Risk factors and prognostic models for preterm birth
Schaaf, J.M.

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Preterm birth affects 10% of all newborns worldwide. The related morbidity and mortality exacts not only a high toll on individuals born preterm, but also on their families and the communities in which they live.\textsuperscript{1,2} The pathogenesis of preterm birth is complex and largely unknown.\textsuperscript{3,4} Despite extensive research, preterm birth remains relatively hard to predict and therefore difficult to prevent and is one of the major clinical and scientific challenges in modern obstetric healthcare.

In this thesis we aimed (1) to study trends and risk factors of preterm birth, (2) to develop prognostic models for preterm birth and its related complications and (3) to explore the impact of preterm birth on the reproductive decision making of the parents.

\textit{Part 1. Trends and risk factors}

In \textit{chapter 2} we presented an analysis of temporal trends in preterm birth in the Netherlands. The overall risk of preterm birth (<37 weeks) was 7.7% and the risk of very preterm birth was 1.3%. Our study showed a significant decrease in total preterm birth risk (from 6.4 to 6.0% in singleton pregnancies) between 2000 and 2007. For singleton pregnancies this was due to a significant decrease in spontaneous preterm birth without premature prelabour rupture of membranes (pPROM). Risk of total preterm birth and its subtypes were higher in nulliparous women compared to multiparous women. For multiple pregnancies there was no significant trend in total preterm birth risk although the subtype of medically indicated preterm birth did increase significantly. This trend towards increasing iatrogenic preterm birth was most pronounced in the 34-36 weeks subgroup of gestational age. We observed a large contribution of preterm birth (<37 weeks) to overall incidence of perinatal mortality (68% of all perinatal deaths). The reported decreasing trend in total preterm birth risk in singleton pregnancies stands in contrast to observations in many other developed countries where the increase in medically indicated preterm birth led to increasing trend of total preterm birth risk. We conjecture that our deviating findings are due to socio-cultural and organisational factors influencing the doctor’s attitude towards interventions.

\textit{Chapter 3} presents a systematic review and meta-analysis of ethnic disparities in the risk of preterm birth. We found 45 studies on the association between maternal ethnicity and the risk of preterm birth, of which 41 reported a significant positive association between at least one ethnic group and preterm birth risk. Blacks appear to have a significantly increased (range of adjusted ORs 0.6 to 2.8, pooled odds ratio 2.0 (95% CI 1.8-2.2)) risk of preterm birth when compared to whites (30 included studies). For women of Asian ethnicity there was no significant association, with ORs ranging from 0.6 to 2.3 (17 included studies).
For women of Hispanic ethnicity there was no significant difference in the risk of preterm birth when compared to whites. Currently recognized risk factors do not appear to explain the increased risk of preterm birth among black women. Despite the heterogeneity of the included studies in defining ethnicity and adjustment for possible confounding, ethnic disparities clearly exist. This merits research on the causal pathways of these differences, and on preventative measures to reduce the incidence of preterm birth. As ethnic compositions of societies differ greatly, future prospective research should also focus on ethnic groups living outside the United States.

In chapter 4 we investigated ethnic disparities in preterm birth and its perinatal complications in the Netherlands. Overall risk of spontaneous preterm birth was 5.4% in a population cohort of 969,491 singleton births in The Netherlands. African women have a significant increased risk of preterm birth (OR 1.33; 95% CI 1.26-1.41), but have a decreased risk of subsequent adverse neonatal outcome (OR 0.51; 95% CI 0.41-0.64). Mediterranean women had a decreased risk of preterm birth when compared to European white women, but also a significant decreased risk of subsequent adverse neonatal outcome (OR 0.84; 95% CI 0.72-0.98).

Compared to European whites, other ethnic groups had a decreased risk of adverse neonatal outcome after preterm birth. For an identical pregnancy length, neonates of African, South-Asian, Mediterranean and East-Asian women seem to be better resistant to the harmful impact of preterm birth. One of the most important risk factors for preterm birth is having a history of previous preterm birth. This recurrence risk of preterm birth is well established in the case of succeeding singleton pregnancies.

In chapter 5 we investigated whether this recurrence risk also occurs in the case of a twin pregnancy followed by a subsequent singleton pregnancy. We found that the risk of subsequent singleton preterm birth is significantly increased after a previous preterm twin delivery when compared to a previous term twin delivery. Twin gestation is thus not only a risk factor for preterm birth in the current pregnancy, but also accounts for an increased risk (5.2% versus 0.8%) in a subsequent singleton pregnancy. We showed that the increased risk of subsequent singleton preterm birth is even higher after a spontaneous preterm twin delivery (aOR 9.9; 95% CI 4.4-22.4) in comparison to an iatrogenic preterm twin delivery. The risk of preterm birth increases as the pregnancy length at the preterm twin delivery is shorter.

In chapter 6 the opposite direction was under investigation: The risk of spontaneous preterm twin birth in women with a history of singleton delivery. We found that the risk of subsequent twin preterm birth is significantly increased after a previous preterm singleton delivery when compared to a previous term singleton delivery. Of the 232 women who had a preterm singleton delivery, 132 women (56.9%) had a spontaneous preterm birth in the subsequent twin pregnancy. The spontaneous singleton preterm birth risk in the 3,839 women who delivered their singleton at term was 20.9% (n=804).
Part 2. Prognostic models

In the second part of this thesis we aimed at developing prognostic models for the prediction of (spontaneous) preterm birth and its related complications.

In chapter 7 we developed and internally validated a prognostic model for predicting the adverse pregnancy outcome of spontaneous preterm birth (<37 weeks). Our model consisted of 13 variables, had an AUC of 0.63 (95% CI 0.63-0.63), and exhibited over-prediction at high predicted probabilities. The strongest predictors were a history of previous preterm birth (OR 9.53, 95% CI 9.03-10.06), drug abuse (OR 4.23, 95% CI 3.54-5.06), and vaginal bleeding in the first half of pregnancy (OR 4.10, 95% CI 3.65-4.61). Our prognostic model, which combines all mentioned predictors, has the potential to facilitate the process of indentifying individual women at higher risk for preterm birth after spontaneous onset of birth. Although the development and validation of our prognostic model is an important next step towards individual risk assessment for spontaneous preterm birth, the moderate performance of the model limits its clinical usefulness. We expect, however, that the inclusion of various other variables such as cervical length, which were not available in the PRN registry, would boost the model’s performance.

Chapter 8 describes the development and internal validation of a prognostic model for antenatal prediction of neonatal mortality after very preterm birth (<32 weeks). The final model consisted of 7 variables and showed a large range of predicted probabilities (0.0035-0.675) and a good discrimination capability (AUC 0.84). Gestational age, administration of antenatal corticosteroids, level of hospital, small for gestational age, maternal age, maternal ethnicity and fetal gender emerged as independent predictors, which can be known before birth.

In current clinical practice, antenatal counseling of women after the threshold of viability who are likely to deliver before 32 weeks of gestation is often based on general information like gestational age. Instead, our model consists of a tool for obstetricians to provide individual risk assessment for women at risk of spontaneous or iatrogenic very preterm birth.

Part 3. Impact of preterm birth

Chapter 9 summarizes comprehensive data on reproductive follow-up of a cohort of 304 patients with a history of iatrogenic preterm birth due to early-onset pre-eclampsia. Our findings indicate that the majority of women become or wish to become pregnant within 5 to 8 years after a first pregnancy that was complicated by a delivery before 34 weeks of gestation due to a severe hypertensive disorder. However, a history of early-onset pre-eclampsia is associated with lower rates of ongoing pregnancies in the first years after delivery, when compared with low-risk women who experienced an uncomplicated first pregnancy. The results from our study provide insight into possible reasons why some women with a history of first pregnancy with an early-onset pre-eclampsia do not wish to achieve a subsequent pregnancy.
From our results, we conclude that different motivational elements play a role in the parents’ decision, which may or may not be directly related to obstetrical history. Improved counselling and psychosocial treatment of women with a history of iatrogenic preterm birth due to early-onset pre-eclampsia might positively influence reproductive decision-making.

**Implications for clinical practice and future research**

The work presented in this thesis introduces some directions for future research and clinical practice. In this thesis several risk factors for preterm birth were further explored. The results may help clinicians in improving their risk assessment of preterm birth, for instance for specific ethnic groups or for women with a history of preterm birth. Furthermore this thesis provides tools for more accurate counselling of women with respect to their risk of preterm birth and/or related complications. On the other hand we must conclude that spontaneous preterm birth is still a difficult event to predict. Despite the population based dataset of the Netherlands Perinatal Registry (PRN) and the robust methodological approach, we were still not able to develop a prognostic model for spontaneous preterm birth that can be applied in clinical practice yet. This is partly due to absence of some relevant variables in the PRN dataset, but is moreover a result of the complexity of the pathogenesis of preterm birth, which makes it still hard to predict.

**Preterm obstetric interventions**

The relatively low risk of medically indicated preterm birth among singletons reported in this thesis in combination with the higher risk of perinatal mortality in the Netherlands seems to be paradoxical. Perhaps the more expectant treatment strategies in The Netherlands play a role in this matter. On the other hand, the scientific evidence for a more proactive intervening approach is limited. At present, major randomized controlled trials investigate the best treatment regime for women with premature prelabour rupture of membranes (PPROMEXIL study\(^6\), PROMPT study\(^7\)) and hypertensive disorders (HYPITAT II study\(^8\)) between 34 and 37 weeks of gestation. The outcome of these studies might influence doctor’s behaviour in the future.

**Defining optimal gestational age**

We presented not only data on ethnic disparities in spontaneous preterm birth risk, but also on the impact of preterm birth and how this differs between the main ethnic groups. We have shown that for African and South-Asian women the risk of preterm birth is significantly increased, whereas the actual impact of preterm birth on neonatal outcome is reduced for infants born preterm from these mothers. This apparent varying impact of preterm birth by ethnic group raises the question about defining the optimal pregnancy duration. The optimal pregnancy length of 40 weeks was based on a simple frequency distribution of gestational age at the time of spontaneous onset of labour in white women. In daily practice, these definitions are generalized for all women.\(^9\)
Our results suggest an ethnic variation in optimal gestational age, with children born from African, Mediterranean and East-Asian women having better outcomes at earlier gestation age than their European white counterparts. In other words, these fetuses appear to be mature at an earlier gestational age.

Therefore, future research should focus on defining ethnic-specific optimal gestational age. Optimal gestational age, in this context, is defined as the gestational age at which risk of perinatal morbidity or mortality is the lowest. This has implication on redefining thresholds for preterm and postterm pregnancies and thus impacting daily obstetric practice. For instance in the Netherlands this might concern the referral pattern for women delivering before 37 weeks of gestation, but it might also imply a less expectant approach for specific ethnic groups who are having an ongoing pregnancy beyond 40 weeks of gestation.

**Recurrence risk of preterm birth**

The increased risk of preterm birth in twin pregnancies, which are often a result of artificial reproductive technology, also impacts subsequent singleton pregnancies. These findings can help clinicians to counsel their patients with a history of spontaneous or iatrogenic preterm delivery of twins and quantify their recurrence risks for spontaneous preterm birth.

Previous singleton preterm birth is often an indication for the use of progestagens in the next singleton pregnancy as a preventive measure for recurrence of preterm birth. With these and previous findings, one should investigate the effectiveness of preventive measures like progestagens in singleton pregnancies following preterm twin deliveries as well.

**Individual risk assessment for preterm birth**

The development and internal validation of our prognostic model for preterm birth is an important next step towards individual risk assessment for spontaneous preterm birth, but the moderate performance of the model limits at present its clinical usefulness and emphasizes the difficulty of predicting preterm birth. In the future, our model and its successors with additional predictors should help clinicians indentify women at high risk for preterm birth. The improved counselling of women should focus on the modifiable predictors during pregnancy and should help patients recognize the early symptoms of threatening preterm labour. Another application of our model is the selection of women at higher risk for trials on preventive treatments strategies. Progestagens and Cerclage procedure have been shown to significantly reduce the risk of preterm birth in women with a history of preterm birth. Using our prognostic model we can investigate whether these treatments are beneficial for a broader group of pregnant women as well. For such an application prediction models should be better calibrated. To assess the model’s generalisability one should aim for external validation of the model in a dataset in other populations.
Although the difficulties in individual preterm birth risk assessment are evident, we should still focus on expanding the development, validation and implementation of prognostic models. To this end, we need the inclusion of more potentially relevant variables and the standardization of the collection of well-defined variables. In particular the combination of maternal demographic and pregnancy characteristics, ultrasound and laboratory results, and other biomarkers merits more research. For this purpose we are currently setting up a prospective cohort in the region of the Academic Medical Center of Amsterdam (ZonMw grant number 50-50200-98-054). In this cohort we aim to study risk factors - in the field of public health and occupation as well as medical technical factors - to enable early detection of pregnant women at increased risk of preterm birth. In the end, integration of these risk factors in a risk prediction model should enable the identification of pregnant women at increased risk for preterm birth. The main challenge is to collect data on not only a large number of pregnant women in an unselected population, but also on their offspring, both short term (neonatal and paediatric care) and long term (child health centers). This will provide a much more complete understanding of the complex pathogenesis and adverse consequences of preterm birth and will in the end lead to a reduction of the harm that is caused by it.


