Management of preterm delivery in women with abnormal fetal presentation
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Summary

This thesis addresses the optimal mode of delivery in women with a preterm and term breech presentation and in women with a multiple pregnancy. We analysed perinatal and maternal outcomes according to the intended as well as the actual mode of delivery in nationwide cohort studies using data from the Netherlands Perinatal Registry (PRN). This chapter summarises and discusses the findings from our research. Furthermore, clinical and future research implications are put forward.

Chapter 1 contains a general introduction on preterm delivery, abnormal fetal presentation and multiple pregnancy and presents the outline of the thesis. In preterm birth, fetal malpresentation occurs more frequently than in term births. Breech presentation is defined as a fetus in longitudinal lie with the buttocks or feet closest to the cervix. For term breech delivery the Term Breech Trial [1] showed that an intended caesarean delivery is safer in terms of combined short term morbidity and mortality which has led to a shift to planned caesarean delivery. Breech presentation occurs more frequently at lower gestational ages, with an incidence of 25% at 26 weeks, 15% at 32 weeks, declining to 3 to 4% in term pregnancy [2]. For women with a preterm delivery in breech presentation knowledge on the optimal mode of delivery is limited. Randomised controlled trials were stopped before reaching large sample size due to recruitment difficulties and were therefore too small to draw meaningful conclusions about the optimal mode of delivery [3-8].

The incidence of multiple pregnancies has increased over the past 20 years by approximately 80%, largely because of the growing use of assisted reproductive technologies and the increase in average maternal age at first childbirth [9]. This makes the issue on the optimal mode of delivery in multiple pregnancies an important topic. However, studies on the optimal mode of delivery in women with a twin pregnancy and a very preterm delivery (<32 weeks) are limited, the same applies for women with a triplet pregnancy.

Chapter 2 describes the results of a systematic review and meta-analysis of non-randomised studies that assesses the association between mode of delivery and neonatal mortality in women with preterm breech presentation. We therefore searched Pubmed, Embase and The Cochrane library for articles comparing neonatal mortality after vaginal delivery versus caesarean section in preterm breech presentation (gestational age 25+0 and 36+6 weeks). Seven studies met the eligibility criteria and were included in this systematic review, thus including a total of 3,557 women with a preterm delivery of a child in breech presentation. The weighted risk of neonatal...
mortality was 3.8% in the caesarean section group and 11.5% in the vaginal delivery group (pooled RR 0.63; 95% CI 0.48 to 0.81). In conclusion, we found no large randomised controlled studies addressing the optimal mode of delivery in women delivering a preterm fetus in breech presentation for this review, the available cohort studies indicate that caesarean section is associated with a reduced neonatal mortality as compared to vaginal delivery. This conclusion should however be carefully interpreted, concerning the lack of intention to treat analysis and other bias that is inevitably in cohort studies.

Chapter 3 provides the results of a nationwide cohort study in the Netherlands on women with a singleton pregnancy in breech presentation who delivered preterm (26+0 and 36+6 weeks of gestation) in the years 2000-2011. We compared perinatal outcomes according to the intended mode of delivery as well as the actual mode of delivery using multivariate logistic regression analysis. We studied a total of 8,356 women with a singleton preterm breech delivery. Intended caesarean delivery (n=1,935) was not associated with a significant reduction in perinatal mortality compared to intended vaginal delivery (n=6,421) (1.3% versus 1.5%, (aOR 0.97; 95% CI 0.60-1.57)). However, the composite of perinatal mortality and morbidity was significantly reduced in the intended caesarean delivery group (8.7% versus 10.4 % (aOR 0.77; 95% CI 0.63-0.93). In the sub-group of women delivering at 28-32 weeks, intended caesarean delivery was associated with a significant reduction of perinatal mortality, from 4.1% after an intended vaginal delivery to 1.7% after a planned caesarean delivery (aOR 0.27, 95% CI 0.10-0.77) and a significantly reduced composite mortality and severe morbidity from 10.1% after a intended vaginal delivery to 5.9% after a planned caesarean delivery (aOR 0.37; 95% CI 0.20-0.68). We concluded therefore that in women with a preterm delivery of a fetus in breech presentation caesarean section is associated with a reduced perinatal mortality and morbidity as compared to vaginal delivery.

In chapter 4 we provide the results of a nationwide population based cohort study on the effect of the mode of delivery in women with a preterm breech delivery on perinatal and maternal outcome of the subsequent pregnancy. We identified all women with a preterm breech delivery (26+0 and 36+6 weeks of gestation) and a subsequent delivery in the years 1999 to 2007 in the Netherlands. We compared perinatal outcomes in both pregnancies according to the intended mode of the index pregnancy (preterm breech presentation). We included 1,543 women in the study period, of whom 259 (17%) women had a planned caesarean section and 1,284 (83%) women had a planned vaginal delivery in the first pregnancy. In the subsequent pregnancy, perinatal mortality was 1.1% for women with a planned caesarean section in the first pregnancy and 0.5% for women with a planned vaginal delivery in the first pregnancy, (aOR 1.8; 95% CI 0.31-10.1). Composite adverse neonatal outcome was 2.3% versus 1.5%, (aOR 1.5; 95% CI 0.55-4.2). We also calculated the average risk of perinatal mortality over the two pregnancies, which was 1.9% for planned caesarean section and 2.0% for planned vaginal delivery, (OR 0.98; 95% CI 0.49-1.9). In conclusion, in women with a preterm breech delivery planned caesarean section does not reduce perinatal mortality, perinatal morbidity or maternal morbidity rate over the course of two pregnancies.

Chapter 5 describes the results of a nationwide cohort study which showed that after publication of the Term Breech Trial there was a shift towards elective caesarean delivery up to 80% of breech birth in the Netherlands. This increase in elective caesarean delivery led to a decrease in perinatal mortality and morbidity among women delivering a child in breech presentation at term. Still, 40% of the women with a term breech presentation attempt a vaginal birth. Presumed risk selection of the women attempting vaginal breech birth since the Term Breech Trial, has not led to better outcome of the planned vaginal deliveries. We were not able to select a subgroup of women based on parity, type of breech, birth weight and onset of labour, with a low risk of adverse neonatal outcome during planned vaginal breech delivery, compared to an elective caesarean delivery.

In chapter 6 we present the results of a population-based cohort study including all women with a twin pregnancy who delivered very preterm (26-32 weeks of gestation) in the Netherlands between January 2000 and December 2010. Perinatal outcomes (mortality and morbidity) were paired taking into account the dependency between the children of the same twin pregnancy and were also analysed for each child separately. We studied 1,655 women with a very preterm twin delivery (3,310 children). Perinatal mortality was higher after a planned caesarean section as compared to planned vaginal delivery (10% versus 6.5%, aOR 2.5; 95% CI 1.5-4.2). The same applied for perinatal morbidity (63% versus 66%, aOR 1.5; 95% CI 1.1-2.0). Maternal morbidity was also significantly higher in women who delivered by planned caesarean section (17%) as compared to planned vaginal delivery (9.9%, (aOR 4.0; 95% CI 2.6-6.3). We concluded therefore that there is not much place for a planned caesarean section for women with a twin pregnancy delivering very preterm (< 32 weeks).

Chapter 7 contains the results of a study on perinatal outcomes in women with a triplet pregnancy in the Netherlands in the years 1999-2008. We identified 386 women (1,158 children), of whom we compared perinatal mortality and morbidity according to
the intended as well as actual mode of delivery. Perinatal mortality was 2.3% for women with a planned caesarean section and 2.4% in women with a planned vaginal delivery (aOR 0.37; 95% CI 0.09-1.5) and neonatal morbidity was 26.0% versus 36.0%, (aOR 0.88; 95% CI 0.51-1.4) respectively. In the subgroup analyses according to gestational age and in the analysis of perinatal outcomes per child separately there were also no large differences in perinatal outcomes. The same applied for perinatal outcomes according to the actual mode of delivery. This is one of the largest cohort studies described until now on women with a triplet pregnancy and perinatal outcomes according to the mode of delivery. We did not find large differences in perinatal mortality and neonatal morbidity between caesarean delivery and vaginal delivery.
General Discussion
General Discussion

Clinical implications
The optimal mode of delivery in case of fetal malpresentation is an important obstetric issue for both obstetricians as well as the women involved. The obstetric labour ward provides a unique setting in which rapid clinical judgement and decision-making skills are important for a safe outcome for both mother and child. The safety and optimal outcome for the baby is often, but not always directly, linked to the outcome of the mother and can lead to conflicting interests. Women have a natural desire to put their babies health before their own, but the anticipated morbidity and mortality for both mother and baby must be carefully weighed and considered in the actions we take at delivery in case of fetal malpresentation. Randomized controlled trials on this subject would therefore be helpful.

A typical example of the possible effect that publication of such a randomized controlled trial can have on daily clinical practice is the publication of the Term Breech Trial [1]. In this trial of 2083 women with a term breech delivery it was shown that perinatal mortality or serious neonatal morbidity was significantly lower for women with a planned caesarean section (17/1039; 1.6%) as compared to women with a planned vaginal delivery (52/1039 (5.0%); RR 0.33, 95% CI 0.19-0.56). Within three months after publication of this trial the elective caesarean section rate doubled in the Netherlands and eventually increased up to 90% in some countries [2,3]. In chapter 5 we showed that this increase in elective caesarean delivery led to a decrease in perinatal mortality from 1.3‰ to 0.7‰ (OR 0.51 (95% CI 0.28 – 0.93)) among women delivering a child in breech presentation at term in The Netherlands. However, still 40% of the women with a term breech presentation attempt a vaginal birth. Subgroup analysis could not identify antepartum parameters that could distinguish between women with a low versus a high risk vaginal breech birth. In view of this relatively large percentage of women attempting term vaginal breech birth it is important that obstetricians are aware of the fact that risk selection is not possible based on patient characteristics. Women opting for a vaginal delivery remain therefore at increased risk and both women and clinicians should be aware of this risk.

In preterm birth, fetal malpresentation occurs more frequently than in term births, with an incidence of breech presentation as high as 25% at 26 weeks. Randomized controlled trials to assess the optimal mode of delivery in case of preterm breech presentation were not as successful as the term counterpart in terms of recruitment of participants; all studies were stopped before reaching the targeted sample size [4-7].
The largest randomized controlled trial on this topic contained 38 women. The optimal mode of delivery in preterm breech presentation therefore cannot be concluded based on these studies, and the optimal mode of delivery remains controversial and subject of debate. In lack of randomized controlled trials we have to rely on evidence available from cohort studies.

The relatively high vaginal delivery rate in The Netherlands gave us the unique opportunity to study the effect of the mode of delivery in preterm breech delivery in a nationwide cohort study. All studies, including our study and a systematic review, are pointing in the same direction: caesarean delivery reduces perinatal mortality and morbidity as compared to vaginal delivery. However, the treatment effect seems smaller than has been found after the randomized controlled trial for term breech delivery by Hannah et al.[1] Women with a preterm breech delivery between 28-32 weeks seem to benefit most from a caesarean delivery, with a 1.7% risk of perinatal mortality as compared to 4.1% in women with an intended vaginal delivery (aOR 0.27; 95% CI 0.10-0.77). An explanation for this could be that in this gestational period there is a more unfavourable abdominal circumference versus head circumference ratio.[8]

In women with a preterm delivery the major determinant of neonatal death is the degree of prematurity, and the additional risk associated with a vaginal delivery is small. This might explain why the health benefit of a caesarean delivery in case of preterm breech delivery for the offspring is smaller than in term delivery. When the subsequent pregnancy is taken into account, the perinatal mortality and morbidity rate over the two pregnancies are equal for women with a planned caesarean section and a planned vaginal delivery in the first pregnancy (with the preterm breech presentation). Therefore the effect on possible future pregnancies should be part of counselling on the optimal mode of delivery. This might be a difficult subject at the moment of an unexpected and overwhelming event such as a preterm delivery for the pregnant woman and her partner. In a very short period of time, the delivery can suddenly take place very rapidly, they have to be able to understand the meaning of having a (very) preterm child, think about the optimal mode of delivery for this pregnancy and take into account what the consequences of the mode of delivery might be on possible future pregnancies.

In women with a multiple pregnancy, dynamics in birth (preterm and term) are different than in singleton pregnancies and fetal malpresentation occurs more often [9]. After vaginal birth of the first child, malpresentation of the subsequent child(ren) is different from malpresentation in a singleton pregnancy, as one child has already passed the birth channel. This potentially reduces the problem of the passing of the fetal head as compared to in women with a preterm delivery of a singleton in breech presentation as described above.

In women with a very preterm delivery below 32 weeks of gestation our study of 1,655 women showed a higher perinatal mortality in women with a planned caesarean section (10.4%) as compared to women with a planned vaginal delivery (6.5%) (aOR 2.5; 95% CI 1.5-4.2). In this very preterm period, the degree of prematurity is the major determinant of neonatal mortality. To find a difference in perinatal outcome according to the mode of delivery sample size of the study probably has to be larger. A potential disadvantage of caesarean delivery in women with threatened preterm labour is timing of the delivery. Obviously, when vaginal delivery occurs further delay of pregnancy was either not indicated or not possible. In caesarean delivery, however, one is not sure whether the preterm birth would actually occur. If the caesarean section is performed too early, the problem of prematurity addressed above has become even larger, which is an important factor in gestational age below 32 weeks. Maternal morbidity (hemorrhage postpartum > 1,000 ml) was higher in women with a planned caesarean delivery in our study, however since this was not the case in other studies we have to be careful to draw firm conclusions on this specific topic. Taking into account that perinatal outcome does not improve by a planned caesarean section and might lead to adverse maternal outcome there is not much place for a planned caesarean delivery in women with a twin pregnancy delivering before 32 weeks of gestation.

In women with a triplet pregnancy the same issue on the mode of delivery occurs. In an effort to minimize intrapartum fetal complications, there has been a tendency to a caesarean delivery in women with a triplet pregnancy. This was also the case in the largest study on women with a triplet pregnancy and perinatal outcome according to the mode of delivery: in this study of 7067 women in the U.S. caesarean section rate was 95%. This study concluded that vaginal delivery was associated with increased risk of stillbirth (RR 5.7); neonatal death < 28 days (RR 2.8) and infant death < 1 year (RR 2.3). The high vaginal delivery rate in the Netherlands gave us the unique opportunity to study the relation between the mode of delivery and perinatal outcome, and we found in our national cohort study 386 women (vaginal delivery rate of 43%) that in women attempting a vaginal delivery, an important question is whether we are able to identify criteria for the decision on the mode of delivery: what is the profile of women who are allowed to deliver vaginally. Since this is still unclear, obstetricians are challenged to discuss all these factors with women with a triplet pregnancy, and the decision on the mode of delivery has to be a shared decision.
Chapter 8

Summary and General Discussion

Future research implications

In this thesis we present the results of nationwide cohort studies, which are all based on data derived from Netherlands Perinatal Registry (PRN). In retrospective cohort studies we have to be careful to draw firm conclusions. These studies can however help us to find associations between for example the mode of delivery and perinatal outcome, and in the absence of large randomised clinical trials we simply do not have better data to underpin our practice. Furthermore, we have to be aware that some bias is inevitable. Ideally, the exact treatment effect of the mode of delivery on perinatal outcomes in preterm breech, twin and triplet pregnancies would be assessed by large randomized controlled trials. These trials will probably face the same recruitment difficulties as other trials on the subject. However, in view of the high vaginal delivery rates we found in our cohort studies in the Netherlands and the large number of clinical trials that were successfully conducted in the Dutch obstetric research consortium we might be able to successfully conduct such a trial in the Netherlands. On the other hand, the PRN data might already have helped to solve particular questions, such as the optimal mode of delivery in women with a preterm breech baby (chapter 3). The better outcome that we observed after caesarean section might affect existing equipoise, thus hampering recruitment in a randomised clinical trial.

We have to realise that a nationwide database like the PRN is very valuable and contains an incredible amount of information, which is used too little to address research questions. One can question whether it is ethical that data presented in chapter 3 only were analysed now, and not 5 or 10 years earlier. Suboptimal use of the information of such nationwide databases does question the effort of registration of the course and outcome of all pregnancies in the Netherlands, and, more importantly, denies important information to women and their babies who face delivery in malpresentation.

References

8) NVOG guideline “fetal growth restriction” www.nvog.nl/richtlijn.