Placental lesions and outcome in preterm born children
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Chapter 9

General discussion and future perspectives

Annemiek Roescher
The primary aim of this thesis was to determine whether placental lesions are associated with neonatal morbidity and neurological development. The secondary aim was to establish possible mechanisms through which placental lesions might lead to neonatal and neurological morbidity. To study these aims we formulated the following research questions:

1. What do we know about the relationship between placental lesions and perinatal death, neonatal morbidity, and neurological outcome? (Chapter 2)
2. What is the relationship between placental lesions and short-term neonatal outcome (Chapter 3) and neurological outcome (Chapter 4) in preterm-born children?
3. What is the relationship between placental lesions and long-term neurological outcome at toddler age (Chapter 5) and early school age (Chapter 6) in preterm-born children?
4. What is the relationship between placental lesions and cerebral tissue oxygen saturation and extraction in preterm infants? (Chapter 7)
5. Are placental lesions associated with cytokine responses directly after birth in preterm infants? (Chapter 8)

By addressing these questions we hope to create more awareness among health professionals of the possible benefit of findings on placental lesions for neonatal care. If placental lesions are associated with neonatal morbidity and neurological development, placental examination immediately after birth may create the opportunity for early interventions with a view to reducing later sequelae.

In this discussion we set out by answering our research questions and summarizing our main findings. Subsequently, we consider the main findings in more detail. These findings include the prevalence of placental lesions, placental lesions that were related to outcome measures, placental lesions not related to outcome measures, and the difficulties encountered in classifying placental lesions. Then, we describe possible disease mechanisms underlying placental lesions that lead to morbidity and the consequences for clinical practice. Finally, we describe future perspectives concerning placental examination and outcome.

**Main findings**

1. **What is known in the literature about the relationship between placental lesions and perinatal death, neonatal morbidity, and neurological outcome?**

The placenta plays a key role in fetal and neonatal mortality, morbidity, and outcome (Chapter 2). Placental lesions are among the main contributors to fetal death and we found that placental lesions consistent with maternal vascular underperfusion contributed most. Several neonatal problems are also associated with placental lesions, whereby ascending intrauterine infection, with a fetal inflammatory response, and fetal thrombotic vasculopathy constitute the greatest problem.
2. **What is the relationship between placental lesions and short-term neonatal outcome and neurological outcome in preterm-born children?**

Both elevated nucleated red blood cells, a placental marker for fetal hypoxia, and fetal thrombotic vasculopathy are associated with short-term outcome measures in preterm-born children. These outcome measures included illness severity and neurological functioning.

We assessed the short-term neonatal outcome during the first 24 hours after birth with the Score of Neonatal Acute Physiology Perinatal Extension (SNAPPE) (Chapter 3). This score provides insight into the illness severity of infants during their first 24 hours after birth. We found that elevated nucleated red blood cells and fetal thrombotic vasculopathy were associated with higher illness severity in preterm infants during the first 24 hours after birth.

We assessed short-term neurological outcome during the first two weeks after birth by determining the quality of general movements (Chapter 4). These movements reflect the infant’s neurological condition shortly after birth and are a predictor of neurological outcome later in life. In this study we once again found that placental lesions consistent with fetal thrombotic vasculopathy and elevated nucleated red blood cells were associated with an abnormal quality of general movement, albeit not statistically significant.

3. **What is the relationship between placental lesions and long-term neurological outcome at toddler age and early school age in preterm-born children?**

Of all placental lesions we studied only ascending intrauterine infection was associated with abnormal outcome measures at two years of age (Chapter 5). Ascending intrauterine infection was associated with abnormal cognitive, fine motor, and total motor outcomes in preterm-born children. In moderately preterm-born and late preterm-born children we found maternal vascular underperfusion and ascending intrauterine infection to be associated with functional outcomes at early school age (Chapter 6). Maternal vascular underperfusion was associated with lower IQ scores, and ascending intrauterine infection was associated with more abnormal motor outcome scores.

4. **What is the relationship between placental lesions and cerebral tissue oxygen saturation and extraction in preterm infants?**

Ascending intrauterine infection was associated with lower cerebral tissue oxygen saturation, and higher fractional tissue oxygen extraction on the second, third, and fourth days after birth (Chapter 7). No other placental lesions were associated with cerebral tissue oxygen saturation and extraction shortly after birth. Both ascending intrauterine infection and lower cerebral oxygen saturation, and higher oxygen extraction shortly after birth, were associated with neurodevelopmental problems. The impact of ascending intrauterine infection on cerebral oxygenation might be the mechanism leading to neurodevelopmental problems.
5. Are placental lesions associated with cytokine responses immediately after birth in preterm infants?

Placental inflammation consistent with AIUI was associated with cytokine responses at or immediately after birth in preterm infants (Chapter 8). The presence of these cytokine responses might be part of the mechanism through which infectious placental lesions lead to neurological morbidity.

General discussion

Placental lesions

During pregnancy the placenta is the link between the mother and her fetus and it plays a crucial role in fetal growth and development. Non-optimal placental performance as a result of placental lesions may lead to maternal or fetal problems or both. One could envisage the placenta as the mirror of pregnancy in the sense that placental examination may provide useful information regarding the intrauterine conditions experienced by the fetus. The types of placental lesion and the frequencies of placental lesions found during examination are diverse and differ according to the neonates’ gestational ages (GA) at birth. Placental lesions are common in preterm infants. In the studies presented in this thesis the incidence of one or more placental lesions in preterm infants of < 32 weeks’ GA ranged from 89 to 93%. This is three times higher compared to fullterm infants in an unselected, random population in which approximately 30% have placental lesions. In Chapter 6 we studied placental lesions in a selected group of moderate preterm and late preterm infants. Here we found that 80% of the infants had one or more placental lesions. Thus the prevalence of lesions in moderate and late preterm infants is more than two-fold higher than in fullterm infants. We point out that the prevalence in our group of moderate and late preterm infants may be overestimated, because only approximately one quarter of the placentas were sent in to the pathologist for histological examination. It might well be that these pregnancies had more complications, resulting in a selected population of children examined.

Placental lesions with signs of maternal vascular underperfusion and ascending intrauterine infection were most frequently seen in the preterm period. The highest prevalence of ascending intrauterine infection is seen in extreme preterm birth, < 28 weeks’ GA, and the highest prevalence of maternal vascular underperfusion in births between 28 and 33 weeks’ GA. The frequency of fetal thrombotic vasculopathy, villitis of unknown etiology, and chronic chorioamnionitis all increase with gestational age. The highest prevalence of fetal thrombotic vasculopathy and villitis of unknown etiology is seen at fullterm birth, whereas chronic chorioamnionitis is most frequently seen in births between 34 and 36 weeks’ GA.

The high prevalence of placental lesions, particularly in the preterm-born group, suggests that placental lesions are a sign of complications that lead to preterm birth or
that even cause preterm birth. The association between ascending intrauterine infection and preterm birth is well known. Especially in spontaneous preterm births it is thought to be the cause of preterm delivery. In the presence of ascending intrauterine infection several cytokines are found to be elevated in the amniotic fluid and cord blood. Tumor necrosis factor (TNF) is thought to activate the cytokines and initiates labor by stimulating prostaglandin production from the decidua. Maternal vascular underperfusion, regularly seen in the presence of hypertensive disorders such as preeclampsia, may also lead to preterm birth. This is, however, an induced preterm birth which must be accomplished prematurely due to maternal or fetal indications.

Despite the high rate of placental lesions in preterm infants, the majority develop without major neurologic problems. This raises the question of the role of placental lesions in general on neonatal morbidity and neurological outcome in the individual infant. Before addressing this question we first discuss whether specific placental lesions relate to outcome measures.

Placental lesions related to outcome measures
In our studies we found that fetal thrombotic vasculopathy, ascending intrauterine infection, maternal vascular underperfusion, and elevated nucleated red blood cells most frequently associated with poorer outcome measures (Table 1).
Table 1: Thesis outcome table

<table>
<thead>
<tr>
<th>Placental Lesions</th>
<th>Chapter 3</th>
<th>Chapter 4</th>
<th>Chapter 5</th>
<th>Chapter 6</th>
<th>Chapter 7</th>
<th>Chapter 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness severity (SNAPPE)</td>
<td>General movements</td>
<td>Neurodevelopment 2-3 years</td>
<td>Neurodevelopment 6-7 years**</td>
<td>Near infrared spectroscopy</td>
<td>Cytokine response</td>
<td></td>
</tr>
<tr>
<td>MVU</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Lower IQ scores</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AIUI</td>
<td>-</td>
<td>-</td>
<td>Abnormal cognition and motor scores*</td>
<td>Lower motor scores</td>
<td>Lower cerebral tissue oxygen saturation</td>
<td>Higher levels of IL-6, IL-8, IL-2R and MIP-1β.</td>
</tr>
<tr>
<td>FTV</td>
<td>Higher illness severity</td>
<td>Abnormal GMs Day 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chronic deciduitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>VUE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chorioamniotic hemosiderosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perivillous fibrinoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Markers</td>
<td>Elevated NRBCs</td>
<td>Higher illness severity</td>
<td>Abnormal GMs Day 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chorangiosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MVU – maternal vascular underperfusion; AIUI – ascending intrauterine infection; FTV – fetal thrombotic vasculopathy; VUE – villitis of unknown etiology; NRBCs – elevated nucleated red blood cells

* After exclusion of the children with cerebral palsy no placental lesions were associated with neurodevelopmental outcome at 2 to 3 years of age.
** moderately preterm-born infants (GA 32-36 weeks)
Both fetal thrombotic vasculopathy and elevated nucleated red blood cells, as a marker of fetal hypoxia, only have their impact shortly after birth, whereas ascending intrauterine infection and maternal vascular underperfusion have their impact later in life. Our findings on early and long-term outcomes were consistent throughout this thesis. In both early outcome studies the same placental lesions were associated with adverse outcomes. In both long-term outcome studies ascending intrauterine infection were associated with adverse outcomes. Maternal vascular underperfusion was only associated with adverse outcome in the study on moderate and late preterm infants, not in the early preterm study (Table 2). In the presence of ascending intrauterine infection we also found changes in the status of cerebral tissue oxygenation during the first days after birth (Chapter 7) and higher cytokine levels immediately after birth.

Table 2: The association between placental lesions and outcome in early preterm-born and moderately preterm-born children

<table>
<thead>
<tr>
<th>Preterm group</th>
<th>FTV</th>
<th>↑ NRBCs</th>
<th>MVU</th>
<th>AIUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>early preterm</td>
<td>+ short-term only</td>
<td>+ short-term only</td>
<td>-</td>
<td>+ ↓ motor outcome (CP)</td>
</tr>
<tr>
<td>Moderately preterm</td>
<td>-</td>
<td>-</td>
<td>+ ↓ cognition scores 7y</td>
<td>+ ↓ motor outcome</td>
</tr>
</tbody>
</table>

Abbreviations: FTV – fetal thrombotic vasculopathy; NRBCs – nucleated red blood cells; MVU – maternal vascular underperfusion; AIUI – ascending intrauterine infection; CP – cerebral palsy; y - years

Early preterm: <32 weeks gestational age
Moderately preterm: 32-36 weeks gestational age

Elevated nucleated red blood cells
Elevated nucleated red blood cells (NRBCs) in the placenta are a marker of fetal hypoxia. Significant hypoxia leads to erythropoietin release and subsequent release of red blood cell precursors in an attempt to maximize tissue oxygen delivery.\cite{4,6} Several hypotheses were proposed concerning the timing of hypoxia in the presence of elevated NRBCs - from 48 hours before delivery to an acute event shortly before delivery. Animal studies showed an increase in NRBCs between 6 to 12 hours after the onset of hypoxia.\cite{5,7} A more recent study suggested that NRBCs emerge into the circulation at least 28 to 29 hours before birth,\cite{8} suggesting a prolonged duration of the long-term hypoxia. There may be several reasons for fetal hypoxia. Whereas other placental lesions are all potential causes of fetal hypoxia, elevated NRBCs are not the cause but an indicator of this disruption.\cite{4} In addition to our findings, elevated NRBCs were also suggested to be associated with early-onset neonatal seizures, cerebral white matter injury, and cerebral palsy.\cite{4,9,10} Our conclusion is that the presence of elevated NRBCs indicate some level of fetal distress. This suggests that fetal distress may be the hallmark in this cascade, leading to higher illness severity and impaired quality of general movements.
Fetal thrombotic vasculopathy

Fetal thrombotic vasculopathy (FTV) is defined as the presence of a thrombus in the fetal circulation of the placenta, which may lead to avascular villi. FTV is known to be associated with neonatal problems and neurological impairment later in life. Perinatal asphyxia was described as being associated with placental lesions affecting fetal vascular supply. These lesions include umbilical cord complications (disrupted velamentous vessels, cord tear, hypercoiled cord, cord hematoma), ascending intrauterine infection with fetal vasculitis, and fetal thrombotic vasculopathy. Our findings that the presence of FTV was associated with higher illness severity shortly after birth were in line with these findings. FTV was also suggested as being associated with ventriculomegaly, neonatal stroke, cerebral ultrasound abnormalities as intraventricular hemorrhages, periventricular leukomalacia and infarction, and neurological impairment later in life. Several hypotheses were proposed explaining the relation between FTV and neurological problems. The etiology of several neurological problems is thought to have an antenatal as well as an intrapartum component. FTV was described as a chronic event with an onset more than one week before delivery, leading to a non-optimal intrauterine environment. This might result in increased susceptibility to brain injury by decreasing the ability of normal infants to withstand the inherent stresses of routine labor and delivery. Another explanation of FTV leading to neurological problems is the presence of thrombi in the fetal circulation of the placenta. Such thrombi may travel into the fetal circulation via the umbilical vein and into large cerebral blood vessels across the foramen ovale or ductus arteriosus, causing embolic cerebral arterial infarction.

It is thought that the pathogenesis of neurological impairment has both an antenatal and an intra-partum component. An event weeks before delivery can result in a non-optimal fetal environment. This might result in lowering the threshold required for more recent events to cause brain injury. This is in line with our findings, and FTV could be such an antenatal event. Our findings also suggested that these placental related neurological problems were already present during the first weeks after birth. Examining the placenta for the presence of this lesion may create the opportunity for intervention to improve outcome early in life.

Ascending intrauterine infection

Ascending intrauterine infection (AIUI) is an acute inflammation of the extraplacental membranes (chorion and amnion) or chorionic plate. In our systematic review (Chapter 2) we found AIUI most frequently associated with neurological problems. We confirmed this in Chapters 5 and 6. In Chapter 5 we reported that AIUI was associated with abnormal cognitive and motor outcomes at toddler age in very preterm infants. Please note that these abnormal outcomes were only seen in children diagnosed with cerebral palsy (CP) in our study group. When we excluded the children with CP, AIUI was no longer associated with outcome, suggesting an association between AIUI and CP. In Chapter 6 we also found AIUI to be associated with lower motor scores, but now in moderately preterm-born and
late preterm-born children. Several other investigators also found a relationship between AIUI and motor outcome and/or CP.4,27-30

It is hypothesized that elevated cytokine levels in the presence of AIUI play a role in the etiology of CP.24,27-30 The elevated blood and brain cytokine levels resulting from maternal infection might lead to central nervous system damage in the fetus. The inflammatory cytokines can be neurotoxic and inhibit oligodendrocytes in the developing white matter. As a consequence, the oligodendrocytes can lose their myelin production. This results in damage of astrocytes, microglia, and white matter, which can in turn lead to cerebral palsy.27,28,30-32

Maternal vascular underperfusion

Maternal vascular underperfusion (MVU) is a chronic placental lesion with its onset more than one week before delivery.18 It is caused by inadequate spiral artery remodeling leading to decidual vasculopathy.33 Decidual vasculopathy may in turn lead to placental underperfusion which leads to a lasting non-optimal intrauterine environment. In our systematic review we found that MVU associated with fetal death (Chapter 2). It is even suggested as being the main cause of fetal death.34 In our study of moderate and late preterm infants, we found that MVU associated with lower IQ scores (Chapter 5). The literature is also unclear about the relationship between MVU and outcome in surviving infants. One investigator found MVU to be associated with neonatal morbidities such as low Apgar scores and the presence of necrotizing enterocolitis in preterm infants,35 while others did not find this relation.36,37 A few studies addressed the relation between MVU and long-term outcome, with a main focus on neurological impairment.4,19,38-40 Only one study on preterm infants addressed the issue of IQ scores in relation to the presence of MVU and found lower IQ scores in its presence.39

The presence of enduring placental hypoperfusion results in a non-optimal intrauterine environment. As in the presence of other chronic placental lesions, this may result in increased susceptibility to brain injury by decreasing the threshold to withstand the inherent stresses of routine labor and delivery.4,12 Placental underperfusion in the presence of MVU can lead to a reduction of the perfusion surface and, as a consequence, non-optimal oxygen delivery to the fetal circulation. This may result in some degree of cerebral underperfusion which may be harmful to the developing brain, perhaps even leading to lower cognitive scores at school age.

Placental lesions not related to outcome measures

Most of the placental lesions we studied were associated with short-term neonatal and long-term outcomes. For a few placental lesions we could not find an association with outcome measures.
Villitis of unknown etiology and chronic deciduitis
Villitis of unknown etiology (VUE) and chronic deciduitis are both lymphohistiocytic inflammations of the stem and chorionic villi, and the decidua, respectively. VUE was suggested to be associated with neonatal infection, neonatal encephalopathy, and neurological impairment. No associations were found regarding chronic deciduitis and outcome. Both lesions are predominantly present toward fullterm age. This might be the reason for the low frequency of these placental lesions in our study groups and the absence of an association with outcome.

Chorangiosis
Chorangiosis, similar to elevated nucleated red blood cells, is a placental marker rather than a placental lesion. Chronic hypoperfusion is thought to increase in the number of villous capillaries leading to chorangiosis. The highest incidence of chorangiosis is seen between 34 and 39 weeks’ GA, which explains the sporadic occurrence of chorangiosis in our study groups. The association between chorangiosis and neonatal outcome is unclear. Only a few studies focused on the relation between this placental marker and outcome. Congenital malformations and low Apgar scores were suggested to be associated with chorangiosis. The low number of placentas with chorangiosis might be the reason why we did not find a relationship with outcome. More studies focusing on chorangiosis are needed to determine its relationship with outcome.

Difficulties in classifying placental lesions
For fullterm infants the definitions of placental lesions are clear as proposed by several committees and textbooks. These definitions focus predominantly on the fullterm placenta. Some lesions considered abnormal in the case of fullterm placentas may be normal for preterm placentas. An example is the presence of NRBCs. In fullterm placentas only sporadic NRBCs may be present in the fetal circulation. But during the preterm period the presence of more NRBCs is normal. The absence of definitions specific for preterm placentas makes it difficult to compare studies that focus on this lesion.

Placental lesions can be classified in several ways: by categories (developmental disorders, infectious disorders, and circulatory disorders), by diagnosis (MVU, AIUI, FTV, VUE, chronic deciduitis, placental markers), or by specific characteristics per placental lesion (for example, infarcts in the presence of MVU, avascular villi in the presence of FTV). During recent years most studies focused on placental diagnosis rather than specific characteristics of placental lesions. This placental diagnosis approach seems most relevant because it is based on a common pathophysiological mechanism per diagnosis. The studies included in this thesis were also based on this classification. The use of placental diagnosis groups enhances comparability between studies focusing on placental lesions and outcome. Classifying by specific characteristics is probably too specific and not relevant for clinical practice.

During our search of the literature we noticed that studies on placental pathology
and perinatal death on one hand, and studies on neonatal outcome on the other, classify placental lesions differently. The majority of studies on placental pathology and stillbirth focus on the presence or absence of placental lesions without specifying the diagnosis of placental lesions. This is probably due to the stillbirth classification systems used. Most of these systems only report the presence or absence of placental pathology. Studies concerning placental lesions and neonatal or neurological outcome do specify the lesions and find several relations between placental diagnoses and outcome. Classifying placental lesions in placental diagnosis groups in stillbirth studies may provide additional information on the cause of death.

Possible disease mechanisms and consequences for clinical practice
We found several associations between placental lesions and outcome. These associations do not necessarily reflect a causal relationship. It is more plausible that placental lesions are part of a multiple interaction model leading to morbidity. Multiple interactions of maternal, placental, and fetal origin are likely to play a role in the etiology of neonatal and neurological morbidity. This is supported by the fact that almost all preterm infants have one or more placental lesion, or more, while only a few of these children develop neurological morbidities. The presence of placental lesions alone is, therefore, not conducive of an adverse outcome. We need additional measures or characteristics to provide a risk profile for placental lesions that lead to morbidity.

We endeavored to gain insight into possible mechanisms which possibly play a role in the development of placenta-related neurological problems. We studied the relation between placental lesions and cerebral oxygenation and the presence of cytokine responses shortly after birth. In the presence of ascending intrauterine infection we found lower cerebral tissue oxygen saturation and higher oxygen extraction on Days 2, 3, and 4 after birth. We found elevated cytokine levels immediately after birth in the presence of ascending intrauterine infection. These findings suggest that several mechanisms may play a role in the development of placenta-related morbidities. In the presence of ascending intrauterine infection the cerebral circulation might be disturbed by higher metabolic activity resulting in higher oxygen extraction. Higher metabolic activity may be the result of elevated cytokines in the presence of ascending intrauterine infection. We did indeed find elevated cytokines at or directly after birth in the presence of ascending intrauterine infection, suggesting an important role of cytokines in the development of placenta-related adverse outcomes.

Other placental lesions, however, were not associated with cerebral oxygenation or the presence of elevated cytokine levels. The other placental lesions we found to be associated with adverse outcome were all chronic lesions, whereas ascending intrauterine infection is a more acute event. The chronic placental lesions probably create a non-optimal intrauterine environment, leading to adverse outcomes.

Strengths and limitations of this thesis
A major strength of this thesis is the consistent classification of placental lesions throughout.
All placentas were examined by the same pathologist using a single case record file. In addition, we studied a broad spectrum of placental diagnostic lesions with respect to several outcome measures.

The studies presented here had several potential limitations. Firstly, our results were based on relatively small study populations. Nevertheless, we did find associations between placental lesions and outcome. Secondly, due to the high incidence of placental lesions in the preterm population we only had a few placentas without placental lesions. When determining associations between placental lesions and outcome, the control groups consisted partly of infants with other placental lesions than the one under study.

Implications and consequences for clinical practice
This thesis focused on placental lesions and outcome and is, therefore, embedded in three disciplines: pediatrics, pathology, and obstetrics. We are of the opinion that the findings presented here have consequences for the specialists involved in each of these disciplines.

Pediatricians: Our recommendation to pediatricians is that they make an effort to obtain placental examination results, particularly in the case of unexpected preterm births or unexpected neonatal morbidities. In the current situation the placenta results are only reported back to the obstetrician and not to the pediatrician as well. It may benefit childcare if reporting placental examination to the pediatrician were to become standard practice. These findings can provide clues towards understanding neonatal morbidities and should, therefore, be taken into consideration. Understanding neonatal morbidities may also provide opportunities for early interventions.

Obstetricians: The question is in which cases placentas should be sent to the pathologist for examination. In this thesis we focused on preterm infants born at less than 32 weeks’ GA and infants born between 32 and 36 weeks’ GA. In both groups we found associations between placental lesions and outcome. We also showed, however, that placental examination alone is not a specific screening method for the individual patient. It does increase the understanding of the reason of preterm birth, and it can give insight into adverse outcome for children as a group. For this reason we recommend that all placentas of all preterm infants be sent to the pathologist. Further research is needed to determine in which cases placental examination can be used as a screening method for adverse outcome, creating a risk profile in combination with additional risk factors. Cost effectiveness should be taken into account in answering this question.

Pathologists: Placental examination categorized as placental diagnostic groups seems most relevant for understanding outcome, as these diagnostic groups are based on pathophysiological mechanisms. Definitions of these diagnostic categories are presented by the committees of the perinatal section of the Society for Pediatric Pathology, and in various textbooks on the pathology of the placenta. The results of the placental examination should be reported not only to the obstetrician, but to the pediatrician as well.
Future perspectives
We demonstrated that several placental lesions are associated with short-term and long-term neonatal and neurological morbidities. As stated before, this association does not imply a causal relationship. Approximately 90% of preterm infants are born with one or more placental lesions, but only a small group will develop neurological problems. Placental lesions are, therefore, not suitable as screening method. More information is needed to discover which children are at risk of adverse outcomes, and for establishing a risk profile. Placental lesions should be part of this profile, but additional measurements are needed as placental lesions alone are not specific enough to predict neonatal or neurological morbidity in the individual patient. This risk profile should exist of both ante partum factors and post partum measurements.

Part of the risk profile may consist of epigenetic factors. Placental lesions might already have their onset early in pregnancy due to epigenetic alterations leading to changes in gene expression. Causes for these placental epigenetic changes may include intrauterine stress due to a maternal disease or adverse insults to the intrauterine environment.\(^48\) This may in turn cause placental dysfunction and hence adverse neonatal outcome. Further research into these epigenetic changes might give more clues as to which children are at risk of adverse outcome.

Placental examination can be used to answer specific clinical questions. For example, placental examination might provide additional information on the question whether to start administering antibiotics to a preterm infant. When there are no signs of infection in the placenta and no signs of clinical infection, it might strengthen the choice not to start antibiotics. Antibiotic exposure in preterm infants is known to be associated with an increased risk of necrotizing enterocolitis and other adverse outcomes. The role of placental examination in such specific situations should be further investigated.\(^49,50\)

In this thesis we addressed questions relating to placental lesions and morbidity in a selected population of preterm-born children. Additional research is needed to address the relevance and implications of placental examination in an unselected group.

We know now that placental lesions play a role in developing adverse short-term and long-term outcomes. The findings of placental examination can be made available in a relatively short time period. This gives an opportunity for early interventions in order to lower the risk of adverse outcomes. These possible early interventions should be studied to improve neonatal and neurological outcome.
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