Placental lesions and outcome in preterm born children
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Chapter 1

General introduction and outline of the thesis

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Placenta
Except for marsupials and egg laying mammals, all mammalian life begins with a placenta. The first common ancestor of all placental mammals is thought to have evolved during the Paleogene Period dating 66 million years ago, some hundred thousand years after the extinction of the dinosaurs. This tiny ancestral placental mammal gradually evolved and diverged and today there are more than five thousand species of mammal, including the human being. After all these millions of years, the placenta is still the single most important organ for the development of any placental mammalian fetus.

In humans too, the placenta is the link between the mother and the fetus during pregnancy, and it is an essential organ for the development of the fetus. A well-functioning placenta is a necessary precondition for a healthy outcome of pregnancy. The placenta has unique characteristics. It is the only organ which is connected to another individual. The blood of both the mother and the fetus flows through the placenta, each in a separate circulation. And it is the only organ which enables the exchange of nutrients and oxygen from the mother to the fetus and removes fetal waste products. Less than optimal placental performance can, therefore, lead to morbidity or even mortality of the fetus.

Placental Examination
Because it is present during the entire duration of pregnancy, examining the placenta can provide insight into the intrauterine environment of the fetus. Useful information can be obtained on the causes, severity, and timing of superimposed pathology, fetal well-being, or neonatal morbidity and mortality. The importance of placental examination was acknowledged by Ballantyne, an obstetrician, as early as 1892. He wrote:

‘A diseased foetus without its placenta is an imperfect specimen, and a description of a foetal malady, unless accompanied by a notice of the placental condition, is incomplete. Deductions drawn from such a case cannot be considered as conclusive, for in the missing placenta or cord may have existed the cause of the disease and death. During intrauterine life the foetus, the membranes, the cord and the placenta form an organic whole, and disease of any part must react upon and affect the others.’

To date, however, the added value of placental examination is not generally acknowledged by pediatricians. The results of placental examination by pathologists are generally reported back to the obstetrician, but this information rarely reaches the pediatrician, even though it could provide useful insight into the possible causes of fetal and neonatal morbidity and mortality.

Placental lesions
The placental lesions we focus on in this thesis can be divided into four categories: umbilical cord complications, circulatory disorders, inflammatory disorders, and placental markers. These categories are presented in an overview of the placenta in Figure 1.
The first category consists of complications of the umbilical cord such as obstruction or disruption of the umbilical cord blood flow. The second category consists of circulatory disorders. These lesions can in turn be divided into maternal and fetal circulatory disorders. Maternal circulatory disorders are maternal vascular underperfusion (MVU) due to inadequate spiral artery remodeling or spiral artery pathology. This can lead to parenchymal pathology such as placental hypoplasia or abnormal villous maturity. MVU is commonly seen in pregnancies complicated with preeclampsia. Fetal circulatory disorders are characterized by the presence of thrombosis in the umbilical cord, chorionic plate, or stem villus vessels with secondary degenerative pathology in the fetal vasculature. As a group these lesions are known as fetal thrombotic vasculopathy. The third category is inflammatory disorders. These can be divided in ascending intrauterine infection (AIUI), villitis of unknown etiology (VUE), and chronic deciduitis. AIUI is an acute inflammation of the extraplacental membranes (chorion and amnion) or chorionic plate. AIUI can emerge as a maternal response (acute chorioamnionitis or chorionitis) or as a fetal response (acute umbilical or chorionic vasculitis). VUE is a chronic lymphohistiocytic inflammation of the stem and chorionic villi, whereas chronic deciduitis is a lymphohistiocytic inflammation of the decidua. The fourth category consists of placental markers for fetal hypoxia and chronic hypoperfusion. These markers are elevated nucleated red blood cells (NRBCs) and chorangiosis. Significant fetal hypoxia leads to erythropoietin release and subsequent release of red blood cell precursors in an attempt to maximize tissue oxygen delivery, resulting in elevated NRBCs. Chronic hypoperfusion increases the number of villous capillaries in the placenta to optimize perfusion, leading to chorangiosis.

Figure 1: schematic drawing of the placenta, adapted from N.O. Lunell et al, *Uteroplacental Blood Flow*
Aims of the thesis
Placental lesions are known to be associated with fetal death. Less is known about the relationship between placental lesions and neonatal and neurological morbidity. Placental lesions associated with fetal death are also found in live-born infants. The question arises whether these placental lesions are also associated with morbidity. The primary aim of this thesis was, therefore, to determine whether placental lesions are associated with neonatal morbidity and neurological development. There are suggestions that several placental lesions are associated with outcome. The mechanism of placental lesions leading to neonatal and neurological morbidity is unclear. Our secondary aim was, therefore, to determine a possible mechanism of placental lesions leading to neonatal and neurological morbidity.

Outline of the thesis
This thesis consists of four parts. In each part we addressed one or two research questions.

Part 1 Literature Overview of Placental Lesions and Outcome
Research question 1: What is known in the literature about the relationship between placental lesions and perinatal death, neonatal morbidity, and neurological outcome?
In Chapter 2 we review what is known about the relationship between placental lesions and outcome. In the review we address the relationship between placental lesions and perinatal death, neonatal morbidity, and neurological outcome.

Part 2 Placental Lesions and Short-Term Outcome
Research question 2: What is the relationship between placental lesions and short-term neonatal outcome and neurological outcome in preterm-born children?
In Part 2 we describe the relationship between placental lesions and short-term neonatal outcome as well as neurological outcome in preterm infants. In Chapter 3 we assessed the short-term neonatal outcome during the first 24 hours after birth with the Score of Neonatal Acute Physiology Perinatal Extension (SNAPPE). This score assesses the illness severity of infants during the first 24 hours after birth. Another outcome measure we used shortly after birth was quality of general movements. In Chapter 4 we describe the relationship between placental lesions and the quality of general movements during the first two weeks after birth. The quality of the general movements reflects an infant’s neurological condition shortly after birth and is a predictor of neurological outcome later in life.
Part 3 Placental Lesions and Long-Term Outcome
Research question 3: What is the relationship between placental lesions and neurodevelopmental outcome at toddler age and early school age in preterm-born children?
In Part 3 we present the relationship between placental lesions and neurodevelopmental outcome at toddler and school age. We determined this relationship in two groups of preterm-born children. The first group was born at less than 32 weeks’ gestational age (GA), the second group were moderately preterm-born children (born between 32 and 36 weeks’ GA). In Chapter 5 we describe the relationship between placental lesions and neurodevelopmental outcome at two to three years of age in preterm-born children (<32 weeks’ GA). In Chapter 6 we determine the relationship between placental lesions and neurodevelopmental outcome at five to six years of age in late preterm-born children.

Part 4 Disease Mechanisms of Placental Lesions Leading to Neurological Morbidity
In part 4 we investigate possible mechanisms of placental lesions leading to neurological problems.
Research question 4: What is the relationship between placental lesions and cerebral tissue oxygen saturation and extraction in preterm-born children?
The first mechanism we studied concerning placenta-related neurological problems was cerebral blood flow. In Chapter 7 we present the relationship between placental lesions and cerebral tissue oxygen saturation and extraction as determined by using near-infrared spectroscopy (NIRS).
Research question 5: Are placental lesions associated with cytokine responses directly after birth in preterm-born children?
The second possible mechanism we studied were cytokine responses in the presence of placental lesions. In Chapter 8 we describe cytokine levels in the presence and absence placental lesions.

Chapter 9 is a general discussion of the findings presented in this thesis and some future perspectives concerning placental lesions, placental examination, and neonatal outcome. In chapter 10 we summarize our findings in English and Dutch.
References
Part I

Literature overview of placental lesions and outcome

Chapter 2: Placental Pathology, Perinatal Death, Neonatal Outcome and Neurological Development: A Systematic Review