Increasing the effectiveness of external cephalic version

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Chapter 9

Summary, general discussion and future perspectives
The work presented in this thesis focuses on improvement of care for women with a fetus in breech presentation at term in order to improve both neonatal and maternal outcome. Nowadays, the dominant mode of delivery for breech presentation is elective caesarean delivery in most countries. As a consequence, breech presentation is the third most common indication for caesarean delivery.\textsuperscript{1} External cephalic version (ECV) is a safe obstetrical procedure that reduces non-cephalic birth and caesarean delivery by approximately 50%.\textsuperscript{2} Implementation varies widely and is between 18% and 72%. In 2015, the World Health Organization reported on the global overuse of caesarean delivery, leading to increased maternal morbidity and risk of mortality due to caesarean sections.\textsuperscript{3} Improving the effectiveness and implementation rate of ECV can highly contribute to the goal to reduce elective caesarean deliveries.

First, we summarize the subject and main findings for each chapter. Subsequently we will discuss novel insights, clinical interpretation, implications for daily practice, and recommendations for further research.
Summary

The introduction (chapter 1) gives an outline of the specific research questions addressed in this thesis. Even though there is an ongoing scientific discussion about the safety of vaginal breech delivery, the clinicians’ and patients’ choice is unambiguous. Since publication of the Term Breech Trial, caesarean delivery rates for breech increased worldwide and, in several countries, even up to 95%. ECV is proven to be effective in reducing breech presentation at birth (pooled RR 0.42, 95% CI 0.29 to 0.61) and thereby the associated caesarean deliveries and thus contributes to reduction of adverse maternal and neonatal outcome during current or subsequent delivery. Several tocolytic agents are used to enhance the outcome of ECV. Their mode of action differs with respect to on which uterine myocyte receptor they act and the majority of studies used beta-mimetics. Meta-analysis demonstrated that beta-mimetics can enhance the ECV success rate compared with placebo (nine studies, pooled RR 1.6, 95% CI 1.2 to 2.0). However, beta-mimetics have more prominent maternal cardiovascular side effects (e.g. flushing, chest pain and palpitations) in comparison with other uterine relaxants and as a result the implementation of its use for routine uterine relaxation is low. Alternative tocolytic agents with less side effects could be useful to increase uptake by patients and professionals. Comparing different tocolytic agents on effectiveness and side effects is an important step to improve clinical practice. In addition, it has to be explored whether tocolytic agents should be offered routinely or if we can distinguish subgroups who benefit in a greater or lesser extent.

Moxibustion therapy is another method asked for by women to prevent breech presentation. Its mode of action is not based on regular medical theoretical principles. A recent published Cochrane review in 2012 found limited evidence to support the beneficial effect of moxibustion, applied alone or in combination with acupuncture or postural measures, compared to observation alone or postural measures. However, this review did not distinguish between studies offering ECV.

In general, when counseling women on the treatment options for breech presentation, an individual a priori chance of success estimate can be helpful. Several prediction models are available and carefully assessing their quality is needed before implementing in clinical practice. Also, women may be at increased risk for caesarean delivery after successful ECV compared to women with a spontaneous cephalic presentation.

In chapter 2 we presented the results of a randomized controlled trial (RCT) in which we assessed the effectiveness of atosiban or fenoterol as uterine relaxant for ECV. We performed a multicenter, open label, RCT in eight hospitals in the Netherlands. Women with a singleton fetus in breech presentation were randomly allocated to either 6.75 mg
atosiban (n=416) or 40 μg fenoterol (n=414) for uterine relaxation. The primary outcome, cephalic position 30 minutes after ECV, occurred significantly less in the atosiban group than in the fenoterol group (34% v 40%, RR 0.73, 95% CI 0.55 to 0.93). Cephalic presentation at birth and caesarean delivery occurred less often in the atosiban group than in the fenoterol group, though not significantly. No significant differences were found in maternal outcome, neonatal outcomes or drug related adverse events.

The RCT revealed important information regarding two specific tocolytic agents for uterine relaxation for ECV. As there are multiple classes of tocolytic agents, we performed a systematic review and network meta-analysis to determine the most effective therapy. A network meta-analysis allows us to combine both direct (available with standard pairwise meta-analysis) and indirect comparisons. Combining them maximizes existing information and contributes to a more precise estimate of the outcome. This study is presented in chapter 3. We identified 18 RCTs on 4 tocolytic agents. We found that, compared to placebo, beta-mimetics were the only tocolytic agents to increase ECV success rate (RR 1.6, 95% CI 1.28 to 2.0). Beta-mimetics had the highest probability (77.5%) of being ranked the best treatment option and had a mean rank of 1.2 for successful ECV.

The results of the systematic review on the effectiveness of moxibustion alone or in combination with acupuncture as a complementary treatment for prevention of breech presentation are described in chapter 4. We identified 13 trials examining 2,555 women and cephalic presentation after moxibustion treatment occurred more in the moxibustion group compared to routine care (RR 2.8, 95% CI 1.6 to 4.7, I² 74%). In studies offering ECV to all women in case of persisting breech presentation after moxibustion, neither cephalic presentation at delivery (RR 1.11, 95% CI 0.96 to 1.28, I² 10%) nor caesarean delivery differed significantly (RR 1.01, 95% CI 0.82 to 1.20, I² 21%).

In chapter 5 we presented the results of a secondary analysis of our RCT presented in chapter 2. In this chapter we aimed to look for a clinical marker or a set of clinical markers to determine who benefits most from tocolysis with atosiban or fenoterol for ECV. Among the studied markers nine of them showed a statistically significant association with successful ECV. Multiparity, higher gestational age, higher estimated fetal weight, higher Amniotic Fluid Index and presence of relaxation of uterus were associated with a higher chance of ECV success. Frank breech, lateral left position of the fetal spine and engaged breech were associated with a lower chance of ECV success. None of the markers were associated with higher or lower chances of a successful ECV following administration of atosiban compared to fenoterol.
In chapter 6 we described the outcome of a systematic review of prediction models for successful ECV. This study was performed to provide an overview of existing models and to assess their quality, development and performance. We identified eight articles reporting on seven prediction models. The most important predictor variables for successful ECV described in the selected articles were parity, placental location, breech engagement and the fetal head being palpable. We found one prediction model to prevent breech presentation at term that was validated in an external cohort and had acceptable predictive performance.

The development and internal validation of a novel clinical prediction model for ECV was presented in chapter 7. This study was conducted alongside the RCT presented in chapter 2. We chose to make a new model, since previous models did not include all important predictors. Including all important predictors could increase the models' accuracy. Ten predictive factors were identified with the stepwise selection procedure to be associated with a successful ECV: fenoterol as uterine relaxant, nulliparity, Caucasian ethnicity, gestational age at ECV, amniotic fluid index, type of breech presentation, placental location, breech engagement, possibility to palpate the head and relaxation of the uterus. Prediction of success of ECV seems feasible with a model showing good performance (c-statics of 0.78, 95% CI 0.75 to 0.81).

In chapter 8 we described the results of our systematic review and meta-analysis on mode of delivery in women after a successful ECV. We identified three cohort studies and eight case–control studies, reporting on 46,641 women. After successful external cephalic version, women were at increased risk for caesarean delivery for dystocia (OR 2.2, 95% CI 1.6 to 3.0), caesarean delivery for fetal distress (OR 2.2, 95% CI 1.6 to 2.9), and instrumental vaginal delivery (OR 1.4, 95% CI 1.1 to 1.7) compared to women with a spontaneous cephalic presentation. The a priori chance to have a caesarean delivery for a woman with a fetus in breech presentation if an ECV is not performed, is much higher. Therefore, we estimated a number needed to treat of 2.6 (95% CI 2.0 to 3.9).
General discussion and future perspectives

The main objective of this thesis was to generate more evidence on how to improve the effectiveness of ECV. This thesis provides new insights on both tocolytic agents for ECV and prediction for successful ECV.

We were the first to evaluate oxytocin receptor blockers compared to beta-mimetics in the largest single trial on uterine relaxation with ECV thus far. This trial confirmed that a beta-mimetic still is the best agent of choice in improving the effectiveness of ECV. The network meta-analysis on the subject further consolidates this conclusion, showing that beta-mimetics were the only tocolytic agent to increase ECV success rate (RR 1.6, 95% CI 1.28 to 2.0) and had the highest probability of being ranked the best treatment option. Therefore, we recommend beta-mimetics to be the preferred tocolytic agent for patients to choose to improve the success rate of ECV. In addition, for new trials comparison should be made against beta-mimetics.

From previous research we know that the implementation of use of beta-mimetics for tocolysis to improve ECV outcome is limited mainly due to the maternal side effects. The frequent occurrence of side effects was confirmed in our trial, in which two third of women participating experienced side effects for the duration of the ECV attempt. Most reported side effects were transient feelings of tachycardia and flushes, while severe hypotension occurred in only one out of 408 patients (0.2%) after the use of fenoterol. The results of a patient's preference study showed that women are willing to undergo this treatment as the gain in success rate outweigh the unpleasant side effects. However, some women will never opt for tocolysis as their decision is often based on a more general personal principle not to expose the fetus to any medication that might harm the fetus, in which this principle outweighs the potential positive effects of the treatment. We believe that tocolysis is safe to use during pregnancy, as the hypothesized transient fetal side effects hypoglycemia and tachycardia do not appear more frequent after administration of a beta-mimetic. In light of this discussion, it is important to stress that the side effects of beta-mimetics are transient and limited to maternal side effects such as palpitation, headaches, nausea and vomiting. In addition, in our network meta-analysis we found that the distribution of fetal and severe maternal outcomes was similar between the intervention and control groups, and therefore, severe outcomes as placenta abruption (0.08%) or fetal or neonatal death (0.19%) seem to occur independent from the use of tocolytic agents. However, as occurrence rate of serious complications is low, larger datasets are needed to confirm this finding.
Women who do not opt for tocolysis or even ECV, as they perceive the risk of harm from medication or manipulation higher than the potential benefit of the treatment, often seek refuge in alternative treatments. In our meta-analysis of moxibustion therapy as a CAM treatment for breech we found that this may increase cephalic presentation. However, the positive effect we found could be due to publication bias as studies with the most positive outcome in favor of moxibustion had the lowest quality. Also, only the outcome cephalic presentation after moxibustion therapy could be derived from these low quality studies and we were therefore not able to compare mode of delivery, which we considered as an important outcome. Heterogeneity was observed among the studies for the outcome cephalic presentation after moxibustion therapy ($I^2$ of 74%). In addition, there was inequality between study procedures regarding quantity of treatment (once a day, or couple times a day), performance of treatment (health professional or by the patient self) and the gestational age at the start of the treatment (30, 32 or 34 weeks of gestation).

For our meta-analysis, we were not able to determine the additional effect of moxibustion therapy to ECV as implementation of ECV was low (for example, 19% of the eligible patients opt for an attempt in the trial with the highest quality\textsuperscript{11}). ECV appeared not to be standard treatment in the five studies that performed ECV. For these five studies, we were not able to obtain information about the experience of health professionals with ECV and if tocolysis was administered. For now, moxibustion followed by an ECV attempt is not proven beneficial in terms of reducing caesarean delivery for breech presentation.

The success rates reported in different prediction models vary from 20 to 80% depending on patient characteristics. Prediction of successful ECV on a more individual level improves shared decision making. Knowledge about the effectiveness of ECV also influences acceptance of ECV.\textsuperscript{8} We reported on six prediction models for successful ECV that are published. None of the models incorporated all important variables (e.g. parity, palpation of the fetal head, breech engagement and amniotic fluid index) determined in literature in their analysis, thereby potentially limiting the performance of the models.\textsuperscript{12,13} Therefore, we have chosen to develop and internally validate a new prediction model using all important variables. The model performance was better compared to the other prediction models.\textsuperscript{14,15} A limitation of our study results is that ECV attempts were undertaken in centers that perform ECV frequently and it is strongly believed that experience of the performing gynecologists or midwife as well as the setting influence the success rate of ECV.\textsuperscript{16,17} Consequently, this could contribute to a higher chance of success compared to centers that do not perform ECV frequently.
We found that women with a successful ECV still have an increased risk for a caesarean delivery compared to women with children in persistent cephalic lie. It is important to weigh this risk with the chance of a caesarean delivery if ECV was not conducted. Therefore, calculation of the number needed to treat could be helpful. In a population without ECV, the rate of elective caesarean delivery for breech presentation is approximately 85%. Compared to approximately 47% in a population with ECV (average success rate of ECV is 59% and chance for a caesarean delivery after successful ECV is 21%). This makes the absolute risk reduction 0.85−0.47=0.38 which corresponds to a number needed to treat of 2.6 (95% CI 2.0 to 3.9). Consequently, we need to perform two to four ECV’s to prevent one caesarean delivery, and therefore, it seems very beneficial. In obstetrics, but also in medical treatment in general, this is a small number needed to treat that can prevent major abdominal surgery in young fertile women.

Clinical implications
This thesis confirms that ECV is a proven effective obstetrical method to reduce breech presentation at birth and thereby the associated caesarean deliveries. Therefore, it should be offered to all women with uncomplicated breech presentation at term. Also, it is considered as a low resource treatment and can be performed all over the world, also in low resource countries.

The data presented in this thesis show that uterine relaxation with a beta-mimetic increase the success rate and decrease caesarean delivery for breech presentation. All women who consider an ECV attempt should be adequately counselled about the effects of administration of a beta-mimetic. An ECV should be discussed with women providing an adequate estimate of the individual a priori chance of success. For uterine relaxation during ECV, uterine relaxants other than beta-mimetics most likely reduce the chance for successful version and if a new class of drugs is developed, their effectiveness should be evaluated in a head-to-head comparison to a beta-mimetic.

Compared to placebo, beta-mimetics decrease caesarean delivery with 20%, which corresponds to a substantial health gain. Table 1 demonstrates the benefits in health gain if beta-mimetics for ECV were routinely administered in the Netherlands. Based on previous studies, that calculated an optimal implementation of 82% (8% of the women have a contra-indication and 10% are reluctant towards this intervention), a live birth rate of 150,000 with an incidence of breech presentation of 4% at term, assuming a caesarean delivery rate of 75% in case of an unsuccessful ECV, we calculated that for the Netherlands 17 women would not experience short term severe morbidity due to caesarean delivery for breech presentation per year. The health benefit would be substantial combining short term and long term consequences of caesarean delivery.
Table 1. Health benefits by preventing caesarean delivery in one year when implementing beta-mimetics for ECV in the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>No use of tocolytic medication (number of women)</th>
<th>Use of tocolytic medication (number of women)</th>
<th>Difference in absolute number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall severe morbidity</td>
<td>52,3</td>
<td>34,9</td>
<td>17,4</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>1,2</td>
<td>0,8</td>
<td>0,4</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3,7</td>
<td>2,5</td>
<td>1,2</td>
</tr>
<tr>
<td>Puerperal venous thromboembolism</td>
<td>1,2</td>
<td>0,8</td>
<td>0,4</td>
</tr>
<tr>
<td>Major puerperal infection</td>
<td>11,6</td>
<td>7,7</td>
<td>3,9</td>
</tr>
<tr>
<td>Obstetric-wound hematoma</td>
<td>25,2</td>
<td>16,8</td>
<td>8,4</td>
</tr>
</tbody>
</table>


Our prediction model should be used for all women who are deciding on an ECV attempt because it supports personalized decision making in clarifying the possible success chance. After external validation, an impact analysis is needed to test for the model's ability to chance and improve shared decision making and evaluate (un)intended effects on patient outcomes. Our model helps to translate data of a large cohort into daily practice on a patient level and truly helps shared decision making on an individual level and therefore, contributes to value based health care. To improve the uptake of ECV and increase personalized medicine, external validation of our prediction model is needed before implementing this in practice.

Despite the fact that ECV is highly recommended in international guidelines, the implementation is low. In the Netherlands, 72% of the eligible women were offered an ECV attempt, and approximately 18% of the women in the United States.\(^1\)\(^8\),\(^1\)\(^9\) In the last decade, the majority of studies on ECV are from Western Europe and Australia, this could be due to differences in approach in the management of breech presentation worldwide. Nevertheless, evidence that ECV is effective is overwhelming, as a consequence, awareness about optimal implementation is needed.

Implications for future research
This thesis clearly demonstrates that a beta-mimetic improves the outcome of ECV, however, to further improve the outcome of ECV, future research should focus on implementation of beta-mimetics, complications of ECV and drug related adverse events, implementation and updating of a prediction model and determining the existing of an operator effect and best setting to perform ECV.
To generate more evidence of the beneficial effect of routine administration of beta-mimetics for ECV, a pragmatic RCT should be performed. This trial should randomize between an attempt with a beta-mimetic immediately, and on the other hand, a first attempt without beta-mimetics and if unsuccessful, a repeat ECV with beta-mimetics. This study can create awareness on implementation of beta-mimetics and could identify a subgroup who benefits from beta-mimetics as first line treatment.

Concerns about complications and adverse events remains for patients who are considering ECV. And now, 12 years after the first systematic review about safety, we need to conclude that this is poorly documented among published cohort studies and RCTs. Therefore, future research should focus on the incidence of complications in ECV and on identifying possible risk factors associated with their occurrence as it is helpful in counseling women. As the incidence of complications is low, these datasets should be of sufficient power and prescribed outcomes are needed. Outcomes of interest are fetal death, placental abruption, preterm birth, vaginal blood loss, the need for caesarean delivery within 48 hours following ECV.

To further confirm the generalizability of the model we developed and internally validated, external validation, and if necessary updating this model, is needed in a cohort of women who are considering ECV. If the model performs well at external validation, impact analysis additionally needs to be performed in order to improve the uptake of the model in clinical practice.

To increase the likelihood of successful ECV, it is strongly believed that experience of the operator and setting is of crucial importance. However, this has thus far not been under proper investigation. Therefore, future studies should focus on measuring the effect of experience on ECV outcome, the effect of evidence based learning programs on improvement of skills, explore the existence of a minimal number of ECV attempts per year needed to remain experienced and in which setting an ECV should be performed. Information on this should be implemented in guidelines to provide the highest a priori chance of success.
References