Risk factors and prognostic models for perinatal asphyxia at term
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Chapter 1

General introduction
Chapter 1

**GENERAL INTRODUCTION**

**Perinatal asphyxia**

Perinatal asphyxia is a rare yet serious complication during labor with immediate consequences and possible long-term neurological impairment. It is suggested that normal labor, expressed per centimeter travelled, is one of the most dangerous journeys in life. In western countries the rates of perinatal asphyxia have decreased considerably in the late nineties. However results from the National Vital Statistics Reports, which contain data on the U.S. births, and data from The European PERISTAT project, which monitors perinatal health in European countries, showed that nowadays still one to two percent of children born suffering perinatal asphyxia. This would suggest that in the Netherlands, with a prevalence of perinatal asphyxia of 1.3% and 175,000 births annually, each year 2200 infants suffer perinatal asphyxia. Among term infants the prevalence of perinatal asphyxia is around 0.88% (1300 infants each year, of which 250 infants suffering severe asphyxia).

Perinatal asphyxia is a clinical condition of impaired oxygen supply or blood flow to the fetus and can occur before the onset of labor (antepartum) or during labor (intrapartum). In order to create a worldwide accepted definition the American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) suggested the following criteria in diagnosing asphyxia: (1) umbilical cord pH less than 7, (2) persistence of an Apgar score of 0 – 3 for longer than 5 minutes, (3) neonatal neurological manifestations (e.g., seizures, coma, hypotonia), and (4) multiple organ involvement (e.g., kidney, lungs, liver, heart).

The Apgar score was proposed by Dr. Virginia Apgar in 1952 as an objective tool to assess the condition of newborns immediately after birth. The score consists of five characteristics of the newborn infant: skin color (pink, blue or pale), heart rate ($\geq$100/minute, $<100$/minute or absent), respiratory effort (normal rate and effort, irregular gasping or absent), muscle tone (active, arms and legs flexed or ‘floppy tone’) and reflex irritability (pulls away, grimace or absent). All contribute equally to the total score each with rating of 0, 1 or 2 points.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Score of 0</th>
<th>Score of 1</th>
<th>Score of 2</th>
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<tbody>
<tr>
<td>Appearance (skin color)</td>
<td>Blue or pale</td>
<td>Blue extremities / body pink</td>
<td>Totally pink</td>
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<tr>
<td>Pulse</td>
<td>Absent</td>
<td>$&lt; 100$ bpm</td>
<td>$\geq 100$ bpm</td>
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<tr>
<td>Grimace (reflex irritability)</td>
<td>No response</td>
<td>Grimace/ Feeble cry when stimulated</td>
<td>Pull away</td>
</tr>
<tr>
<td>Activity (muscle tone)</td>
<td>None / ‘floppy tone’</td>
<td>Some flexion</td>
<td>Active</td>
</tr>
<tr>
<td>Respiration</td>
<td>Absent</td>
<td>Weak / Irregular gasping</td>
<td>Strong cry</td>
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Because of the very small number of term newborns with a five-minute Apgar score < 3, most studies examine perinatal asphyxia as a five minute Apgar score < 7 and/or umbilical cord pH \( \leq 7.0 \) “severe acidosis”. Indeed, in term infants without severe congenital malformations, a low five-minute Apgar score most likely reflects intrauterine asphyxia. 3

**Perinatal asphyxia and perinatal mortality**

Perinatal mortality (stillbirth and neonatal mortality) at term is often unexpected and not entirely explicable, however it is indisputable that asphyxia plays a major role in this. The European PERISTAT project showed that the perinatal mortality rates in the Netherlands are among the highest in Europe. 6 85% of these perinatal deaths can be contributed to one of the so called BIG 4 determinants: preterm birth, intra-uterine growth restriction, congenital anomalies and perinatal asphyxia. 9 Although term neonates (born between 37.0-41.6 weeks) have the lowest risk for perinatal mortality, they account for 25% of the total number of perinatal mortality in the Netherlands and perinatal asphyxia plays a major role (>75%) in this. 10 Except the high risk of mortality, the surviving infants could experience long-term consequences on their physical and mental development. Most infants with severe asphyxia are admitted to an neonatal intensive care unit (NICU) and receive specialized care during the first years of their lives. So besides the individual consequences for the neonates suffering perinatal asphyxia, the related morbidity and mortality also exacts a high toll on their families and the communities in which they live and generates are considerable costs for the society. Therefore scientific research to predict and prevent perinatal asphyxia and asphyxia related health problems in general and specific for term infants are needed.

**Perinatal asphyxia and obstetric interventions**

The obstetric caregiver constantly needs to weight the risk of an adverse pregnancy outcome when deciding between continuing labor versus obstetric interventions. Obstetric interventions consist of caesarean delivery or assisted vaginal delivery with a vacuum or forceps. The World Health Organization (WHO) stated “a population-level caesarean section rate above 15% is hardly justified from the medical perspective”. 11 However the caesarean delivery rates are continuing on the rise worldwide. Various reasons have been suggested for this increase, including advanced maternal age at first pregnancy, improved surgical techniques and obstetricians’ as well as patients’ perception on the safety of the procedure as compared to vaginal delivery. Higher rates of obstetric interventions can be justified if they improve neonatal outcome, without causing unnecessary maternal harm. As fetal distress (or suspected asphyxia) if often an indication for an obstetric intervention during labor, one may conjecture that the rising trend in obstetric interventions observed in developed countries would influence the incidence of perinatal asphyxia.
Risk factors and prognostic modeling of perinatal asphyxia and the need of an intervention for non-progressive labor

A lot of research has been done on the risk factors of perinatal asphyxia. These risk factors pertain to basic demographic characteristics, medical diseases, obstetric history and current pregnancy characteristics. 2, 12, 13 Examples of antepartum risk factors related to the pregnant woman are hypertension, advanced maternal age, (gestational) diabetes, medically assisted reproduction (MAR). Some of the neonatal characteristics are congenital anomalies and severe growth retardation. Despite the identification of maternal and fetal risk factors their prognostic interaction is not well understood. Prognostic models are used in various settings and for various reasons. The main reasons are to inform individuals about the future course of their illness (or their risk of developing illness) and to guide doctors and patients in joint decisions on further treatment. 14, 15

In the Netherlands, where women with low risk for pregnancy complications receive care in a separate midwifery led care system as compared to high risk women, who receive care in an obstetric led care system. Thus, optimal antepartum risk assessment is important to identify pregnant women with a high(er) risk of developing adverse neonatal outcome, so obstetric management can be individualized. 16 In literature, few prognostic tools have been presented for assigning the risk of perinatal asphyxia, but none of them were generalizable for the whole term population as they were based on small datasets or did not include some important antepartum and intrapartum variables. 17, 18 Furthermore, in labor there is continuous weighing of the risk of adverse outcome for either the neonate (asphyxia) or the mother (obstructed labor). An integrated model assessing both adverse pregnancy outcomes simultaneously could assist obstetric caregivers and guide subsequent interventions during labor and delivery.

This thesis will focus on the risk factors and prognostic models for adverse perinatal outcome at term, with a special focus on perinatal asphyxia and obstetric interventions during labor to reduce adverse pregnancy outcomes. For the majority of the studies in this thesis we were allowed to use data of the Netherlands Perinatal Registry (PRN). The PRN consists of national population-based data containing information on pregnancies, deliveries and (re)admissions until 28 days after birth. For one study the database of the Foundation Perinatal Audit in the Netherlands (PAN) was used.
AIM OF THIS THESIS

- To identify risk factors for asphyxia related morbidity and mortality at term singleton pregnancies.
- To investigate the practice variance according to obstetric interventions and explore the association between variation in caesarean delivery rates with maternal and neonatal outcomes.
- To develop prognostic models to predict adverse neonatal and pregnancy outcomes at term.

OUTLINE OF THIS THESIS

Part I: Trends of perinatal asphyxia and obstetric interventions among terms.
In chapter 2 we describe trends in perinatal asphyxia, perinatal mortality and obstetric interventions for fetal distress among term singletons in the Netherlands.

In chapter 3 we describe the variation in planned and unplanned caesarean rates among general hospitals in the Netherlands. Furthermore we studied the possible association between caesarean delivery rates and maternal and neonatal outcomes.

Part II: Risk factors for perinatal asphyxia related mortality and morbidity.
In chapter 4 we studied the influence of a previous pregnancy complicated by low Apgar score. We assessed the recurrence risk of perinatal asphyxia in a subsequent pregnancy among term singletons.

Since the introduction of medically assisted reproduction (MAR) over 35 years ago, the number of children born after MAR has rapidly increased. Chapter 5 studies the risk of a poor neonatal outcome at term after MAR.

In chapter 6 we explored maternal and neonatal risk factors for asphyxia related mortality at term in order to improve the identification of low-risk and high-risk pregnant women. Optimal antepartum risk assessment is crucial in reducing adverse pregnancy outcomes.
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Part III: Prognostic modelling of adverse pregnancy outcomes at term.

The Apgar score consists of five components all contributing equally to the total score. In chapter 7 we studied the association of these five individual components with neonatal mortality and morbidity at term.

The risk of perinatal asphyxia as well as obstructed labor can be predicted. Chapter 8 describes the development of a two-dimensional decision tool to predict the risk of a poor neonatal outcome (asphyxia) and the need of an intervention for non-progressive labor simultaneously. Such a tool with combined predictions could facilitate in decision making during labor.
REFERENCES


