Outcomes 8 years after preterm birth

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Chapter 9

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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ABSTRACT

Preterm-born children and adults comprise an increasing part of the population and are at risk for later neurodevelopmental problems and cardiometabolic diseases. Early-life growth restriction and suboptimal neonatal nutrition have been recognized as important modifiable risk factors for these long-term sequelae. Nutritional intervention studies have been conducted aimed at prevention of extrauterine growth restriction and subsequent harmful catch-up growth. Adequate supply of protein and energy in the first weeks of life (i.e., energy > 100 kcal per $kg^{-1} \cdot day^{-1}$ and a protein-to-energy (P:E) ratio > 3 g/100 kcal) were found to improve early growth and later neurodevelopment. However, caution is warranted with the continuation of a high-energy diet beyond 32–34 weeks postconceptional age, because excess fat mass may predispose to cardiometabolic risks. After discharge, nutrition with a higher P:E ratio (i.e., > 2.5–3.0 g/100 kcal) may improve short-term growth and body-composition. Long-term follow-up of nutritional interventions is important but scarce.

Conclusion There is no doubt that preterm infants in their first weeks of life require a high protein/high energy diet, starting shortly after birth. Subsequent adjustments in nutritional composition, aimed at minimizing long-term cardiometabolic risks without jeopardizing the developing brain, should be guided by growth pattern. The long-term impact of this strategy remains to be studied.

INTRODUCTION

Preterm-born children and adults comprise an increasing proportion of the population. Over the past decades, the incidence of preterm birth (i.e., before 37 weeks gestation) has increased from 7.2% in 1990 to 8.6% in 2010 in developed countries, with a relatively stable proportion of 15% very preterm births (i.e., before 32 weeks gestation).[1-4] Meanwhile, neonatal mortality after very preterm birth has decreased due to improvements in perinatal care.[5] Nowadays, mortality rates of 5%–17% are reported for infants born before 29 weeks 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 has even increased over time,[5,7] and the same trend was observed for long-term cognitive and motor impairments.[8,9] Preterm birth has also been associated with later cardiometabolic risks.[10] Therefore, it remains important to develop strategies aimed at improving long-term outcomes after very preterm birth.

Here we review the evidence on the impact of suboptimal early-life growth and nutrition after very preterm birth. Findings from nutritional intervention studies performed during the in-hospital period as well as during the first 6–9 months after discharge are briefly summarized and translated into recommendations for the nutritional management of very preterm infants from birth to 6 months corrected age (CA, i.e., after term age/40 weeks postconceptional age).

LONG-TERM CONSEQUENCES OF PREMATURITY

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 impairments.[13] In a meta-analysis, prematurity was associated with a 0.86 SD lower intelligence quotient score.[9] 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.[12]

Preterm birth has also been associated with (components of) the metabolic syndrome in later life. The metabolic syndrome consists, depending on the definition, of a cluster of cardiovascular risk factors that includes obesity, high blood pressure (BP), an atherogenic lipid profile, and diabetes or decreased insulin sensitivity.[14] Large cohort studies showed that prematurity and/or VLBW were associated with an increased (systolic) BP[15,16] and an increased risk of diabetes[17-19] and insulin sensitivity,[20] which may contribute to a 2-fold higher risk of cardiovascular disease[21,22] and a 4-fold higher risk of the metabolic syndrome[23] compared to their term-born peers. In addition, studies showed that adults who were born preterm or with VLBW had more fat mass relative to lean mass,[24] a 2-fold higher risk of obesity, and a more atherogenic lipid profile, albeit not unequivocally for the latter.[10]

Among preterm infants, suboptimal nutrition and postnatal (extrauterine) growth restriction have been recognized as important (modifiable) risk factors for impaired neurodevelopment and increased cardiometabolic risks.

EXTRAUTERINE GROWTH RESTRICTION

Adequate early postnatal growth can only be attained under optimal nutritional circumstances. For a number of reasons, early postnatal growth restriction is common among preterm infants during their extrauterine 'third trimester'. First, at birth, with the severance of the umbilical cord, the continuous placental supply of nutrients is suddenly disrupted. Second, preterm infants generally have high nutritional demands due to factors like acute illnesses, rapid brain growth and increased thermogenesis. Third, rapid advancement of enteral feeding is complicated by gut immaturity.[25] Therefore, during the first weeks after birth, there is often a discrepancy between nutritional demands and supplies, which may be particularly evident in ill preterm infants.[26] As a result, accumulating energy and macronutrient deficits result in extrauterine growth restriction (EUGR). EUGR has been described in 33% up to 90% of VLBW infants.[27,28]

Long-term consequences of extrauterine growth restriction

The third trimester of pregnancy is a period of rapid fetal brain growth and development in terms of vascularization, myelination, axonal development, cortical thickening, and cerebellar growth.[29] Preterm infants, specifically those who had experienced EUGR, showed impairments in cortical development until term age,[30] and in neurologic performance in childhood[31] and adolescence.[32] In contrast, rapid growth during the neonatal phase as well as catch-up growth after a period of growth restriction have been associated with more favorable neurodevelopmental outcomes.[33,34]

The risk of cardiometabolic disease in preterm-born individuals who had experienced EUGR may be strongly dependent on their growth pattern after discharge. Preterm infants with EUGR have been demonstrated to show a virtually similar growth pattern as compared to those born small for gestational age (SGA), with the majority showing catch-up growth during early infancy.[35] This type of catch-up growth 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.[36,37] This may be partly explained by tracking of fat mass from infancy into childhood and adulthood.[38] In line with these findings, increased neonatal weight gain relative to length during the first 3 months after preterm birth has been associated with increases in fat mass, waist circumference, triglycerides, and total cholesterol at age 18 to 24 years.[39]

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 has been the focus of multiple nutritional intervention studies.[40,41] Most of these studies aimed to achieve neurodevelopment comparable with term-born children and postnatal growth similar to intrauterine growth without excess fat accretion. Long-term follow-up of nutritional intervention studies is scarce, although it is important to assess their effects beyond infancy.[42]

Despite major improvements in early nutritional composition for preterm infants over the past decades,[43,44] cumulative nutritional deficits as well as EUGR are still common at the time of hospital discharge.[45] Therefore, nutritional interventions after discharge may also contribute to achieving adequate growth with favorable long-term outcomes.[40,41]

NUTRITION DURING HOSPITAL ADMISSION AND ITS (LONG-TERM) CONSEQUENCES

Nutritional deficits during a critical period of rapid brain development are likely to disturb the normal proliferation and differentiation of neurons and glial cells.[46,47] Studies conducted thus far 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 a significant increase in blood urea nitrogen or metabolic acidosis.[48] Two trials showed that increased protein and energy intakes in VLBW infants during their first weeks of life improved neurodevelopmental outcome at 18 months of age.[49,50] However, the extent of neurodevelopmental improvement, in particular on the longer term, is still unclear.[47]

Nutritional interventions during hospital admission aim at attaining a growth rate similar to that of fetuses of the same postconceptional age. A Cochrane review concluded that a protein intake of > 3.0 but < 4.0 g per $kg^{-1} \cdot day^{-1}$ from formula was associated with an

9

increase in weight gain.[51] Insufficient protein intake during the first weeks of life after preterm birth resulted in lower lean mass and energy metabolism in adulthood.[52] Excess energy intake (i.e., exceeding the amount needed for appropriate growth) has been associated with harmful catch-up growth, which may predispose to later adiposity.[53,54] Fortification of human milk (HM) resulted in small increases of weight, length and head circumference.[55] In addition, there is some evidence suggesting that HM might protect against the development of the metabolic syndrome.[56] This protective effect of HM might be explained by a favorable early growth pattern as compared with formula-feeding.[56]

NUTRITION AFTER DISCHARGE AND ITS (LONG-TERM) CONSEQUENCES

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 combinations of both. These formulas were compared to either standard (60−70 kcal/100 mL) or preterm (≥ 80 kcal/100 mL) formulas.

Studies showed little benefit on neurodevelopment of protein enrichment after hospital discharge, although the duration of follow-up was limited.[57] We found that children fed a protein-enriched formula during the first 6 months after hospital discharge scored lower on the cognitive scale of the Bayley Scales of Infant Development, second edition (BSID-II) at 24 months CA compared with children fed standard formula, although this difference was no longer present at 8 years. (Ruys et al., submitted) An explanation for the lack of effect may be that protein can only be used for anabolism, provided that other energy sources are sufficiently available.[51]

A recent systematic review (gestational age 26−34.5 weeks, birth weight 870−1990 g) concluded that most studies on nutritional interventions after discharge showed no differences in auxological parameters during the first 2 years of life.[57] Nevertheless, there was a trend toward increased weight, length and head circumference gains when a higher P:E ratio was provided.[57] Furthermore, 2 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.[58,59] Our long-term follow-up data showed that the short-term benefits on body composition of a protein-enriched formula after discharge (P:E ratio 2.52 g per 100 kcal) were no longer present at 8 years.[60] Post-hoc analyses suggested that infants with limited postnatal weight gain during the first 6 months after term age may benefit from protein-enriched formula compared to standard term formula, resulting in a greater height and lean mass at 8 years.[60] This may suggest the need for specific attention for preterm infants born SGA and/or experiencing EUGR. Overall, these studies emphasized the importance of a higher P:E ratio for the prevention of excess fat mass accretion. However, demonstrating a direct relation between early nutrition and later (risk factors for) metabolic syndrome is complicated by the strong coherence between early nutrition, early growth, lifestyle factors and disease.

RECOMMENDATIONS FOR DAILY PRACTICE

During the first weeks to months after very preterm birth, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition (ESPGHAN) advises the following ranges for enteral nutrient intake (per $kg^{-1} \cdot day^{-1}$): energy, 110–135 kcal; protein, 3.5–4.5 g; lipids, 4.8–6.6 g; and carbohydrate, 11.6–13.2.[61,62] Human milk, either own mother's milk or donor milk is the feeding of choice for preterm infants during hospital admission.[61,63] Fortification of HM is recommended because the nutritional needs of preterm infants are not met by unfortified HM.[63] If HM is not available, preterm formulas with high energy (around 80 kcal/100ml) and protein (around 2.6 g/100ml) contents provide an alternative during hospital admission (**Table 9.1**).[61]

Similar to the in-hospital period, HM is the preferred type of nutrition after discharge. The use of fortifiers after hospital discharge does not seem to contribute to improved growth.[64] Moreover, infants are likely to drink directly from the breast, which makes milk fortification impractical. If HM is not available, the ESPGHAN recommends the use of an enriched formula at least until 40 to 52 weeks postconceptional age, in particular in case of EUGR.[62]

Based on the available evidence, we propose a recommendation for the nutritional management of very preterm infants from birth until 6 months CA. This practical recommendation is summarized in **Figures 9.1&9.2**.

From very preterm birth to 32–34 weeks postconceptional age

There is sufficient evidence to recommend early initiation and rapid advancement of protein and energy intakes in very preterm infants. Parenteral nutrition is often necessary during the first 2–3 weeks of life to fulfil their nutritional needs. Meanwhile, enteral nutrition is being gradually increased. According to the most recent ESPGHAN recommendations, parenteral protein (amino acid) intake should be 1.5–2.5 g per $kg^{-1} \cdot day^{-1}$ immediately after birth, increasing to 3.5 g per $kg^{-1} \cdot day^{-1}$ from day 2 (**Figure 9.1**).[65] A gradual increase

9

Table 9.1. Composition of different types of (preterm) infant nutrition per 100 mL[1]

	HM term[2]	HM preterm[2]	HMF	HMPF[3]	Preterm formula	E&P enriched formula	P enriched formula	Standard term formula
Energy, kcal	68	65	14–16	3.4	79–100	74–77	66–68	64–68
Protein, g	1.0	1.5	1.0–1.2	0.8	2.6–3.0	2.0–2.1	2.0–2.2	1.3–1.4
P:E ratio	1.5	2.3	-	-	3.0–3.6	2.7–2.8	3.0–3.3	2.0–2.1
Carbohydrates, g	7.0	7.2	1.8–2.8	0.02	7.8–9.6	7.5–7.8	6.6–7.3	6.9–7.6
Lipids, g	4.0	3.5	-	0.001	3.9–6.7	4.0–4.1	3.4–3.7	3.4–3.6
Calcium, mg	30	25	66–116	5.2	96–183	53–120	66–165	44–57
Phosphate, mg	15	14	38–64	5.2	54–101	46–66	39–90	26–43
Iron, mg	0.1	0	0–0.32	-	1.5–1.8	1.2–1.8	0.9–1.8	0.4–1.8
Vitamin D, µg	0	0	3.0–5.0	-	1.9–7.5	1.3–3.1	1.3–7.5	1.2–1.5

[1] Based on product information of products available in Europe (Nenatal/Nutrilon Nutricia, HeroBaby, Humana, Nutriprem Cow&Gate, Enfamil Mead Johnson, Similac Abbott).
[2] Based on Lafeber HN, van Zoeren-Grobben D, van Beek R, Gerards L. Enteral and parenteral nutrition in newborns (In Dutch: Werkboek enterale en parenterale voeding bij pasgeborenen). 2nd ed. Amsterdam: VU University; 2004.
[3] Per sachet of 1 gram.
(E&)P enriched formula, (energy&) protein enriched formula; HM, human milk; HMF, human milk fortifier; HMPF, human milk protein fortifier; P:E ratio, protein to energy ratio; STF, standard term formula.

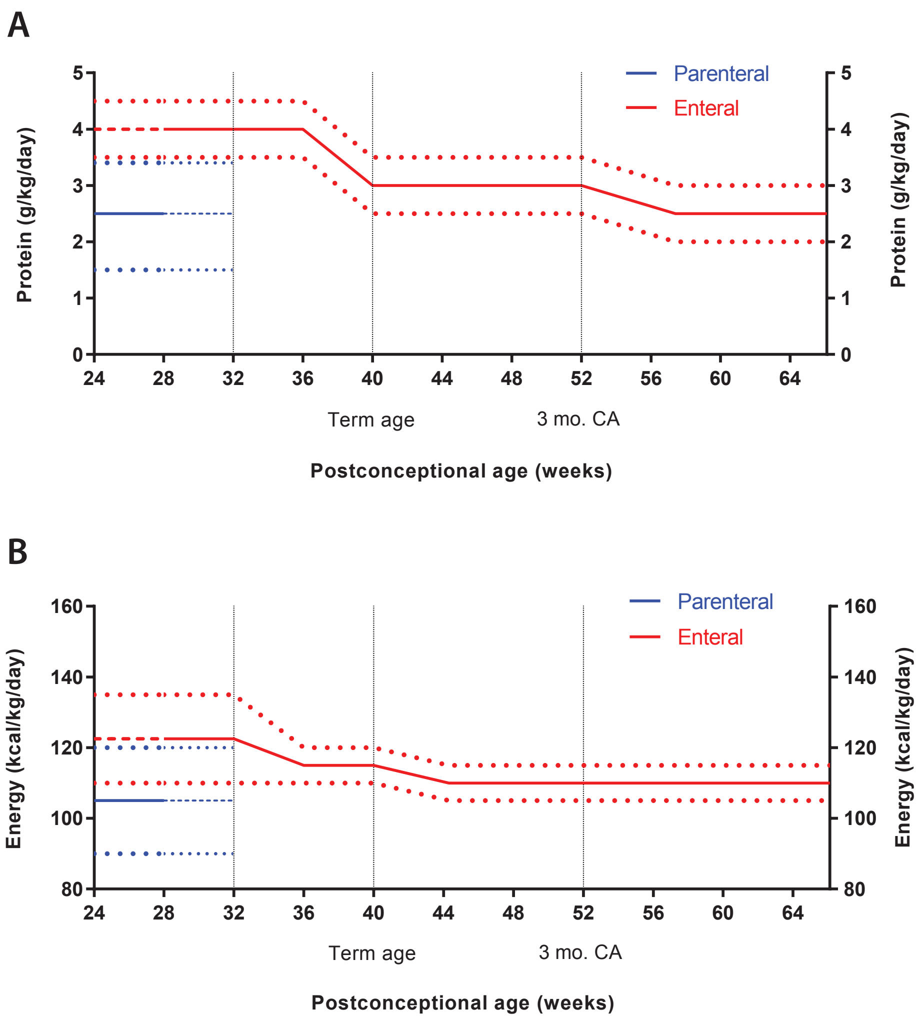

Figure 9.1. Recommendation for protein intake (A) and energy intake (B) from birth until 6 months corrected age (CA) represented as means with ranges (colored dotted lines).
Vertical dotted lines represent 'transition periods' where a change in nutritional composition should be considered. Please note: total protein intake from parenteral and enteral nutrition, when combined, should not exceed 4.5 g per $kg^{-1} \cdot day^{-1}$. Total energy intake from parenteral and enteral nutrition, when combined, should not exceed 135 kcal per $kg^{-1} \cdot day^{-1}$.

of enteral nutrition should result in a total protein intake of 3.5–4.5 g per $kg^{-1} \cdot day^{-1}$ with an energy intake of 110–135 kcal per $kg^{-1} \cdot day^{-1}$ (**Figure 9.1**).[61,66] There is a prominent role for the use of HM, either own mother's milk or donor milk.[61,63] The number of HM banks has increased rapidly over the past decade.[67] Consequently, donor milk has become available to increased numbers of preterm infants. In the near future, fortified (donor)

9

HM is expected to become the primary source of nutrition during hospital admission, together with parenteral nutrition. Only if parents refuse the option of donor milk, preterm formula will be used.

From 32–34 weeks postconceptional age to term age

We suggest that nutritional decisions from 32–34 weeks postconceptional age should be guided by the infant's growth pattern. After 32–34 weeks postconceptional age, we recommend that energy intake is decreased to around 115 kcal per $kg^{-1} \cdot day^{-1}$ if growth is age-appropriate (10–15 g per $kg^{-1} \cdot day^{-1}$ for at least 1 week, similar to fetal growth) (**Figure 9.1**). A high-calorie diet beyond this point may lead to an excessive gain in fat mass.[68] An 'early switch' to a mainly protein-enriched diet might be desirable to ensure optimal growth with predominantly lean mass instead of fat mass accretion. While gradually tapering the amount of energy from 32–34 weeks postconceptional age onward to prevent excess fat mass accretion, in both formula-fed and fortified HM-fed infants, high protein intake must be maintained to meet the needs of the developing brain. For infants fed fortified HM, a transition to predominantly protein fortification should be considered during this period (**Figure 9.2**).

From term age until 6 months CA

At term age, we recommend to maintain energy and protein intakes of around 110 kcal per $kg^{-1} \cdot day^{-1}$ and 3 g per $kg^{-1} \cdot day^{-1}$, respectively (**Figure 9.1**). Preterm infants who are

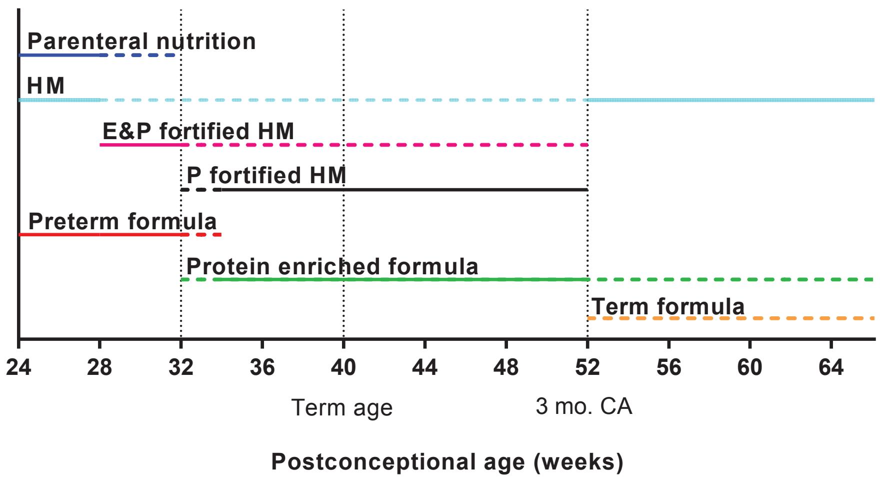

Figure 9.2. Recommendation for type of nutrition from birth until 6 months corrected age (CA). Vertical dotted lines represent 'transition periods' where a change in nutritional composition should be considered. CA, corrected age; (E&)P fortified HM, (energy &) protein fortified human milk.

completely HM-fed will most likely drink directly from the breast by this time, thereby making fortification with HMF practically impossible. However, the estimated protein and energy intakes from solely HM are lower than recommended. Therefore, we suggest close monitoring of the infants growth pattern. Protein fortification beyond term age should only be considered if steady growth has not yet been established. In case of formula feeding, the recommended protein and energy intakes are covered by protein-enriched (sometimes called ‘postdischarge’) formulas (**Table 9.1** and **Figures 9.1&9.2**).

There are limited data on the long-term effects of formula-feeding from term age onward. The ESPGHAN advises a protein-enriched formula until 40 to 52 weeks postconceptional age (i.e., until term age to 3 months CA). Because of the large numbers of infants that are growth restricted at term age, we would recommend continuation of a protein-enriched formula until at least 3 months CA. However, this recommendation should be balanced against observations in term-born children, suggesting that excess protein intake during the first 1 to 2 years of life may predispose to later obesity.[69] Therefore, caution is warranted with protein-enriched formulas beyond 3 months CA. Evaluation of the growth pattern should guide the decision whether or not to continue the protein-enriched formula beyond 3 months CA up to a maximum of 6 months CA.

CONCLUSIONS

Adequate supply of nutrients shortly after preterm birth reduces the risk of EUGR. Human milk is the most important source of early-life nutrition, especially with the increasing possibilities to provide preterm infants with donor HM. A nutritional switch from a high energy/high protein diet to a high protein only diet should be considered already during hospital admission from postconceptional age 32–34 weeks. From 3 months CA onward, continuation of a protein-enriched formula should be reconsidered based on the infant’s growth pattern. More individualized nutritional care, based on the assumption that the long-term cardiometabolic risks can be mitigated by ensuring appropriate linear growth without excess fat mass accretion, seems warranted. These recommendations may contribute to acknowledging the in-hospital and postdischarge periods as a continuum instead of separate entities, resulting in healthier early growth and a reduction in the associated risks of neurodevelopmental problems and cardiometabolic diseases. In the future, parameters such as insulin-like growth factor type 1, which is considered an important effector of nutritional intervention,[70] may also contribute to nutritional decision making.

What is known?

- Preterm infants are at risk for nutritional deficiencies and postnatal growth restriction
- Nutritional intervention studies, in-hospital and after discharge, are inconclusive with respect to long-term health outcomes

What is new?

- Pre-discharge and postdischarge nutrition should be considered a continuum and growth pattern may guide the decision to adjust the nutritional composition
- An early switch to mainly protein-enrichment may be considered from 32–34 weeks postconceptional age. Shortening the period of feeding a high-energy diet may prevent excess fat mass accretion and its associated cardiometabolic risks.

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