discontinuation of medication, direct costs and absence of rare but serious side effects.

Knowledge transfer
No major obstacles are to be foreseen in knowledge transfer or implementation as the outcome of the proposed study will clearly indicate whether to use tocolytic maintenance therapy in the future or not. The results of the project will be presented in the 'Otterlo' group and the Dutch Society for Obstetrics and Gynaecology (NVOG). As gynaecologists from all Perinatal Centres in The Netherlands are actively participating in the writing of the guidelines for the NVOG, the results of the study should be incorporated in the guidelines soon after publication.

The study will be performed in a consortium of perinatal centers collaborating already on seven protocols in the subprogram 'effects and cost' of 'Doelmatigheidsonderzoek 2004-2007' (http://www.studies-obsgyn.nl/). This will guarantee recruitment of patients, it also implicates that participating level III perinatal centers will be familiar with the study protocol and the results. This is likely to facilitate implementation of the study results. Results will be published in articles and immediately translated into guidelines. Obstetrical guidelines are a national reference for local hospital protocols. So midwives and gynaecologists are likely to follow the guidelines based on the result of the study.

Purpose
To evaluate the effectiveness of tocolytic maintenance therapy for postponing delivery after initial 48-hour tocolytic therapy in women with threatened preterm birth from 24-32 weeks gestational age in terms of:

A. Neonatal mortality and neonatal morbidity i.e. 1. severe respiratory distress syndrome, 2. bronchopulmonary dysplasia 3. severe intraventricular haemorrhage more than grade II 4. periventricular leukomalacia more than grade I 5. proven sepsis 6. necrotizing enterocolitis

B. Birth weight, gestational age at delivery, number of days on additional oxygen, days on supported ventilation, number of days in intensive care, total days in hospital until 3 months corrected age

C. Costs

D. Additional financing for long term follow up will be sought. Although it is the ambition of the projectgroup to evaluate long term outcomes, this aim cannot be obtained within the present application, as the duration of the programm is only three years.
Plan

PRELIMINARY ACTIVITIES BY THE RESEARCH GROUP
In two of the participating centres (VUMC and AMC) a randomized controlled trial comparing the calcium antagonist nifedipine versus ritodrine for initial tocolysis was successfully carried out in the past (16). This trial showed a clear benefit for nifedipine over ritodrine in terms of neonatal outcome. In the trial sustained tocolysis was used up to 34 weeks with no maternal complications for nifedipine. (DIMITRI ACCORD? Aantallen in n poot)

Between November 2006 and January 2007 we have asked patients who were admitted for threatened preterm delivery or patients who had experienced preterm delivery in the past, if they would be prepared to participate in a hypothetical randomized trial with a design as the one proposed in the present study. We confronted 52 patients in seven hospitals with the trial design. There were 26 women who were willing to participate in such a trial, whereas 19 women stated that they would decline randomization. The other seven patients could not make a choice. This means a 50% consent.

The proposed study will be performed within a consortium of all perinatal centres in The Netherlands. At present, six trials are performed in this network. This has resulted in an infrastructure with research nurses in all perinatal centres, a secretarial office for the handling of ethical approval, the use of webbased data-entry, and collaborate analysis (http://www.studies-obsgyn.nl/index.asp).

The APOSTEL trial will study pregnant patients following 48 hours of standard treatment with tocolytics and administration of steroids for threatened preterm labour.

DESIGN
Randomized double-blind multicentre placebo-controlled trial.

PATIENTS
All women with a gestational age between 24 and 31 completed weeks who are spontaneously in labour, and who have been treated for 48 hours with tocolytics, are eligible for the trial. Not eligible are women with signs of intra-uterine infection, determined by local protocol, women whose child has signs of fetal distress (abnormal CTG or biophysical profile) or major congenital malformation, and women with any contraindication for the use of nifedipine or having a maternal disease (severe hypertension, HELLP syndrome, preeclampsia or other) or other reason for delivery. Centres are requested to register all preterm laboring women and reasons for exclusion or non-eligibility in the database.

Prior to randomization, patients will undergo an examination of the cervix with a speculum, at which time a swab will be placed in the posterior vaginal fornix for 10 seconds to absorb cervicovaginal secretions for fibronectin measurement. Fibronectin measurement will not be performed in women with ruptured membranes, more than 3cm dilatation or vaginal bleeding. The swab will be stored, and fibronectin will be measured after the patient has completed the study. Standard bacterial cultures are taken. Moreover, in all women cervical length will be
measured transvaginally. Excluded for randomisation are women with a cervical length more than 30 mm and disclosure less than 10 mm or patients that are participating in the randomized arm of the APOSTEL I study.

**INTERVENTION:**

Eligible women will be randomized by a central randomization system to either tocolytic maintenance therapy with nifedipine in a maximum dosage of 90 mg/24 hours or placebo for the duration of 12 days. Randomization will be done using the Dutch Obstetrical Consortium website and will be stratified for whether or not membranes are ruptured, gestational ages of 24-28 or 28-32 weeks, and parity, with random block sizes of 2, 4 or 6 patients. Commercially available nifedipine tablets and placebo tablets are provided by the Pharmacy of the Academic Medical Centre, Amsterdam in coded opaque boxes with expiration date. The pharmacy already provided nifedipine placebo tablets for a randomized trial concerning external cephalic version (ISRCTN 28715121).

The administration of prophylactic treatment with antibiotics in case of ruptured membranes is to the decision of the attending physician. Every other day, C reactive protein and leukocytes in maternal venous blood sample will be determined, in case of ruptured membranes temperature is taken twice a day. Cardiotocography is done at least once a day and stored. After 12 days, i.e. two weeks of total duration of treatment of threatened preterm labour, tocolytic medication is stopped. The use of further therapy is at the discretion of the attending obstetrician and will be registered. Medication is stopped within the 12 days’ trial medication in case delivery is deemed necessary by the attending clinician, or if serious adverse side effects of the trial medication are suspected. Trial coordinators are available 24 hours a day.

**OUTCOME MEASURE:** The main outcome measure will be a composite poor neonatal outcome status at 40 weeks corrected age, because the incidence of single outcomes is too low for practical trial purposes. The outcome includes severe respiratory distress syndrome (RDS), and chronic lung disease (CLD), intraventricular haemorrhage grade 3 or worse (IVH), periventricular leucomalacia (PVL), necrotizing entercolitis (NEC), and death before discharge. Neonatal outcome will be assessed by neonatologists according definitions in the Dutch perinatal registry and blinded for treatment allocation. Secondary outcomes will be gestational age at delivery, number of days on ventilation support, in neonatal intensive care and total days in hospital.

Moreover, we will register maternal morbidity or complications that might be related to the prolonged use of tocolytics during the study. A Data Monitoring committee blinded for treatment will follow the study for any adverse events and subsequently judge whether the complication is due to the use of tocolytics or not. The study will be terminated if interim analysis shows serious maternal adverse events attributable to the trial medication. Interim analyses are planned after 150 and 300 patients included.

Additional application for long-term follow up of children (2 and 5 years) and mothers will be performed, if additional funding can be obtained.

**SAMPLE SIZE:** A difference in reduction of compound morbidity from 25% to 15%, with a beta-error of .20 and an alpha-error of 0.05 can be detected if 400 patients can be analysed (200 in each arm).
During a previous trial in two perinatal centres (VUMC, AMC) concerning acute tocolysis 40 patients were randomised per centre per year (27). Assuming that 75% of these patients are undelivered after 48 hrs, it means that an average of 30 patients per centre per year can be randomized. For the participating centres this means 300 patients can potentially be randomised each year, thus indicating that 400 patients in 30 months is a reasonable objective. Declarations for participation are attached with this proposal.

Estimated is an incidence of compound morbidity of 25% for the whole group, based on the earlier trial and historical data extracted from the electronic registry from the AMC. The initial analysis will be according to the intention to treat principle. In a second analysis, we will assess the effectiveness of tocolytic maintenance therapy in those women in whom the treatment could be applied according to plan.

Data will be collected using Oracle Clinical Remote Data Capture (RDC). Oracle Clinical RDC is new generation of application system that enables collection and cleanup of clinical trial data using the Internet. By entering trial data directly at the CRO and conducting real-time validation check, we will be able to reduce significantly the time to collect trial data. For detailed information on Oracle RDC, please visit the page of Oracle RDC products (http://www.ctc-g.co.jp/~CTCLS/opd/en/).

The analysis of the randomised clinical trial will be by intention to treat. First, the nifedipine and placebo group will be compared. Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures. Time to delivery will be assessed using Kaplan-Meier curves and Cox proportional hazard analysis. The analysis will be stratified for whether or not membranes are ruptured, gestational age of 24-28 and 28-32 weeks, and parity.

In case of equivalence between outcomes, the analysis will be repeated on a par protocol basis. Subsequently, planned subgroup analysis will be done for cervical fibronectin status as well as cervical length at study entry. We will then use decision analysis to evaluate whether measurement of cervical fibronectin and/or cervical length is helpful in the triage of women undergoing tocolytic maintenance or not.

ECONOMIC EVALUATION: The time horizon for the economic evaluation will be at 40 weeks corrected post-term neonatal age. The cost analysis will be performed from a societal perspective. A distinction will be made between costs of medical interventions (direct costs) and costs resulting from productivity losses (indirect or time costs).

Standardised unit costs will be calculated for all centres based on actual expenses made during the study. Subsequently, unit costs will be applied to resource use as observed in the participating centres. Resource utilisation will be documented using individual patient data in the case record forms. In addition, each woman will be sent a questionnaire for details on indirect costs concerning professional care, transportation costs and productivity loss. Resource unit prices will reflect the unit of staff, materials, equipment, housing, depreciation, and overhead. Productivity loss will be valued using Dutch reference data (hand book of the Dutch health Council). Costs will be expressed in Euro.

On the basis of the earlier trial, we assume that it will be possible to include 400 patients in two years divided over the perinatal centres. This means that after 30 months all patients should have delivered. Subsequently, there is 6 months for data analysis and reporting.

NOTE: In the same program, Dr. Mol is applying for a grant on the potential role of fibronectin and transvaginal sonography in the prevention of unnecessary treatment and transfer in
women with threatened preterm labour (projectnet number 7416). As the present proposal and Dr Mol’s proposal deal with different clinical problems (tailored start of tocolysis in women with threatened preterm labour versus maintenance of tocolysis in women who have been treated for 48 hours), we have chosen to formulate both proposals in different applications. However, we are prepared to make both applications a collaborative effort in case both proposals are granted.

**Systematic review:**

**Search terms**
Calcium channel blockers, calcium antagonists, calcium channel blockers, nifedipine, nicardipine, preterm labour, premature labour.
- Population: Pregnant women who have at least one episode of threatened preterm labour that stopped without delivery.
- Intervention: calcium channel blockers as maintenance therapy by any route and dose given before delivery.
- Comparison: any other tocolytic agent, placebo or no treatment.
- Outcome measures: The main outcome measure will be neonatal and perinatal morbidity or mortality, maternal morbidity, and long term follow-up of children and mothers.
- Methodological filters: none.

**Databases**
- National library of medicine (Medline): http://www.pubmed.nl
- Cochrane Library: http://www.nelh.nhs.uk/cochrane.asp
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts on Reviews and Effectiveness (DARE)
- Cochrane Controlled Trial Register (CCTR)
- Current Controlled Trials (CCT): http://controlled-trials.com/
- ClinicalTrials.gov: http://clinicaltrials.gov/
- NHS Centre for Reviews and Dissemination (CRD): http://agatha.york.ac.uk/welcome.htm

**Selection procedure, validity assessment, results**
Selected were: randomized trials (12). Excluded were articles with quasi randomized trials, animal research, non-english papers.

Only one randomized trial (Carr 1991) concerning maintenance tocolysis comparing nifedipine with no treatment was found with 74 women (37 in each arm). After cessation with intravenous magnesium sulphate patients were randomized to either nifedipine or no treatment. Nifedipine was given 20 mg every 4-6 hours (80-120 mg daily) versus no treatment. No differences were seen for pregnancy prolongation, gestational age at birth, neonatal morbidity or mortality, or maternal readmission for threatened preterm labour. Carr et al.[1] had a study with 76% power to detect a 14-day difference in pregnancy prolongation between maintenance therapy and control group that would be of clinical relevance. The study was underpowered to detect these and other outcomes. The study also did not have a placebo group as control.

Eleven studies were excluded: 10 studies [2-11] because women were randomized for acute tocolytic therapy rather than for maintenance therapy. These studies are included in the Cochrane review “Calcium Channel Blockers for inhibiting preterm labour”(King 2003). One study (El Sayed12) compared one calcium channel blocker (nifedipine) with another calcium channel blocker (diltiazem) and was therefore excluded.

There were no trials comparing calcium channel blockers with alternative tocolytic agents.
There is one ongoing study (Nifty study13) registered who compared oral nifedipine with placebo. In this study women with singleton pregnancies between 24 and 34 weeks, intact membranes and a positive fibronectin test, after completion of a full course corticosteroids are randomized to either nifedipine or placebo. The primary aim of this study is to prolong pregnancy for at least seven days compared with placebo. Secondary outcomes are duration and number of NICU admissions and, maternal and neonatal hospital costs.

Groups size is not calculated to detect a difference in neonatal morbidity or mortality between the groups, but only to have a difference in prolongation of pregnancy for at least seven days. Therefore a trial is warranted to see if maintenance therapy with nifedipine compared with placebo is associated with a lower neonatal morbidity in the management of threatened early preterm labour.

Additional data sources: Dutch Perinatal Registry

References


Personal Communication

Expertise
Prof Dr FK Lotgering: Is head of the Department of Obstetrics in the Radboud University Nijmegen Medical Centre. His expertise is maternal hemodynamics, foetal monitoring, foetal brain damage, physical exercise in pregnancy, electronic record keeping. Current projects: cervical ripening in early and normal delivery, and development of neurological damage in the foetus.

He is Member of the American Physiological Society; Member of the Society for Gynecologic Investigation; Member of the Society for Maternal-Fetal Medicine, and Member of the Dutch Society of Obstetrics and Gynaecology and several of its working groups.

Dr AC Bolte: Is clinical director of the department of obstetrics and gynaecology at the VUMC and has led several randomised trials in pregnant patients e.g concerning parenteral hypertensive treatment.

Dr DNM Papatsonis: Is a gynaecologist with special interest in obstetrics. His thesis was on nifedipine as tocolytic agent in preterm labour. He is (co)author of two Cochrane systematic reviews on this subject and about 15 publications in peer reviewed journals. He is participating in several RCT's in obstetrics.

Dr BWJ Mol: Has been involved in many projects in the field of Obstetrics and Gynaecology, and is (co-) author of >150 international publications. His thesis, which focussed on the evaluation of diagnostic and prognostic tests in subfertility, was awarded with the Jan Swammerdam prize. In the field of reproductive medicine, he published papers on the cost-effectiveness of IVF and on the work-up for tubal pathology. Moreover, he has an interest in the methodology of diagnostic test evaluation. Over the last three years, he has supervised four doctorates. For 2006 and 2007, five more PhD students will finish their projects successfully.

In 2006, he has complete the OFO-project, a nationwide study that evaluated the effectiveness and cost-effectiveness of the basic fertility work-up. In this study, which is supported by ZON-MW, about 40 fertility clinics in The Netherlands are collaborating. This has resulted in the formation of a large cohort of 6,000 subfertile couples, and several multicenter trials. The study has > 20 planned publications, with the key paper published in The Lancet (2006;368:216-21).

He was instrumental in founding a Dutch consortium of obstetricians that cooperates in performing studies in perinatology. At present, six large multicenters studies are running in the Consortium.

A study proposal entitled: Use of probabilistic decision rules in Obstetrics and Gynaecology was granted in the VIDI program of ZonMw, The Netherlands.

Other work in progress concerns randomized clinical trials in obstetrics and benign gynaecology, meta-analyses on the prediction of pre-eclampsia, breech delivery, diagnostic testing for tubal patency and diabetes gravidarum.

Prof Dr JAM van der Post: Is head of the department of obstetrics in the AMC and his main research focus is high risk pregnancy. His thesis dealt with pathophysiology of pre-eclampsia. He is currently involved in management of the Perinatal Research Unit, a collaborative initiative from the departments of obstetrics and neonatology for the monitoring of multicenter clinical studies, and a Consortium of perinatal centers in the Netherlands. Work in progress concerns genetics and early diagnosis of pre-eclampsia, external version for breech presentation (RCT) and treatment of recurrent abortion (RCT), the value of the intrauterine pressure catheter (IUPC) trial (RCT).
Publications
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