Preterm birth, long-term outcome: how an early start affects school-aged children

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PART TWO

GENERAL INTRODUCTION

Preterm birth is defined as birth before 37 completed weeks of gestation [1]. Globally, an estimated 15 million babies are born preterm every year, with the rate of preterm birth ranging between countries from 5% to 18%. Prematurity can be divided into three groups, based on gestation:

1. Extremely preterm born infants (born below 28 weeks' gestation)
2. Very preterm born infants (born between 28 and 32 weeks' gestation)
3. Moderate to late preterm born infants (born between 32 and 37 weeks' gestation)

With the improvement of fetal and neonatal care in high-income countries, perinatal mortality after preterm birth has significantly decreased over the last decades [2]. However, the challenges following preterm birth can have a profound impact on long-term development. All preterm infants are susceptible to experiencing difficulties in a wide variety of domains, including motor skills, cognitive capacities, academic attainment and behavior [3, 4].

The purpose of this thesis is to describe a longitudinal cohort of children born below 32 weeks' gestation and study the associations between neonatal factors, early outcomes at two years and school-aged outcomes at ten years of age. In this chapter, we will start with an outline of preterm birth in the Netherlands and the Dutch neonatal follow-up program. We will give a brief overview of what is known about neurodevelopmental outcomes of very preterm infants until now and describe known risk factors of adverse outcomes. Finally, we will present the design and aims of this thesis.

Preterm birth and follow-up in the Netherlands

In the Netherlands, approximately 11.000 infants are born preterm every year, accounting for 6.5% of all live births [5]. Nearly 2500 of the preterm infants are yearly admitted to one of the Neonatal Intensive Care Units (NICU's) due to extreme or very preterm birth. Because children born preterm are at risk of neurodevelopmental impairments, all children born below 30 weeks' gestation and/or with a birthweight below 1500 grams are enrolled in the national Dutch neonatal follow-up program [6]. This program is designed to assess children in four domains, including growth and health, neuromotor development, cognitive development, and social-emotional development. Since the implementation of the national guideline [6] in 2015,

children and their parents are invited for five follow-up visits; at the corrected age of six and twelve months, and at the age of two, five, and eight to nine years. All children are assessed by a neonatologist, physical therapist and child psychologist in order to capture the child's functioning.

There are several reasons why follow-up of children born preterm is important. First of all, it provides insight for parents in the development of their child. By discovering potential developmental challenges at an early stage, children might possibly benefit from early adapted intervention strategies. Furthermore, the collection of follow-up data is essential in order to increase our knowledge and our ability to adequately counsel the expectations of parents of preterm infants born today. The collection of follow-up data also allows us to assess changes in (long-term) developmental outcome over time and provides feedback about the effects of clinical practice.

Developmental outcome

The outcome of children born preterm has been a topic of interest for many years [7, 8]. Most studies have focused on neurodevelopmental outcome at 24 months of age, although the impact of preterm birth reaches far beyond toddlerhood.

Toddlerhood

During the first years of life, major abnormalities in motor, cognitive and sensory functioning will be identified, including cerebral palsy, severe mental retardation, hearing loss and visual impairment [9]. Approximately a quarter of very preterm infants shows substantial difficulties at 24 months of age, corrected for prematurity [2].

School-age

During school-age, preterm birth is associated with lower cognitive scores and difficulties in executive functioning and academic attainment [4, 7, 10]. This leads to an increase in special educational needs, including learning support and/or enrolment in special education [11]. Furthermore, children born preterm have a 2 to 4 fold higher risk for experiencing internalizing and externalizing behavioural problems, including symptoms of attention deficit hyperactivity disorder, autism spectrum disorder, and anxiety disorders [12].

Adolescence and adulthood

Adolescents born very preterm have more difficulties in establishing and maintaining social contacts [13] and have diminished social skills. Compared to the general Dutch population, very preterm adolescents are more likely to be poorly educated and/or to be unemployed or not enrolled in school activities at 19 years of age. Reassuringly, as adults, the majority of preterm infants rates their functioning similar to their term-born peers, even though they remain at risk for general health issues and anxiety and/or depressive disorders [14].

Initial studies reporting on outcomes after very preterm birth mainly focused on major impairments (sensory impairments, cerebral palsy and/or mental retardation), and found the occurrence to remain relatively stable among different birth cohorts over time[15, 16]. In contrary, the prevalence of more subtle problems, including behavioral difficulties and learning problems, seems to increase. This might be the result of more sensitive assessment tools for older children, but also because subtle problems usually don't appear until a later stage of life.

Factors associated with developmental outcome

With increasing knowledge of the developmental challenges faced by children born very preterm, an understanding of factors associated with adverse outcome and the ability to predict who is at risk becomes clinically relevant. The aetiology of neurodevelopmental impairments is complicated and includes multiple facets such as genetic, maternal, peri- and postnatal, and sociodemographic factors. Additionally complex is that, with increasing age, environmental factors become of greater influence in predicting outcome compared to the factors known at birth [17].

One of the strongest and most consistent predictors of neurodevelopmental functioning is gestational age. With each completed week of gestation, the risk of (severe) impairment decreases [18]. Linsell and colleagues reported in multiple systematic reviews on prognostic factors for cognitive development, motor impairment and behavioural problems. Factors found to be associated with cognitive impairment were male sex, ethnicity, lower birthweight and lower levels of parental education in children younger than 5 [17]. Interestingly, only the influence of parental education sustained as a predictive factor in older children. Intraventricular haemorrhage and periventricular leukomalacia were especially predictive for

cerebral palsy [19] and there was a lack of evidence concerning the prediction of general behavioural problems [20]. One of the most important and frequently seen complications in preterm infants is neonatal brain injury, a factor that has gained increasingly more attention in predicting early outcome.

Neonatal brain injury

The brain of children born very preterm is often organized differently compared to the brain of full-term born children, due to the disruption in development of brain structures and brain maturation [21]. Neonatal brain injury can be detected by either cranial ultrasound or magnetic resonance imaging (MRI). Nowadays, most children with neonatal brain damage have subtle brain abnormalities, which are difficult to detect without an MRI [22, 23]. However, as the prognostic implications of MRI are still debated, the use of neonatal MRI is currently not recommended as standard care. In particular, the associations between MRI findings and long-term developmental outcomes are still largely unknown.

Purpose and design of the study

The general aim of this thesis was to report on long-term developmental outcomes in children born very preterm and to investigate the association between outcome and brain abnormalities as seen on neonatal MRI. Because this study has been part of a broader prospective study investigating developmental outcomes after preterm birth (*PReterm brain injury, long-term Outcome and brain Development study (PROUD)*), participants were recruited from an ongoing longitudinal cohort of 113 children, born at the Leiden University Medical Center (LUMC) between May 2006 and October 2007. All infants underwent an MRI at term-equivalent age, and were invited for a follow-up study at two years of age, creating a database with perinatal outcomes and developmental outcomes in toddlerhood. For the current study, all children of the original cohort were invited at 9-10 years of age for a clinical neurodevelopmental follow-up visit, and an additional MRI and EEG. The neurodevelopmental follow-up focused on four domains and included neurological functioning, motor skills, cognition and behavior. The first three domains were assessed by a child neurologist, child physical therapist and child psychologist. Parents completed questionnaires on their child's behavior for the behavioral domain.

Outline

Chapter 1 describes the rate and stability of impairments in children born preterm by assessing early and school-age outcome in four developmental domains (neurological functioning, motor skills, cognition and behavior) at both 2 and 10 years of age. The individual change in outcome between both timepoints was also assessed. This gives an insight not only in the rates of impairment at both timepoints, but also in the course of development over the years for individual children. As early prognostic markers can have an important role in predicting development, **Chapter 2** associates neonatal neuroimaging findings with both early and school-age outcome within a cohort of very preterm children. Chapter 3 and 4 will focus on outcome measures other than those derived from standardized assessments. **Chapter 3** describes how children perform at school, by reporting their grades on reading, spelling and mathematics and comparing these to their Dutch peers. Most studies reporting on outcomes include an intelligence test. However, intelligence measured in a clinically controlled environment is not always (fully) predictive of school results, which are assessed in a classroom filled with other children and many distractions. Besides reporting on classroom-evaluated performance, we also tried to identify those children most at risk to fall behind at school. **Chapter 4** covers a qualitative study reporting on social-emotional and behavioral issues after very preterm birth. In this study we examine both the parents' and teachers' perspectives. What are the themes parents worry about and do these change between two and ten years of age? Because children of ten years of age spend much time at school, we also included teachers' perspectives and reported on differences compared to the parental view. Lastly, the main findings of this thesis are discussed and directions for future research are suggested.

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