Risk factors and prognostic models for perinatal asphyxia at term
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Chapter I

SUMMARY

The work presented in this thesis focuses on perinatal asphyxia related morbidity and mortality among term singleton pregnancies. In this thesis we aimed:
1. to study trends and risk factors for perinatal asphyxia at term,
2. to explore the practice variation in obstetric interventions among general hospitals in the Netherlands,
3. to develop a two-dimensional prognostic tool for the simultaneous prediction of risk of perinatal asphyxia and risk of obstetric interventions for non-progressive labor.

In chapter 2, we described temporal trends in perinatal asphyxia at term in the Netherlands. The prevalence of perinatal asphyxia (Apgar score < 7) was 0.85% (1,285/151,680) and severe asphyxia 0.16% (262/151,680) (Apgar score < 4). Between 1999 and 2010 the risk of perinatal asphyxia decreased significantly with approximately 6%, this translates to a decrease of 80 neonates who suffer from asphyxia per year. And, although we observed stable rates in the total obstetric interventions (around 20%), the decline in perinatal asphyxia was accompanied by a significant increasing number of interventions for suspected fetal distress. The proportion of interventions for fetal distress increased from 5.9% to 7.7%. This trend towards increasing obstetric interventions for suspected fetal distress was most pronounced for Cesarean deliveries, a possible effect of improved fetal monitoring. One would expect that a rising trend in obstetric interventions for suspected fetal distress, together with a decrease in perinatal asphyxia at term, would contribute to a decrease in perinatal mortality for this cause. However, the contribution of perinatal asphyxia (87%) to the overall perinatal mortality did not change during the study period. The continuous and relative high risk of perinatal mortality within the first week after birth (0.98 per 1000 births) requires attention and underlines the need for improved risk assessment of pregnant women with high(er) risk for adverse pregnancy outcomes.

In chapter 3, we described the practice variation in elective and emergency caesarean rates among nulliparous women delivering a fetus in cephalic position at term in general hospitals in the Netherlands. Of the 458,712 infants born, 1.8% were delivered by elective caesarean delivery. Elective caesarean rates varied between 0.72% and 5.2% among the hospitals, whereas the emergency caesarean rates varied between 8.2% and 28%. Higher rates of elective caesarean sections could result in better neonatal outcomes, although hospitals performing few elective caesarean sections have no significant increased risk of adverse neonatal outcomes. Neonates born after intended vaginal delivery in hospitals with restraint in emergency caesareans have an increased risk for neonatal mortality and morbidity. This was mainly seen among infants who were delivered by caesarean (aOR 1.69, 95%CI 1.18 – 2.41 and
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aOR 1.63, 95%CI 1.31 – 2.12 respectively), suggesting there may be deficiencies in the timing or selection of cases during the delivery process.

In chapter 4, we examined the recurrence risk of perinatal asphyxia in the subsequent pregnancy. In current practice, obstetric history is used as an important determinant to assess the risks in subsequent pregnancies and influences clinical management. Risk for an Apgar score < 7 was 0.99% among first term singleton pregnancies and overall halved in the subsequent pregnancies (0.50%). It was shown that women with birth asphyxia of the first born have twice the risk of renewed asphyxia at the next birth compared to women without birth asphyxia of their first child. This increased risk was independent of the mode of delivery of the first born. Despite the low prevalence of asphyxia, an obstetric history of perinatal asphyxia and the interaction with other risk factors, like intrauterine growth retardation, should be incorporated in the risk estimation for the subsequent pregnancy.

In chapter 5, we presented the risk of asphyxia related adverse neonatal outcomes after medically assisted reproduction (MAR). In this observational study cohort of over 45,000 children conceived after MAR, we found that MAR singletons had an increased risk of a 5 minute Apgar score < 4 compared to spontaneous conceived (SC) singletons (aOR 1.29, 95%CI 1.14 – 1.46). Because subfertility patients differ from fertile patients on numerous factor contributing to adverse neonatal and pregnancy outcomes, we used propensity score matching analysis to minimize the selection bias and maternal confounding factors. After propensity score matching the risk of adverse neonatal outcomes was similar between MAR infants and SC infants, suggesting that characteristics of subfertile women are associated with the increased prevalence of health problems in term MAR newborns. Until it is possible to identify women at risk for adverse neonatal outcomes, obstetric caregivers classify MAR pregnancies as potentially high risk. This contributes to high rates of obstetric interventions and their potential negative consequences for both mother and child.

Perinatal asphyxia plays a major role in perinatal mortality at term and in chapter 6 we presented the most important risk factors for this adverse neonatal outcome. We found that nulliparity, non-western ethnicity, smoking, being small for gestational age SGA and medical conditions indicating high-risk pregnancy are the most important risk factors for asphyxia related mortality at term. Population Attributable Risk (PAR), based on the Relative Risk and Prevalence of a certain risk indicator, were calculated to investigate the potential improvement that could be reached when eliminating that certain risk factor. The highest PAR was found for SGA below 10th percentile (17%), nulliparity (20%) and smoking (16%). Also, prelabor classification of high-risk pregnancy based on medical features had a high PAR (39%). As in the Netherlands
women with low risk of pregnancy complications receive care in a separate primary care system, with less strict fetal surveillance, optimal antepartum risk assessment is of crucial importance to improve perinatal outcomes. In women who started labor in a primary care setting, the PAR of SGA below the 10th percentile was 24% as compared to 13% for women who started labor in secondary care. The contribution of SGA, particularly in women who started labor in primary care, show the potential improvement of adequate antenatal detection of SGA.

In chapter 7 we assessed the association of the five individual components of the Apgar score with neonatal mortality and morbidity among term singletons. Logistic regression and penalized variable selection showed that only heart rate score of zero (aOR 18, 95%CI 3.7 – 86) and respiratory effort with a score of zero (aOR 6.0, 95%CI 1.3 – 28) were independently associated with poor neonatal outcome in our study sample. And although the Apgar score is probably the most used prognostic test in obstetrics, we showed that a reduced model based on both these variables had comparable predictive performance in terms of discrimination as the current model.

In chapter 8, we described the development of a two-dimensional prediction tool, in which for each laboring woman the predictions for failure to progress (FTP) and perinatal asphyxia were assessed simultaneously. The predicted probabilities for an intervention due to failure to progress varied between 0.30% to nearly 100%. The intrapartum model consisted of 22 variables and showed good calibration and an AUC of 0.78 (95%CI 0.77 – 0.79). Multivariable regression analysis showed that, nulliparity, previous caesarean delivery, artificial reproduction techniques and hypertensive diseases are most strongly associated with interventions for FTP. The intrapartum model for the prediction of perinatal asphyxia consisted of 21 variables and showed a limited discrimination with an AUC of 0.67 (95%CI 0.66 – 0.68). Again previous caesarean delivery, non-Caucasian ethnicity and hypertensive diseases were identified as important predictors, together with fetuses being small for gestational age and. The predicted probabilities for perinatal asphyxia varied between 0.10% and 13%. Combining the predicted probabilities into a two-dimensional prediction model showed that the probability of an intervention due to FTP increased with an increased risk of perinatal asphyxia. However, in some cases the risk of FTP was high while the risk of perinatal asphyxia was low and vice versa. In current clinical practice, individual risk assessment and antenatal counseling of women at risk for adverse outcomes for both the mother and child become increasingly important. We believe that, after external validation, integrating the two-dimensional prediction graph in obstetric care, in conjunction with other methods of corroborating the predictions of adverse outcomes, could guide clinicians in the choice of interventions during labor and delivery.
GENERAL DISCUSSION

Clinical implications and future research
It is already known that certain maternal, fetal and pregnancy characteristics are associated with an increased risk of perinatal asphyxia and related pregnancy complications at term. We introduced some new insights in the interrelationship among these factors and provided a basis for more individualized risk assessment and counseling of pregnant women with respect to their risk of an adverse (asphyxia related) pregnancy outcome at term.

On the other hand, we must conclude that perinatal asphyxia at term is still a difficult event to predict. We were not able to develop a robust prognostic model that can be immediately applied in clinical practice. This is partly due the absence of some relevant variables in the dataset of the Netherlands Perinatal Registry (PRN), for example the Bishop score at start of labor, maternal smoking habits and Body Mass Index (BMI), but moreover dedicated to the complexity of predicting rare events as perinatal asphyxia.

Risk factors for perinatal asphyxia
Maternal
The general health, physical condition and lifestyle factors of pregnant women influence her risk for complications during pregnancy and delivery. Women with a pre-existing medical condition, for example hypertension, are at increased risk of pregnancy complications and perinatal asphyxia due to these complications. 1 With the advancing age in which women get pregnant nowadays, the likelihood of pre-existing comorbidities and the need for medical assisted reproduction are increasing. 2 We have shown, using propensity score matching techniques, that the increased risk of impaired neonatal outcomes among term singletons conceived by MAR are at least partly explained by the maternal and parental characteristics of subfertile couples. The same problem of confounding factors applies to maternal ethnicity. Non–western ethnicity was previously described as a risk factor for adverse neonatal outcomes at term. 3 We confirmed this association for asphyxia related complications. However, we cannot distinguish whether the observed differences can be explained by genetic differences or by (un)known other confounding factors.

Behavioral factors like smoking during pregnancy are strongly associated with adverse outcomes. 4 Our results show the great potential of health care programs designed to reduce the number of pregnant women smoking, as this contributes to the decreased perinatal mortality at term. Smoking not only directly increases the risk of perinatal mortality, it also works as a mediator due to increased risk for intrauterine growth retardation (IUGR) among smoking women. 5
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**Fetal**

The increased risk of asphyxia related mortality of fetuses being small for gestational age (SGA), and the interplay between fetal growth and many maternal (hypertension), pregnancy (MAR), and lifestyle factors (smoking) underline the importance of early detection of IUGR. However, consensual scientific evidence on the accuracy of detecting IUGR by ultrasound screening is lacking. At present, a nationwide study on prenatal detection of IUGR by routine third trimester ultrasound screening is being performed [The IRIS – study]. The outcome of this study might influence obstetricians’ behavior in the future.

**Obstetric history**

After a previous vaginal delivery at term, in general a pregnant woman is considered at low risk for pregnancy complications in the next birth. This also counts for women who delivered a baby suffering from perinatal asphyxia. According to our findings, in which women with birth asphyxia of the first born had twice the risk of renewed asphyxia at the next birth, this low risk classification is remarkable. So despite the low prevalence of asphyxia at term, an obstetric history of birth asphyxia and the interaction with other risk factors should be incorporated in the risk estimation for subsequent pregnancies.

**Obstetric interventions and pregnancy outcomes**

Historically, in the Netherlands there is a conservative attitude towards caesarean delivery. Our caesarean delivery rates around 10% for term singletons in cephalic presentation are among the lowest in Western countries. Although many Western countries focus on lowering caesarean delivery rates, too few caesarean deliveries may effect neonatal outcomes adversely. On the other hand, a caesarean delivery does not guarantee improved neonatal outcomes. The rising trend in obstetric interventions for fetal distress in the Netherlands, together with a decrease in perinatal asphyxia did not result in change in perinatal mortality. This underlines the difficulties in timing and selection of cases during the delivery process. This delicate balance surrounding caesarean deliveries together with the presented practice variation in caesarean delivery rates should be debated and emphasizes the need for more general management in obstetric healthcare.

**Individual risk assessment for adverse pregnancy outcomes**

To improve poor pregnancy outcomes, risk estimation and individual prediction of adverse health outcomes is needed to allow targeted interventions. Before one can apply individualized risk estimation for a certain health outcome such as perinatal asphyxia and related mortality and morbidity, first the association between potential risk factors and the proposed outcome needs to be understand completely, thus allowing more targeted intervention.
The development and internal validation of our prognostic model for perinatal asphyxia and combining the risks for perinatal asphyxia and an intervention due to failure to progress (FTP) in a two-dimensional prediction graph is an important next step towards individualized risk assessment of women during pregnancy and delivery. The characteristics used in the development of the prediction models are readily available in clinical practice and are generally recorded in national registries. To assess the two-dimensional prediction graph’s performance one should aim to integrate the tool into the Electronic Medical Record (EMR) and validate this tool in a large obstetric population.

The limited model’s performance to predict perinatal asphyxia impedes at present its clinical usefulness and emphasizes the difficulty of predicting asphyxia at term. The main challenge is not only to collect data of a large number of pregnant women and their offspring’s, but also to include more potentially relevant variables and standardization of the definition of these variables. Ideally, an integrated tool into the medical record of pregnant women should be modifiable at all time during pregnancy and labor by the continuous addition of maternal, fetal, pregnancy and labor characteristics and measurements. Such a continuously adjustable decision tool could guide clinicians with subsequent interventions during pregnancy, labor and delivery.
REFERENCES


