Management of breech presentation: external cephalic version with tocolysis: a multi-centre randomised controlled trial

Study protocol

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Academisch Medisch Centrum
External cephalic version with tocolysis
Proposal summary

Research question
For women with a singleton at term fetus in breech presentation, what is the success rate of external cephalic version (ECV) with a calcium antagonist nifedipine compared to version without medication?

Background
Breech presentation occurs in 3-4% of the at term pregnancies(1). Breech presentation is associated with higher neonatal mortality and morbidity compared to cephalic presentation. One reason is the higher incidence of congenital anomalies for the breech presenting fetus(2), breech delivery is also associated with higher short-term neonatal morbidity and mortality. A large multicentre RCT was published two years ago(3). According to this trial the fetus is better off with a primary caesarean section in terms of morbidity and mortality. Therefore, after this trial the number of caesarean sections (CS) on breech presentation is rising. The national CS rate has risen from 45% to 85%. Consequences of a higher CS rate: increased maternal morbidity, longer hospital admission and future consequences for the next pregnancy (hospital delivery and probably higher perinatal morbidity and mortality due to uterus rupture).

ECV without tocolysis after 36 weeks of gestation can reduce the breech presentation by 41%. ECV with tocolysis is more successful and has a success rate of 57%(4). Currently used tocolytics have maternal cardiovascular side-effects in terms of flushing and palpitations and therefore seldom used in clinical practice. A new tocolytic nifedipine, a calcium antagonist exists which has significant less side effects(5).

Research design
The proposed research is a multi-centre randomised double-blinded placebo controlled trial of ECV with tocolysis. This is an effectiveness trial that will be carried out by physicians and midwives who have experience in the ECV manoeuvre.

Selection criteria
Inclusion criteria: live singleton at term fetus in breech presentation. Exclusion criteria: 1. contraindications to labour or vaginal birth, 2. any contraindication to ECV, 3. contra-indications for nifedipine.

Randomisation
Women who meet the eligibility criteria will be randomly assigned to two categories: version with nifedipine or version with a placebo with stratification by centre and parity. Randomisation will be controlled by the pharmacy of the AMC.

Outcomes
The primary outcome is the number of cephalic presentations at birth in each category. Secondary outcomes include: 1. caesarean section rate, 2. fetal complications, 3. maternal complications.

Sample size
To be able to show a difference of 17% between the two tocolytics with a power of 80% we will need 146 participants in each arm. So the total sample size is 292.
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External cephalic version with tocolysis
RESEARCH PROPOSAL

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1.0 Background

1.1 scope of the problem

Breech presentation occurs in 3-4% of the at term pregnancies (1). Breech presentation is associated with more neonatal mortality and morbidity compared to cephalic presentation. One reason is the higher incidence of congenital anomalies for the breech presenting fetus (6), otherwise the breech delivery is associated with higher neonatal morbidity and mortality. The Term Breech Trial, a large multicentre RCT investigated these adverse outcomes of the vaginal delivery of the at term breech fetus (3). According to this trial the fetus is better off with a primary caesarean section in terms of morbidity and mortality (relative risk 0.33 [95% CI 0.19-0.56]; p<0.0001). As could be expected, after this trial the number of caesarean sections on breech presentation is rising. The CS rate in the AMC has risen from 42% to 85%. More caesarean sections will have consequences for the mother and for a possible second child.

ECV without tocolysis after 36 weeks of gestation can reduce the breech presentation by 41%. ECV with tocolysis enhances the success rate of the version attempt by almost 40% (from 41% to 57%) (4). Current used tocolytics have maternal cardiovascular side-effects in terms of flushing and palpitations. Alternative tocolytics have been developed, but they are not tested yet for this purpose.

1.2 maternal and fetal consequences of CS

Given the higher incidence in serious neonatal morbidity and mortality after vaginal delivery of the breech presenting fetus the primary CS rate is rising. This will have consequences for mother and child:

Short term: hospital admission of at least 4 days, higher maternal morbidity and mortality.

Long term: consequences for the next pregnancy in terms of higher incidence of placenta previa and uterine rupture.

A retrospective cohort analysis from 1987 through 1996 with a total of 20,095 women showed that uterine rupture was more likely among women with spontaneous onset of labour (relative risk, 3.3; 95 percent confidence interval, 1.8 to 6.0) (7). A higher risk for uterine rupture in the next pregnancy means a higher risk for neonatal morbidity and mortality for the next child. Observed neonatal death in this study was 0.5% in the group without uterine rupture (100 out of 20,004) and 5.5% in the ruptured uterus group (5 out of 91). So, preventing serious morbidity and mortality for the first child can have harmful consequences for the next.

A meta-analysis of 36 studies with a total population of 3.7 million pregnant women showed a RR of 2.6, 95% CI [2.3-3.0] for placenta previa for the next pregnancy for women with at least one prior caesarean delivery (8). A placenta praevia is not without obstetric risks and affects the perinatal outcome. A retrospective cohort study of 78,524 deliveries of which 298 were complicated by a placenta previa showed for example an increased risk of second-trimester bleeding (OR 156.0, 95% CI [87.2-277.5]), abruptio placentae (OR 13.1, 95% CI 8.2-20.7), perinatal mortality (OR 2.6, 95% CI 1.1-5.6), perinatal apgar scores at 5 min lower than 7 (OR 4.4, 95% CI 2.3-8.3) and post partum hemorrhage (OR 3.8, 95% CI 1.2-10.5) (9).
1.3 ECV to reduce breech presentation

1.3.1 ECV at term without tocolysis

ECV at term is considered as an effective method to reduce the number of breech presentations. ECV without tocolysis after 36 weeks of gestation can reduce the breech presentation by 41%(10).

1.3.2 ECV at term with tocolysis

Various studies have investigated the use of tocolytics and the effect on the success rate of the ECV procedure. ECV with tocolysis can enhance the success rate with 40% (from 43% to 59% [RR 0.74 95% CI 0.64-0.87]) (10). The kinds of tocolytics currently available are the betamimetics, calcium antagonists, nitrates and oxytocin antagonists.

The most widespread used tocolytics are the betamimetics and most data we have about the success rates of ECV with tocolysis are with this group of medicines. There is however a high incidence in maternal discomfort due to the cardiovascular side-effects of these agents.

Calcium antagonists like nifedipine have been studied for the use as a tocolytic to prevent preterm labour. It is proven to be equally effective in inhibiting pre term labour for the first 48 hours compared to beta mimetics (RR 0.80 [0.61-1.05]), but significantly less participants discontinued treatment because of side effects (0.2% vs 7% RR 0.14 [0.05-0.36]) (5). No studies so far have been done to evaluate the use of nifedipine in ECV.

Glyceryl trinitrate has recently come to the attention as a potent uterus relaxant. Thus far one RCT investigated the use of glyceryl trinitrate spray for ECV (11). There were no significant differences found between placebo and treatment group. The numbers studied in this trial however were too small for meaningful statistical analysis. As for maternal discomfort there was also no statistical difference, 9/30 in treatment group and 7/21 in placebo group (RR 0.90 [0.4-2.03]).

The most recently developed tocolytic is the oxytocin antagonist atosiban. A number of studies have been done to evaluate the potency to prevent pre term labour. A Canadian double-blind randomised controlled trial of atosiban (n = 128) versus ritodrine (n = 124) showed equally effectiveness, but atosiban was better tolerated. The incidence of maternal cardiovascular side effects was substantially lower in the atosiban group (4.0% vs 84.3%, p<0.001) (12). No trials for the use with ECV have been expedited.

Table 1. Summary of Term ECV Trials using tocolysis vs placebo: effect on success rate

<table>
<thead>
<tr>
<th>Author, date, Tocolytic regime</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails using terbutaline</td>
<td></td>
</tr>
<tr>
<td>Fernandez 1997(13) Terbutaline: 0.25 mg sc, 15-30 min prior to ECV Conclusion: increased succes rate of ECV</td>
<td>n=52 52% successful version n=51 27% successful version</td>
</tr>
<tr>
<td>Trails using salbutamol</td>
<td></td>
</tr>
<tr>
<td>Tan 1989(14) Salbutamol 4mg orally three times a day for at least one day or Salbutamol IV until maternal HR &gt; 100 bpm Conclusion: no significant increase in success rate</td>
<td>n=30 50% successful version n=30 40% successful version</td>
</tr>
</tbody>
</table>

| Trial using ritodrine          |          |

Robertson 1987(15)  
Ritodrine IV 200 μg/min for 20 min prior to ECV  
Conclusion: tocolysis did not increase success rate  
n=30  
67% successful version  
n=28  
68% successful version

Stock 1993(16)  
Ritodrine IV 0.3 mg/min for 30 min prior to ECV  
Conclusion: no significant increase in success rate  
n=21  
67% successful version  
n=25  
43% successful version

Marquette 1996(17)  
Ritodrine IV 111 μg/min ≥ 20 min prior to ECV  
Conclusion: improved success rate in nulliparous women   
n=138  
52% successful version  
n=145  
42% successful version

Chung 1996(18)  
Ritodrine IV 0.4 mg/ml at 1.5 ml/min for 15 min prior to ECV; increased by steps of 200 μg if contractions interfering  
Conclusion: improved success rate in nulliparous women and where doctors are learning  
n=25  
52% successful version  
n=25  
28% successful version

Trials using hexoprenaline

Stock 1993(16)  
Hexoprenaline IV 10 μg 5 min prior to ECV  
Conclusion: significant improved success rate  
n=21  
76% successful version  
n=21  
43% successful version

Trials using glyceryl trinitrate

Yanni 2000(11)  
Glyceryl trinitrate sublingual spray 800 μg  
Conclusion: no significant increase in success rate  
n=31  
29% successful version  
n=26  
12% successful version

Table 2. Summary of Term ECV Trials using tocolysis vs placebo: effect on CS rate

<table>
<thead>
<tr>
<th>Author, date</th>
<th>Tocolytic used</th>
<th>outcomes</th>
<th>ECV with tocolysis</th>
<th>ECV with placebo</th>
</tr>
</thead>
</table>
| Fernandez 1997(13) | Terbutaline: 0.25 mg sc, 15-30 min prior to ECV  
Conclusion: tocolysis decreases CS rate | n=52        | 57% CS             | n=51              | 76% CS           |
| Marquette 1996(17)| Ritodrine IV 111 μg/min ≥ 20 min prior to ECV  
Conclusion: tocolysis decreases CS rate | n=138       | 55% CS             | n=145             | 65% CS           |
| Robertson 1987(15)| Ritodrine IV 200 μg/min for 20 min prior to ECV  
Conclusion: tocolysis did not lower CS rate | n=30        | 26% CS             | n=28              | 18% CS           |

1.3.3 fetal risks associated with ECV

The risks associated with the procedure are minimal when there are strict inclusion criteria and fetal monitoring with ultra sound and fetal heart rate registration takes place.

In a series on fetal complications associated with ECV in a total of 2,601 attempts no occurrences of fetal death have been reported. However, two stillbirths have been reported. The first in a fetus with an already abnormal heartrate before the procedure and one placental abruption 20 hours after a failed version attempt(19).

In a review of studies in which a Kleihauer-Betke test was performed in a total of 664 tests performed in 16 the test was positive (2.4%, 95% CI [1.4-3.9]). A positive test result however was not associated with adverse perinatal outcome(19).

Emergency delivery following the procedure occurred in 5 cases out of 3,151 attempts (0.2%). No adverse neonatal outcome was reported(19).
1.4 Why a RCT of ECV with a calcium antagonist

There is enough evidence that shows that external cephalic version at term is effective and reduces the caesarean section rate. It is also known that ECV with tocolysis is even more successful. Furthermore, caesarean section rates are rising after the publication of the results of the Term Breech Trial, therefore it is becoming more important to reduce the number of breech presentations before delivery.

ECV is a safe procedure with minimal fetal complications. On the other hand, most tocolytics used have a high incidence of maternal cardiovascular side effects and are therefore seldom used in clinical practice. Currently there is a new tocolytic nifedipine, known for its effectiveness in inhibiting preterm labour, which has not yet been tested for the use of ECV. Compared to betamimetics it has significant less cardiovascular side effects and is easier to administrate.

The proposed trial will be a collaborative project of practising midwives and physicians. The selection criteria for entry to the study will ensure that only those women who are most likely to benefit from ECV will be included.
2.0 protocol

2.1 research questions

2.1.1 primary research question

For women with a singleton at term fetus in presentation, what is the success rate of ECV with tocolysis with a calcium antagonist?

2.1.2 other research questions

1. Is there a difference in caesarean section rate of ECV with tocolysis with a calcium antagonist compared to placebo?
2. Is there a difference in the incidence of fetal complications of ECV with tocolysis with a calcium antagonist compared to placebo?
3. Is there a difference in the incidence of maternal complications of ECV with tocolysis with a calcium antagonist compared to placebo?

2.2 study design: double-blind randomised controlled trial

Women who meet the eligibility criteria will be randomly assigned to two arms: A ECV with nifedipine, B ECV with placebo. Stratification by centre and parity. Randomisation will be controlled by the pharmacy. All participants will receive a capsule containing 10 mg nifedipine or a placebo 30 and 15 minutes prior to ECV.

2.3 Selection criteria for participants

2.3.1 inclusion criteria

1. Live singleton fetus
2. Breech presentation
3. Gestational age > 36 weeks

2.3.2 exclusion criteria

1. any contraindication to labour or vaginal birth (e.g. placenta previa)
2. any contraindication for version (e.g. scar uterus, uterine anomaly, abruptio placenta, pre-eclampsia, blood loss, placenta previa, ruptured membranes, anhydramnios, IUGR)

2.4 selection criteria for clinicians

Clinicians undertaking ECV in this study must be either qualified physicians or midwives or physicians in training. To ensure competency and to uniform the used method all participating clinicians will attend a demonstration of ECV by an experienced physician. Competency will be classified by categorisation of the expertise into number of versions done a year.
2.5 manoeuvre

2.5.1 prior to randomisation

Women with life singleton fetuses in breech presentation will be identified from 36 weeks’ gestation and the study will be explained to them. If they wish to participate in the study an ultrasound will be scheduled. This ultrasound should provide the following information: a description of the position of the fetus including identification of type of breech (frank, complete or footling); a detailed description of placental location; an estimate of fetal weight; an estimate of amniotic fluid volume including the measurement of the largest pocket depth; and identification of fetal anomalies. Eligible women will give informed consent prior to randomisation. After collecting baseline information and consenting randomisation will take place.

2.5.2 flowchart

2.5.3 timing of randomisation

After inclusion and consenting participants will be randomly allocated to each of the two arms of treatment. Randomisation will be controlled by the pharmacy. There will be stratified by centre and for parity.

2.5.4 External Cephalic Version

ECV will be initiated between 36 and 38 weeks’ gestation in a clinical setting. Immediately prior to the ECV procedure, the woman will be reassessed to ensure she is still eligible for ECV.

The ECV procedure will be undertaken by experienced clinicians.

Prior to beginning the procedure Fetal presentation will be confirmed by using an ultrasound. This ultrasound will be used along with clinical assessments to determine any contraindications to ECV prior to each procedure. Before initiating the ECV manoeuvre, the maternal bladder should be emptied, the procedure should be explained again to the woman, and the fetus should be palpated to assess the fetal position.

Tocolysis. Half an hour and 15 minutes before ECV participants receive a capsule which will be a placebo or will contain 10 mg of nifedipine.
Description of the procedure  The procedure begins with the woman lying comfortable on her back with legs slightly flexed at the knee. Arms should be extended and lying along side the woman in order to enhance abdominal relaxation. The clinician begins by palpating the fetus to ascertain the position of the cephalic pole and fetal back. The next step involves lifting the breech out of the pelvis and to one side, usually on the side opposite the cephalic pole. When the fetus has been manoeuvred out of the pelvis, it is often useful to have a second attendant supports the breech pole in that position, thereby minimising the likelihood of the breech returning to the pelvic area. The fetus will usually version most easily in a forward somersault. Once the breech has been successfully dislodged from the pelvic basin, the clinician will encourage the fetal head downward toward the pelvis. The fetus should respond to firm but gentle pressure by moving through the uterine midpoint and into a cephalic presentation. Follow up palpation should be done to confirm that the fetus has moved into a cephalic presentation, and not merely returned to its previous presentation. Fetal well being will be monitored intermittently during the ECV attempt using either auscultation or ultrasound viewing of fetal heart activity.

Duration of the procedure  When undertaking the ECV manoeuvre, the practitioner may pause for varying periods of time, to assess the fetal heart sounds, to allow the mother to relax her abdominal muscles, or to allow the fetus to settle into the new position. Because of the breaks in the procedure, the total time for the procedure will vary. However, the total time spent in the actual manipulation of the fetus (that is, the time putting pressure on the fetus to move or change its position) during any one attempt should not exceed 5 minutes.

Unsuccessful attempts  A repeat version with tocolysis will be carried out in the secondary tocolysis group according to the previous described methods. For the primary tocolysis group a second attempt is not allowed so only the results of the first attempt will be used in this study.

Rhesus negative women  Because Rhesus sensibilisation is a risk of ECV, non-sensitised Rhesus negative women will be provided with anti-D immunoglobulin following the ECV procedure.
2.6 outcomes

2.6.1 primary outcome: number of cephalic presentations after ECV with tocolysis

Various randomised controlled trials have established that both ECV with and without tocolysis is successful with minimal fetal complications. For the used new tocolytic the success rate is not yet specified. Thus the primary outcome is the number of cephalic presentations at delivery after ECV with tocolysis with nifedipine.

2.6.2 other outcomes

1. Caesarean section rate in each arm.
2. Serious neonatal complications: serious neonatal complications will be defined as one or more of the following:
   a) Fetal bradycardia
   b) Feto-maternal haemorrhage
   c) Ruptured membranes
   d) Prolapsed umbilical cord
   e) Placental abruption
3. Maternal complications: maternal complications will be defined as one or more of the following:
   a) Palpitations
   b) Flushing
   c) Hypotension

2.7 Methodologic issues

2.7.1 Compliance

Collected data will be reviewed to ensure patients are included only after they met all inclusion criteria. Centres with persisting poor compliance will be excluded from this trial.

2.7.2 Losses to follow-up

Women enrolled in the trial will be followed from 37 weeks’ gestation to delivery. It is unlikely that women will move unexpectedly during this period of time. If women know they will move to a non-trial centre prior to delivery, they will not be invited to participate. Every effort will be made to obtain all outcome information on all women enrolled in the study.

2.7.3 Generalizability

It is anticipated that a high percentage of the midwifery clientele who meet the eligibility criteria will participate in the study. This should enhance the degree of Generalizability. It will not be feasible to collect information on non-randomised eligible women.
2.8 Sample size and justification of sample size

From the Cochrane analysis of ECV with tocolysis we expect a success rate of 40% in the placebo group and tocolysis should yield a success rate of 57%. To be able to show this difference with a power of 80% we need 146 participants in each arm. Thus we need to enrol a total of 292 participants to be able to carry out statistical meaningful analysis.

2.9 Statistical analysis

2.9.1 Interim analysis

A safety monitoring committee will be installed which will perform an interim analysis after the inclusion of each 25 patients to guard trial quality and to anticipate on serious adverse events and superior effectiveness.

2.9.2 Final analysis

The incidence of non-cephalic presentation at birth, fetal and maternal complications and caesarean section rates in the two groups will be compared using Chi-square analyses. If there are differences in potential confounding variables between groups these will be controlled for in a multivariate logistic regression analysis. A p value of < 0.05 will indicate statistical significance for the comparison between groups.

2.10 Ethics

Women will be informed about the study when a breech presentation is noted from 36 weeks of gestation by their attending physician. The risks and benefits will be explained to them and eligible women will be invited to participate. In practice already women with a near term breech presented child will be offered an ECV attempt. As in this study different clinics have different approaches of ECV: some hospitals offer women primary tocolysis while other perform ECV only without tocolytics or use a tocolytic after failure of the first attempt. Therefore this study is not in variance with reality.

Entry to the study will be contingent upon women of age understanding the study and agreeing to participate. Before being entered into the study, women will be asked to sign an informed consent form. All women will continue to receive their usual prenatal care from their chosen care provider. A woman’s choice around study participation will not in any way influence her ongoing prenatal care. All information obtained in the trial will remain confidential.

2.11 Electronic data management and data validation

The baseline data and procedure related data will be collected directly by the clinicians involved in the trial. The data from the hospital birth record will be collected at each participating site. In the case of home births, midwives in attendance will be asked to complete the birth data form.

Data will be collected with an electronic CRF. The electronic CRF will store all data in a file which will be sent to a central database through the browser used for this study: www.stuitonderzoek.nl. All data are protected during transmission as they will be sent in an encrypted file of which only the researchers have the key. Data will be stored in an MySQL
database and transferred to an SPSS database with which statistical analysis will be carried out.
APPENDIX 1: Informed consent form

Uitwendige versie met nifedipine: een dubbel blind gerandomiseerd placebo gecontroleerd onderzoek.

De heer/mevrouw ________________________________ ,

heeft mij schriftelijk en mondeling ingelicht over de aard, het doel, de procedure en de consequenties van dit klinische onderzoek. Ik ben geïnformeerd over mijn rechten tijdens dit onderzoek. Al mijn vragen zijn naar tevredenheid beantwoord.

Ik geef toestemming voor deelname aan dit onderzoek.

Ik ga er wel / niet (doorstrepen wat niet van toepassing is) mee akkoord dat medewerkers van de studie in de toekomst eventueel contact met mij zullen onderhouden gedurende de eerste jaren na de bevalling om het kind op een aantal momenten te beoordelen met een eenvoudige ontwikkelingstest.

Ik wil wel / niet (doorstrepen wat niet van toepassing is) geïnformeerd worden over de uiteindelijke uitslag van deze studie.

Ik kan mijn toestemming en deelname aan dit onderzoek te allen tijde intrekken zonder dat dit op enige wijze nadelige gevolgen voor mijn behandeling heeft.

Amsterdam,

Datum

Handtekening patiënt Handtekening arts
Reference List

(1) Hickok DE, Gordon DC, Milberg JA, Williams MA, Daling JR. The frequency of breech presentation by gestational age at birth: a large population-based study


(5) King JF, Flenady VJ, Papatsonis DN, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour


