Risk factors and prognostic models for preterm birth
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In an uncomplicated pregnancy the optimal gestational age at the time of delivery is approximately 40 weeks. According to international guidelines we consider deliveries between 37 and 42 weeks as term births. If the birth takes place before 37 completed weeks of gestation we consider it to be preterm. Preterm births are further categorized depending on the gestational age at the time of delivery (figure 1).

The WHO report *Born too soon* describes that worldwide, more than 10% of the babies born in 2010 were delivered preterm. The incidence of preterm birth varies between countries and ranges from 5-18%.

Studies on trends in the incidence of preterm birth showed that in many developed countries the incidence of preterm birth is increasing. The estimated 15 million preterm births in 2010 were related to more than 1 million neonatal deaths. Prematurity is the single most important cause of death in the first month of life and the second-leading cause of death in children less than 5 years old.

The impact of preterm birth extends beyond the neonatal period and throughout the life cycle. Besides perinatal deaths, preterm birth also causes severe neonatal morbidity, mostly due to respiratory immaturity, intracranial haemorrhages and infections. These conditions can have long term consequences such as cerebral palsy, intellectual impairment, chronic lung disease, and hearing and vision loss. All these adverse effects of preterm birth exact not only a high toll on individuals born preterm, but also on their families and the communities in which they live.

Preterm birth can either be a result of medical intervention or can occur spontaneously. In the case of severe maternal and/or fetal complications, such as preeclampsia or intra uterine growth restriction, obstetricians can decide to deliver the baby through induction of labour or elective caesarean section.

<table>
<thead>
<tr>
<th>&lt; 37 weeks</th>
<th>Preterm birth</th>
<th>37 - &lt;42 weeks</th>
<th>Term birth</th>
<th>≥ 42 weeks</th>
<th>Postterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32 weeks</td>
<td>Very preterm birth</td>
<td>32 - &lt;37 weeks</td>
<td>Moderate preterm birth</td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 1. Overview of definitions for preterm birth.
In daily practice, these are difficult decisions as the caregiver has to balance the possible harmful effect of preterm birth versus the possible harmful effect of lengthening a complicated pregnancy. In the majority of cases, however, preterm birth occurs spontaneously with or without prelabour rupture of membranes (PROM). A lot of scientific effort has been put in the unravelment of the pathogenesis of preterm birth. Multiple risk factors have been identified, and preterm birth appears to be a multifactorial and heterogeneous adverse outcome of pregnancy. The risk factors pertain to basis demographic characteristics, medical or obstetrical history, and specific characteristics of the current pregnancy. The most important risk factors are summarized in figure 2. The figure shows the complexity of the problem; the separate risk factors not only play a role in the pathogenesis of preterm birth, they are also strongly interrelated (indicated with the arrows).

Despite the identification of these risk factors, their prognostic interaction is not well understood. As a result it is often difficult to assign risk of preterm birth to individual women. This hinders caregivers from selecting women at higher risk of preterm birth for early referral to secondary care and selecting women for trials on preventive measures such as the admission of progesterone during pregnancy.

Prognostic models are promoted as helpful tools to support clinicians: by producing an individual’s risk score they can be applied in selecting patients for clinical trials, clinical decision making and counselling patients. In literature, few clinical scoring systems have been presented for assigning risk of preterm birth to individual women, but none of them was accurate enough to be applied in daily practice. Most of the risk assessment tools were based on small datasets or did not present predictions in a quantitative manner.

The complexity of the pathogenesis of preterm birth, the related difficulties in early risk assessment and the small amount of effective preventive measures makes preterm birth one of the major challenges in clinical obstetric practice and scientific research. On the side of the neonatologists the improved care of premature infants during the last decades has led to significant better outcomes on the short- and the long term. However, on the side of the obstetric caregivers still lies a big challenge to reduce the number of preterm births and in that way improve perinatal care.

Outline of this thesis
For the majority of our studies in this thesis we were allowed to use the data of the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands.
Figure 2. Risk factors for preterm birth and their interrelationship.
Part 1. Trends and risk factors

Chapter 2 investigates temporal trends in the incidence of preterm birth in The Netherlands and compares the Dutch figures to those of other developed countries. In the next chapters we further explore some important risk factors for preterm birth. Chapter 3 is a systematic review and meta-analysis of literature on ethnic or racial disparities in the risk of preterm birth. It summarizes all relevant studies which of which the majority was performed in the United States. Chapter 4 explores ethnic disparities in the risk of preterm birth in The Netherlands and thus focuses more on the European ethnic composition of society. Furthermore we investigate ethnic disparities in the risk of preterm birth related adverse neonatal outcome.

As shown in figure 2, preterm birth is associated with an increased risk of preterm birth in the subsequent pregnancy. This increased risk is well established and reconfirmed in several studies.\textsuperscript{17,18} However, these studies only focused on the risk of singleton preterm birth after a previous singleton birth. Little is known whether the recurrence risk also holds for twin pregnancies following a preceding singleton preterm birth or the other way around. Chapter 5 investigates the recurrence risk of preterm birth in subsequent singleton pregnancy following previous preterm twin delivery. The exact opposite is under investigation in the next chapter. Chapter 6 presents the recurrence risk of preterm birth in subsequent twin pregnancy following previous preterm singleton delivery.

Part 2. Prognostic models

In the second part of this thesis we aim to improve the individual risk assessment for preterm birth and for adverse neonatal outcome after preterm birth. Chapter 7 describes the development and internal validation of a prognostic model for predicting spontaneous preterm birth. The intended model should be useful for a risk assessment around 20 weeks of gestation. Chapter 8 presents the development of a prognostic model for predicting neonatal mortality after very preterm birth. In neonatology, similar prognostic models are already used for clinical decision making and counselling. However, these models are based on variables which can only be known after birth (e.g. birth weight or Apgar score).\textsuperscript{19} We aim to develop a model which is solely based on variables that are known before birth, which enables an earlier risk assessment in these complicated pregnancies.

Part 3. Impact of preterm birth

Chapter 9 provides an insight in the psychological consequences of preterm birth for the parents. For this we analyse data of a cohort of women who suffered from early onset pre-eclampsia, a severe pregnancy-related hypertensive disorder leading to (medically indicated) preterm birth. We investigate the rates of subsequent pregnancies in women with a history of preterm birth due to early-onset pre-eclampsia and interview women without the wish of a subsequent pregnancy to determine the reasons not to attempt a subsequent pregnancy.


