Outcomes 8 years after preterm birth

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Chapter 1

General introduction

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Improving long-term health outcomes of preterm infants: how to implement the findings of nutritional intervention studies into daily clinical practice.

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TRENDS IN PRETERM BIRTH

Preterm-born children and adults comprise an increasing proportion of the population. Of the 169,136 infants born in the Netherlands in 2016, 11,622 (6.9%) were born preterm (i.e., before 37 weeks gestation) and 2,295 (1.4%) were born very preterm (i.e., before 32 weeks gestation). Over the past decades, in developed countries the incidence of preterm birth increased from 7.2% in 1990 to 8.6% in 2010, with a relatively stable proportion of 15% very preterm birth.[1-4] Meanwhile, neonatal mortality after very preterm birth, specifically in the extremely preterm range, has decreased due to improvements in perinatal care.[5] Nowadays, mortality rates of 5%–17% are reported for infants born before 29 weeks of gestation and rates of up to 30% for those born at 24 weeks gestation.[2,6] In contrast, the incidence of neonatal morbidities has remained unchanged or even increased over time,[5,7,8] and the same trend was observed for long-term cognitive and motor impairments.[9,10] Preterm birth has also been associated with an increased risk of cardiometabolic diseases in later life.[11-13] Therefore, it remains important to develop strategies aimed at improving long-term outcomes after very preterm birth.

LONG-TERM CONSEQUENCES OF PRETERM BIRTH

Infants who are born (very) preterm spend most of what would normally be the third trimester of pregnancy in an extrauterine environment. With preterm birth, numerous developmental processes, along with the transplacental supply of nutrients and hormones, are suddenly disrupted. In addition, preterm infants generally have high nutritional demands due to factors like acute illnesses, rapid brain growth and increased thermogenesis, while enteral feeding is difficult because of gut immaturity. As a result, early postnatal growth restriction and impaired brain growth are common among preterm infants, which may have serious consequences for later health and (neuro)developmental outcomes.

Neurodevelopment

The third trimester of pregnancy is a period of rapid brain growth and development in terms of vascularization, myelination, axonal development, cortical thickening, and cerebellar growth.[14] In this thesis we will focus on the consequences of suboptimal early-life nutrition and growth restriction that may lead to neurodevelopmental impairment in preterm infants. Other factors, such as ischemia, inflammation and toxic noxes like free-radicals and drugs, could also damage the preterm infants' vulnerable brain. Together, these factors may result in 'encephalopathy of prematurity', the all-encompassing term for

different types of structural and functional damage of the preterm infants' brain.[14] As a consequence, very preterm-born children are at increased risk for cognitive, behavioral and motor problems:[11,12] 24% of them were found to have moderate to severe long-term impairments.[15] In a meta-analysis, prematurity was associated with a 0.86 SD lower intelligence quotient score.[10] Another meta-analysis showed that children born very preterm or with a very low birth weight (VLBW, < 1500 g) had lower motor-functioning scores than term-born children.[11]

Cardiometabolic risks

In 1989 Barker et al. described associations between the intrauterine and childhood environment, and later hypertension and mortality from cardiovascular disease.[16,17] In the early 1990's, the 'thrifty phenotype or Barker hypothesis' was postulated,[18,19] stating that fetal malnutrition may lead to a lower beta-cell mass in an attempt to selectively spare brain growth at the expense of somatic and visceral growth.[19,20] A nutrient deprived environment in the womb with subsequent fetal growth restriction may result in permanent changes in body structures and functions that predispose to chronic diseases in adulthood, as also stated in the 'fetal origins of disease' hypothesis.[21] If the deprived fetus is exposed to a nutrient rich environment after birth, this may lead to accelerated growth with excess fat mass relative to lean mass and an increased risk of insulin resistance and cardiovascular disease.[22] After Barker and Hales, the associations of fetal undernutrition, suboptimal fetal growth and low birth weight with the long-term risk for cardiometabolic diseases have been extensively researched. The concept of adverse early-life events increasing the risk of (cardiometabolic) diseases in later life is now known as the 'Developmental Origins of Health and Disease' (DOHaD) concept.

While most of the above mentioned associations were described for full-term pregnancies, preterm birth itself has also been associated with (components of) the metabolic syndrome and cardiometabolic disease in later life.[23,24] The metabolic syndrome consists, depending on the definition, of a cluster of cardiovascular risk factors that includes obesity, high blood pressure (BP), diabetes or decreased insulin sensitivity, and an atherogenic lipid profile.[25] Large cohort studies showed that adults who were born preterm have a higher BMI and a more adipose body composition.[26] This is associated with a 2-fold higher risk of obesity[27] and cardiovascular disease,[28] and a 4-fold higher risk of metabolic syndrome[29] compared to term-born peers.

Hypertension is more frequent in adults born preterm. Meta-analyses reported an estimated rise in systolic BP of 2.5–4.2 mmHg in adults born very preterm or with VLBW

compared to term-born adults.[30,31] Mechanisms that have been suggested to underlie the association between preterm birth and higher BP in later life include activation of the sympathetic nervous system and renin-angiotensin-aldosterone systems, and alterations in hypothalamic-pituitary-adrenal (HPA)-axis activity.[32,33] Furthermore, salt sensitivity of BP, a risk factor for cardiovascular disease in later life through hypertension as well as independently,[34] has been associated with low birth weight.[35] A relation between salt sensitivity of BP and prematurity has not been described before.

Prematurity was found to increase the risk of glucose intolerance and diabetes at later age.[36-38] At age 4–10 years, preterm-born children were found to have a reduced insulin-sensitivity as assessed by an intravenous glucose tolerance test compared to term-born peers.[23] There is some evidence suggesting that prematurity predisposes to a more atherogenic lipid profile with higher total cholesterol, higher LDL and lower HDL, albeit not unequivocally.[13]

Bone health

During the last trimester of pregnancy the placental transfer of minerals (i.e., calcium, phosphorus and magnesium) as well as fetal bone mineral accretion reach their peak.[39] In case of preterm birth this process is disrupted, resulting in a lower bone mineral content and density (BMC and BMD, respectively) at term-equivalent age compared to term-born infants. Catch-up in BMC/BMD (relative to body size) seems to occur often within the first 6 months of life.[40] However, it is uncertain whether peak bone mass, an important predictor for later osteoporosis and fracture risk, may be influenced by the adverse early-life bone mineralization. Long-term results are conflicting with some studies showing lower BMC in preterm-born children and others showing no association.[39]

For all of the above mentioned consequences of preterm birth, suboptimal fetal growth, neonatal morbidity, insufficient nutrition, and growth restriction during the first weeks to months after preterm birth have been recognized as important and potentially modifiable risk factors.

INFLUENCES OF PRENATAL AND POSTNATAL GROWTH

The importance of defining prenatal and postnatal growth patterns in preterm infants

Disruptions in prenatal growth (intrauterine growth restriction – IUGR) as well as postnatal growth (extrauterine growth restriction – EUGR) have been related to unfavorable long-

term outcomes, including impaired longitudinal growth, impaired neurodevelopment and cardiometabolic diseases.[41-43] On the other hand, increased growth rates during hospital admission and thereafter are associated with favorable later growth and better neurodevelopmental outcomes in extremely low birth weight infants (i.e., birth weight < 1000 g).[44-47] Consequently, when assessing the long-term consequences of early-life growth, both intrauterine/prenatal growth (represented as small- or appropriate-for-gestational-age at birth, SGA or AGA, respectively) and extrauterine/postnatal growth (either steady growth, growth restriction (GR) or catch-up growth (CUG)) should be taken into account.

In this thesis the following definitions will be used:

- Appropriate-for-gestational-age (AGA): birth weight and birth length > -2 SDS
- Small-for-gestational-age (SGA): birth weight and/or birth length ≤ -2 SDS
- Growth restriction (GR): weight and/or length ≤ -2 SDS at 6 months CA after being born AGA
- Catch-up growth (CUG): weight and length > -2 SDS at 6 months CA after being born SGA (definitions in the literature are highly heterogeneous)

Prenatal

Intrauterine growth restriction can be caused by multiple (interacting) maternal, placental and fetal factors and may result in infants being born SGA.[48,49] Perturbations in the intrauterine environment may, for example, be induced by altered maternal HPA-axis activity in combination with an altered endocrine function of the placenta. In 1993, the 'fetal cortisol hypothesis' was proposed as an alternative for (or maybe addition to?) the 'thrifty phenotype or Barker hypothesis', explaining the association between low birth weight and later cardiometabolic disease risk.[50] It states that IUGR is associated with fetal cortisol overexposure due to a reduced expression and activity of placental 11β-hydroxysteroid dehydrogenase (11β-HSD2) that normally protects the fetus from excess cortisol.[50,51] In addition to lower birth weight, an altered fetal HPA-axis development and shorter gestation have been described.[52] In full-term pregnancies, the third trimester is crucial for maturation of the fetal HPA-axis.[53] Infants that are born preterm lack this intrauterine period of maturation and often experience the consequences of an immature HPA-axis, such as hypotension and hypoglycemia, in the neonatal period.[33] Furthermore, an altered HPA-axis setting (i.e., initial suppression followed by increased activity later in life) has been associated with higher BP and increased fat mass accretion in childhood and higher fasting cortisol in adulthood.[52]

In addition, insulin-like growth factor (IGF) types 1 and 2, together with insulin, are part of the complex regulation of prenatal and early postnatal growth.[48,54,55] Fetal growth is largely dependent on IGF's of which the activity is strongly related to nutritional status.[56,57] Impaired fetal growth has been associated with low umbilical cord blood levels of IGF-1.[48] During pregnancy, IGF levels increase to reach a peak in the third trimester.

Postnatal

In term infants, growth regulation gradually shifts from nutrition dependency towards growth hormone dependency which is only fully established in the second year.[58] Adequate postnatal growth of preterm infants can only be attained under optimal nutritional and endocrine circumstances, and was found to be associated with IGF-1, protein intake and insulin, until 6 months CA.[56,59,60] After preterm birth, low serum IGF levels have been found in the first postnatal weeks to months.[58] Complications of prematurity such as growth restriction, retinopathy and bronchopulmonary dysplasia have been associated with low IGF-1.[58]

For a number of reasons, early postnatal growth restriction is common after preterm birth. First, preterm infants experience the third trimester of pregnancy in an extrauterine environment, and, with cutting the umbilical cord, the continuous supply of nutrients is suddenly ceased. Second, preterm infants have high nutritional demands due to factors like acute illnesses, rapid brain growth and increased thermogenesis. Third, the rapid advancement of enteral nutrient supplies is complicated by gut immaturity.[61] As a result, there is often a discrepancy between the nutritional demands and supplies during the first weeks after birth, that is particularly evident in ill preterm infants.[62] The accumulating deficits in energy and macronutrients subsequently lead to EUGR. EUGR has been described in 33% up to 90% of VLBW infants.[63,64]

Early-life growth and neurodevelopment

Both IUGR and EUGR have been associated with impairments in neurodevelopment. Magnetic resonance imaging studies showed structural differences in brain tissue between preterm and term infants. A reduction in absolute cortical gray matter volume as well as regional white matter differences were found in preterm infants with IUGR as compared to their appropriate sized counterparts.[65,66] A systematic review showed that IUGR children born < 35 weeks gestation scored on average 0.7 SD lower on all neurodevelopmental domains.[67] Preterm infants who experienced EUGR showed impairments in cortical development until term age[68] and in neurologic performance in

childhood[69] and adolescence.[70] In contrast, increased neonatal growth is associated with favorable neurodevelopmental outcomes.[46,70] The association between adverse early-life growth and unfavorable neurodevelopmental outcomes might either be causal or might, at least in part, be explained by clustering of adverse perinatal characteristics (such as lower birth weight or neonatal illnesses) with prenatal and postnatal GR.

Early-life growth and cardiometabolic risk factors

Cardiometabolic disease in preterm-born individuals who experienced IUGR and/or EUGR may be related to their subsequent growth patterns. Preterm infants with EUGR have a similar growth pattern as those born SGA with the majority showing CUG during early infancy.[71] This CUG is often characterized by excess fat mass relative to lean mass accretion which has been associated with obesity, insulin resistance and raised BP in adulthood.[22,42] This may be partly explained by tracking of fat mass from infancy into childhood and adulthood.[72] In line with these findings, increased neonatal weight gain in relation to length during the first 3 months after preterm birth has been associated with increases in fat mass percentage, waist circumference, triglycerides, and cholesterol at age 18 to 24 years.[73]

Fat mass is associated with leptin, a hormone that is secreted mostly by subcutaneous adipocytes and to a lesser extent by visceral adipocytes. An increase in leptin concentration induces satiety and increases energy expenditure.[74] Besides the apparent association with fat mass, leptin has also been associated with (fetal) growth and development[75] as well as bone metabolism.[76] Research towards leptin in preterm infants has shown a rapid increase after 34 weeks gestation, coinciding with fat accumulation in the third trimester.[77]

IMPROVEMENT OF NUTRITIONAL STATUS AND POSTNATAL GROWTH

The high nutritional needs of preterm infants can only be met with a diet rich in carbohydrates, protein and fat, starting immediately after birth. This window of opportunity, during hospital admission and after discharge, has been the focus of multiple nutritional intervention studies in VLBW infants.[78,79] Most of these studies aimed to achieve postnatal growth similar to intrauterine growth without excess fat accretion, and to achieve neurodevelopment comparable with term-born children. Long-term follow-up of nutritional intervention studies is scarce, although it is important to assess the effects beyond infancy.[80]

Despite major improvements in early nutritional composition for preterm infants over the past decades,[81,82] cumulative nutritional deficits as well as EUGR are still common at the

time of hospital discharge.[83] Therefore, nutritional interventions after discharge may also contribute to achieve adequate growth with favorable long-term outcomes.[78,79]

NUTRITIONAL INTERVENTIONS

Nutrition during hospital admission and its (long-term) consequences

It has been demonstrated that early parenteral administration of lipids and amino acids was well tolerated and resulted in a reduction of postnatal GR in preterm infants.[81,84] Enteral feeding is initiated shortly after birth and gradually increased until it can be used as the sole source of nutrition. So far, studies have shown that providing preterm infants with 1.5 g of parenteral amino acids per $kg^{-1} \cdot day^{-1}$ within the first 24h after birth and increasing it stepwise to 3.5–4.0 g per $kg^{-1} \cdot day^{-1}$ is safe and does not result in significant increases in blood urea nitrogen or an increased risk for metabolic acidosis.[85] Nutritional deficits during this critical period of rapid brain development are likely to disturb the normal proliferation and differentiation of neurons and glial cells.[86,87] Trials showed that increased protein and energy intakes during the first week(s) of life are related to improved brain growth[82] and better neurodevelopmental outcome at 18 months of age.[87,88] The extent of neurodevelopmental improvement, in particular on the longer term, is still unclear.[87] Moreover, considering the strong associations between early nutrition, early postnatal growth, and neonatal morbidities such as bronchopulmonary dysplasia or intraventricular hemorrhage, assessing the separate effects of those factors on later neurodevelopmental outcomes is complicated.

Nutritional interventions during hospital admission aim at attaining a growth rate similar to that of fetuses of the same postconceptional age. Insufficient protein intake during the first weeks of life results in lower lean mass and a lower energy metabolism in adults born preterm.[89] A Cochrane review concluded that a protein intake of > 3.0 but < 4.0 g per $kg^{-1} \cdot day^{-1}$ from formula during initial hospital stay was associated with an increase in weight gain.[90] In addition, total energy intake during the first 7 days of life was associated with growth until 2 years CA.[64] Excess energy intake (i.e., exceeding the amount needed for appropriate growth) has been associated with harmful catch-up growth, which, in turn, may predispose to later adiposity.[91,92] In addition, neonatal nutrition has been suggested to contribute to programming leptin concentrations in later life. Children that were fed preterm formula instead of standard formula or human milk (HM) in their first months of life had a higher leptin to fat mass ratio at age 13–16 years.[93] For the risk of higher BP, early sodium intake may play a role, as neonatal salt intake is an important determinant of BP in later life.[94,95]

Fortification of HM resulted in small short-term benefits in gain of weight, length and head circumference.[96] In addition, there is some evidence suggesting that HM might protect against developing metabolic syndrome.[97] This protective effect of HM might be explained by a favorable early growth pattern as compared with formula-feeding.[97] With respect to bone mineralization, HM may be beneficial for later bone health,[98] whereas results of feeding (mineral-enriched) preterm formulas are inconclusive.[39,98]

Nutrition after discharge and its (long-term) consequences

Similar to the in-hospital period, HM is the preferred type of nutrition for preterm infants after discharge. The use of fortifiers after hospital discharge does not seem to contribute to improved growth.[99] Moreover, infants are likely to drink directly from the breast which makes fortification impractical. Several nutritional intervention studies after hospital discharge have been performed. Different types of enriched formulas have been used in these studies, including formulas with either increased energy density (70–80 kcal/100 mL) or higher macronutrient concentrations, in particular protein or protein-to-energy (P:E) ratios, or a combination of both. These formulas were compared to either standard (60–70 kcal/100 mL) or preterm (≥ 80 kcal/100 mL) formulas. It might be expected that feeding preterm infants a (protein-) enriched formula after discharge may support catch-up growth and improve neurodevelopment. However, studies showed little benefit on neurodevelopment of protein enrichment after hospital discharge, although the duration of follow-up was limited.[100]

A recent systematic review concluded that most studies on nutritional interventions after discharge show no differences in auxological parameters during the first 2 years of life.[100] Nevertheless, there was a trend toward increases in weight, length and head circumference when a higher P:E ratio was provided.[100] Furthermore, two studies reported higher lean mass and lower fat mass accretion during the first 6 months after term age when a higher P:E ratio (i.e., 2.54–2.70) was provided.[101,102] Others demonstrated proportionally increased lean mass and fat mass as a result of feeding a preterm formula for 6 months (P:E ratio 2.72–2.75).[103,104] Some studies have demonstrated a benefit of enriched diets specifically for male preterm infants,[101,103] as well as for those born SGA.[101,102,105] Overall, these studies seem to emphasize the importance of a higher P:E ratio because this may promote growth while preventing the accretion of excess fat. No long-term data on the effect of different types of nutrition on bone mineralization are available.

Drawing clear conclusions about the effects of using enriched formulas after discharge is complicated because meta-analyses and reviews are challenged by a significant heterogeneity in study design, study population, and intervention period, but most of all in studied

formulas. Furthermore, demonstrating a direct relation between early nutrition and later (risk factors for) metabolic syndrome is hampered by the strong coherence between early nutrition and growth and its consequences, as well as the influence of later environmental factors such as lifestyle.

THIS THESIS

This thesis aims to contribute to expanding the knowledge on different aspects of early-life growth and nutrition after preterm birth by:

- Evaluating the effects of different types of nutrition after discharge on growth, body composition, neurodevelopment, and endocrine variables at age 8 years;
- Assessing the influence of prenatal and postnatal growth patterns on neurodevelopment and development of the HPA-axis from infancy to age 8 years;
- Describing the association between leptin and bone mineralization and body composition from infancy to age 8 years;
- Exploring salt sensitivity of BP and its associations with early-life growth.

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