When an organism is malnourished during fetal or early postnatal life, it anticipates to receiving a low nutrient supply in later life by adjusting the setting of hormones and metabolism

Ann Nutr Metab 2011;58(suppl 1):20–29

Feeding Very-Low-Birth-Weight Infants: Our Aspirations versus the Reality in Practice

by Willemijn E. Corpeleijn et al.

Key insight

This article looks critically at the premature infant's first weeks of life and the clinical strategies needed to minimize the occurrence of nutritional deficits.

Current knowledge

Inadequate feeding or restricted growth during early life has profound effects on several physiologic and metabolic factors throughout life. The cause of inadequate intake in the early neonatal phase is multifactorial and partly iatrogenic. Waiting e.g. 8 h before a catheter is replaced will result in an additional protein deficit of 1.4 g in a 1.2 kg infant who receives 3.5 g/kg protein per day.

Practical implications

A prerequisite to meet the recommended daily intakes in premature infants is that hospital staff recognizes that preterm birth is a nutritional emergency. A reliable infrastructure, early initiation of parenteral nutrition, transition to fortified breast milk or preterm infant formula and monitoring nutritional tolerance can help optimize nutritional intakes during the first weeks of life.

Recommended reading

van den Akker CH, Vlaardingerbroek H, van Goudoever JB: Nutritional support for extremely low-birth weight infants: abandoning catabolism in the neonatal intensive care unit. Curr Opin Clin Nutr Metab Care 2010;13:327–335.

Multifactorial causes of inadequate nutritional intake. The preterm infant is in nutritional/metabolic emergency (see text for details).

Feeding Very-Low-Birth-Weight Infants: Our Aspirations versus the Reality in Practice

Willemijn E. Corpeleijn^c Marijn J. Vermeulen^a Chris H. van den Akker^a
Johannes B. van Goudoever^{a–c}

^aErasmus Medical Center, Sophia Children's Hospital, Rotterdam, ^bAmsterdam Medical Center, Emma Children's Hospital, and ^cDepartment of Pediatrics, Free University Medical Center, Amsterdam, The Netherlands

Key Messages

- Cumulative nutritional deficits are present in most preterm infants, creating adverse consequences that are hard to recover from.
- Preterm birth is a nutritional emergency and requires a well-equipped neonatal intensive care unit (NICU) with well-trained staff.
- Proper and frequent monitoring as well as further research is required to increase our understanding of the nutritional requirements in these vulnerable infants.

Key Words

Breast milk • Enteral nutrition • Neonatal intensive care unit • Outcome • Parenteral nutrition • Premature infant • Protein

Abstracts

Recently, new guidelines for enteral feedings in premature infants were issued by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition. Nevertheless, practice proves difficult to attain suggested intakes at all times, and occurrence of significant potential cumulative nutritional deficits 'lies in wait' in the neonatal intensive care unit. This review describes several aspects that are mandatory for optimizing nutritional intake in these vulnerable infants. These aspects range from optimal infrastructure to the initiation of parenteral nutrition with proper transition to enteral breast or formula feedings. Proper monitoring of nutritional tolerance includes serum biochemistry although proper specific markers are unknown and safety reference values are lacking. Although a lot of progress has been made through research during the last few decades, numerous questions still remain unanswered as to what would be the optimal quantity and quality of the various macronutrients. The inevitable suboptimal intake may, however, contribute significantly to the incidence of neonatal diseases, including impaired neurodevelopment. Therefore, it is pivotal that all hospital staff acknowledges that preterm birth is a nutritional emergency and that all must be done, both in clinical practice as well as in research, to reduce nutritional deficits.

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Managing Nutrition according to the Latest Guidelines of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition: What Is Realistic?

The overall goal of feeding very-low-birth-weight (VLBW) infants, as agreed upon by neonatologists around the globe, is to achieve growth similar to fetal growth rates with similar body composition, coupled with satisfactory functional development. Recently, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) released new guidelines for the nutritional management of enterally fed preterm neonates (table 1) [1]. The latest ESPGHAN guidelines on parenteral nutrition (PN) were released in 2005 (table 2) [2]. Although over the last decades much progress has been made in the field of neonatal nutrition, many uncertainties still remain about the exact requirements of premature neonates. While the short- and long-term consequences of inappropriate feeding and hampered growth are increasingly being recognized, a large proportion of premature neonates still end up growth restricted at discharge from the NICU. Hulst et al. [3] showed that 44% of preterm infants drop >1 SD in weight for age during NICU admission. The percentage of infants that are >2 SD below the mean weight for age increases from 14 to 55% from birth to discharge [3]. The cause of this growth restriction is multifactorial but it has been estimated that about 50% of the variance in early postnatal growth can be attributed to nutrition [4]. In the majority of preterm infants, there is a large discrepancy between daily recommended dietary intakes (RDI) and actual intake during the first few weeks of life, resulting in substantial nutritional deficits. In the report by Embleton et al. [4], energy deficits were as high as 813 ± 542 kcal/kg and protein deficits as high as 23 ± 12 g/kg by the 5th week of life. The latest ESPGHAN guidelines rec-

ommend even higher intakes than previous ones and, as the magnitude of the deficits depend on the criteria used for RDI, true deficits rise accordingly. Can these deficits be prevented? Or is the development of nutritional deficits inevitable after premature birth? Are the new ESPGHAN guidelines realistic when considering the high complication rate after premature birth?

The cause of inadequate intake in the early neonatal phase is multifactorial and partly iatrogenic. In this article, we address the difficulties that are most frequent-

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ly encountered when feeding VLBW infants and provide strategies to minimize the occurrence of nutritional deficits in early postnatal life. Obscurities in our knowledge on feeding premature neonates are pointed out and recommendations for future research are made. Lastly, the consequences of early improper feeding are discussed.

Initiation of PN

A prerequisite to meet the RDIs in premature infants is the recognition by hospital staff that preterm birth is a nutritional emergency. A small preterm infant of 1 kg contains only 1% fat and 8% protein and has a non-protein caloric reserve of 110 kcal/kg body weight (BW) [5]. With these small reserves, survival from starvation then will

Table 1. Fluid and macronutrient guidelines for parenterally fed premature infants by ESPGHAN and ESPEN (European Society for Clinical Nutrition and Metabolism) in 2005 [2]

	Goal, per kg/day	When to start
Fluid, ml		
BW <1.5 kg	160–180	immediately with 80–90 ml/kg per day
BW >1.5 kg	140–160	immediately with 60–80 ml/kg per day
Energy, kcal	110–120	
Protein, g	1.5–4.0	postnatal day 1
Lipids, g	up to 3–4	postnatal days 1–3
Carbohydrates, g	up to 11.5–18.0 (8.0–12.5 mg/kg per min)	immediately with 5.8–11.5 g/kg per day (4–8 mg/kg per min)

only last for 4 days in the absence of exogenous substrates being administered [2, 6]. However, during conditions such as sepsis and respiratory insufficiency, the metabolic rate may even be higher and reserves will be depleted much faster. It is, therefore, compulsory that PN is started immediately after preterm birth. In the past, physicians often refrained from administration of intravenous amino acids to premature neonates in the immediate neonatal phase to avoid metabolic derangements such as hyperammonemia and acidosis. We have come to realize that these complications were partially caused by the method of manufacture and the suboptimal composition of the solutions and not so much by intolerance to amino acids or fat itself. However, the fear of metabolic derangements is still deeply rooted in clinical practice. At present, the timing of commencement of total PN (TPN) and the amount of parenterally administered nutrients varies enormously between NICUs [7–9]. In most NICUs, amino acids are infused to premature infants from birth onwards; elsewhere, sometimes a considerable delay is introduced before the commencement of parenteral amino acid administration. In addition, starting doses vary widely between different NICUs; some start at 0.5 g/kg per day followed by a stepwise increase, others start directly with 3.5 g/kg per day. There is no evidence that a stepwise increase is better tolerated by infants. In fact, mainly from animal fetal studies, we know that large amounts of amino acids are continuously transported over the placenta [10]. These amounts exceed the amount that is required for growth or tissue accretion and they are used for energy generation after oxidation [11, 12]. The preterm infant should have the capacity to metabolize the same amount of amino acids as its postconceptionally age-matched intrauterine counterpart, although the preterm infant misses the maternal metabolic clearance possibility its fetal counterpart has. However, it has been shown that early administration of intravenous amino acids is safe and brings the preterm newborn in an anabolic state [13–15]. We have studied immediate and 2-year follow-ups from our own cohort, where we infused 2.4 g of amino acids per kilogram BW per day from birth onwards, compared to a stepwise increment in 2–3 days. We demonstrated that the infants became anabolic, had improved albumin and whole body protein synthesis and that anti-oxidant defense systems were upregulated [14,

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16–18]. Long-term effects demonstrated that boys in particular seem to benefit from the early amino acid administration, in that they had a tendency to fewer neurological disabilities. No differences in major neurological complications were observed in girls between both groups.

However, protein deposition is an energy-costing process and, in order to let protein synthesis proceed at optimal rates, sufficient non-protein calories should be administered as well. Lipids are an attractive candidate, as early parenteral lipid administration might prevent a period of essential fatty acid depletion. Due to its high energy density (9 kcal/g) compared to glucose (4 kcal/g), it can help to reduce the risk of fluid overload. However, data on the safety and efficacy of

early parenteral lipid administration are conflicting. Early lipid administration has been associated with chronic lung disease [19, 20], whereas in other trials, no adverse effects were found [21–24] and even beneficial effects of lipids on lung development have been described [25]. It has also been hypothesized that fatty acids competitively bind to albumin and therefore cause an increase in free bilirubin or medication to dangerously high levels [26, 27]. However, a small recent study shows that early lipid administration is safe and well tolerated. Ibrahim et al. [13] randomized VLBW infants between receiving either

Table 2. Fluid and macronutrient guidelines for enterally fed premature infants by ESPGHAN in 2010 [1]

	Goal (per kg/day)	Goal (per 100 kcal)
Fluid, ml	135–200	not applicable
Energy, kcal	110–135	not applicable
Protein, g		
BW <1 kg	4.0–4.5	3.6–4.1
BW >1 kg	3.5–4.0	3.2–3.6
Lipids, g	4.8–6.6	4.4–6.0
Carbohydrates, g	11.6–13.2	10.5–12.0

full-dose PN (amino acids 5 g/kg per day and lipids 3 g/kg per day) within 1 h after birth or solely glucose for the first 48 h followed by a stepwise increase in amino acids and lipids. This aggressive TPN did not result in an increased risk of metabolic acidosis, hypercholesterolemia

or hypertriglyceridemia, or an increased incidence of clinical neonatal diseases. There was a small but significant increase in bilirubin concentration, although without clinical implications. Nevertheless, long-term consequences of such feeding regimens on mental development, growth and metabolism are unknown.

Differences in timing and amount of nutrient administration are also observed between individual physicians working in the same NICU adhering to the same nutritional protocol [28]. Reasons for these variations are partly explained by the varying degree of reluctance that physicians have regarding fluid overload and intolerance to intravenous amino acids and fat. A stepwise increase and/or a delayed [13] commencement of nutrient administration inevitably result in the occurrence of considerable deficits during the first few days of life [4]. These deficits have proven to be very hard to recoup and every effort should be made to prevent their occurrence [29].

Infrastructure

Several facilities are required to safely prepare, administer and monitor PN. These facilities include a hospital pharmacy that is equipped to prepare PN in an aseptic manner and to store it under the right conditions. X-ray facilities are necessary to confirm correct positioning of central venous catheters. Laboratory facilities to accurately and rapidly measure serological parameters to monitor tolerance to PN are of paramount importance. Furthermore, the attending physicians need to know when and how to prescribe PN, and have knowledge about its effects and potential side effects in premature neonates. Although these facilities are uniformly present in tertiary hospitals in the developed world, they are often lacking in most clinics in third-world countries. It is possible that a number of secondary hospitals that care for larger VLWB infants might also be lacking some of these facilities.

Prescribing PN

In an ideal world, dietary needs of preterm infants are addressed in detail on a daily basis, taking changes in the nutritional and clinical status into account. However, the attending neonatologist usually has a large number of patients under his or her care, of whom most have complex respiratory and circulatory conditions. A daily intake that is slightly beneath the RDI, e.g. because an infant has increased his or her BW without a correction being made in the amount of nutrients administered, will contribute significantly to the nutritional deficit over the course of several days. It has been shown that instituting a multi-

disciplinary nutritional support team (including a dietitian) that provides constant individualized nutritional care to each infant leads to a higher intake of protein and higher growth rates during NICU admission [30]. Although requiring an initial financial investment, hiring a registered dietitian is likely to be cost-effective or even profitable. Optimal nutritional care can result in a shorter period of time on TPN, leading to a decreased length and cost of hospital stay, morbidity and mortality. Furthermore, it has been shown that computerized ordering of TPN leads to a significantly reduced time to order TPN [31] and in an improvement in PN composition (energy, protein, calcium and phosphate content) [32]. Introduction of individualized computerized ordering of TPN brings about a significant reduction in cumulative energy deficit over the first 28 days of life and an improvement in early growth [33].

Optimal nutritional care can result in a shorter period of time on TPN, leading to a decreased length and cost of hospital stay, morbidity and mortality.

Securing Venous Access for Administration of PN

Central venous access is paramount for the delivery of parenteral substrates in sufficiently high amounts. Peripheral venous access is suitable for partial (short-term) nutritional supplementation, but phlebitis of peripheral veins can be expected when solutions with a higher osmolality (>600 mosm), such as glucose 20%, are administered. Complications of peripheral administration of parenteral nutrients can be severe and extravasation of PN may even result in necrosis and amputation of the affected limb. When tolerance of full enteral feeding is not expected soon, central venous access should be ensured as soon as possible after birth by insertion of an umbilical vein catheter, a peripherally inserted central catheter or a central venous catheter directly placed in a deep vein (e.g. subclavian, internal jugular or femoral vein). Catheters are, however, associated with complications such as thrombosis, sepsis and catheter malfunction. Insertion and care of catheters should be done by highly trained staff under aseptic conditions. A malfunctioning catheter in an infant still dependent on PN should be replaced as soon as possible. Waiting for example 8 h before a catheter is replaced will result in an additional protein deficit of 1.4 g in a 1.2-kg infant who receives 3.5 g/kg of protein

Table 3. Safety levels and interventions for parenteral amino acid and lipid administration in VLBW infants

Serum urea mmol/l	Corresponding blood urea nitrogen, mg/dl	Intervention	Check serum values	Serum triglycerides mmol/l	Intervention	Check serum values
<10	<28	continue according to normal protocol	according to local protocol	<3	continue according to normal protocol	according to local protocol
10–12	28–34	continue at 50% of dosage	next day	3–4	continue at 50% of dosage	next day
12–14	34–39	continue at 25% of dosage	next day	4–5	continue at 25% of dosage	next day
>14	>39	stop	next day	>5	stop	next day

per day. To avoid this situation requires a good infrastructure, with e.g. round-the-clock availability of X-ray services and no shortages of well-trained staff and equipment.

Monitoring Tolerance of TPN

There is consensus that during administration of intravenous nutrients, serologic parameters should be routinely checked to prevent development of serious metabolic derangements. Parameters frequently tested include concentrations of urea and sometimes ammonia (for tolerance of amino acids), cholesterol, triglycerides and bilirubin (lipids), blood glucose (carbohydrates), electrolytes and acid/base balance. However, none of these parameters are specific as they are all affected by non-nutritional physiologic and pathologic states as well; besides, in premature infants safe threshold levels are not known for each molecule. Long-term consequences of disturbances in most of these parameters remain to be determined, but it is plausible to assume that the levels found in utero are safe. For example, reference urea concentrations in the fetus range from 7.5 to 14.3 mmol/l [34]. Effects of higher urea concentrations are unclear [29], although urea concentrations >30 mmol/l were accompanied with slightly elevated ammonia concentrations of around 100 μ mol/l in premature infants below 24 weeks of gestation receiving up to 4 g amino acids/kg per day during the first few days of life [35]. However, in most NICUs, urea cutoff values for discontinuing or decreasing parenteral amino acids are much lower. Table 3 shows the threshold values for several parameters that can be used to monitor the utilization and clearance of parenteral-administered substrates. Further research is warranted to establish appropriate parameters and reference values to monitor safety and efficacy of PN in preterm neonates.

Composition of PN

Although the quality of intravenous solutions has improved considerably over the last decades, it is likely that further improvement in the composition will increase the tolerance to PN. Ideally, the individual need for different components would be monitored and supplemented. In clinical practice, the exact needs are not clear and thus the provided PN might be inadequate. Although all essential amino acids are present in all amino acid solutions intended for pediatric use, some may not contain enough 'semi-essential amino acids', e.g. those listed in table 4. It is thought that under specific conditions, like preterm birth, some non-essential amino acids in adults are essential to the infant. Due to various reasons, the premature infant is not capable of synthesizing enough of these amino acids [36–38]. In order to let protein synthesis proceed at optimal rates, all amino acids must be present in sufficient amounts. Protein synthesis comes to a halt and proteolytic rates increase when an essential amino acid is deficient. As all other amino acids, they cannot be stored by the body and are disposed through the process of oxidation, which results in elevated urea levels.

Precise requirements for individual amino acids are not known. Specific techniques such as the indicator amino acid oxidation method are needed to estimate individual amino acid requirements; an example of such a technique is shown in figure 1. The principle underlying this technique is that when a specific essential amino acid, e.g. threonine, is lacking in the diet, the plasma threonine level will fall. To compensate for this deficiency, proteins will be broken down with a subsequent release of threonine. However, not only threonine will be released, all other amino acids, e.g. phenylalanine, will also be released. If the preceding phenylalanine level is appropriate, this will result in increased phenylalanine concen-

trations. The liver will react to reduce the high phenylalanine level by hydroxylating phenylalanine to tyrosine and further oxidative pathways downstream. By measuring the oxidation of tyrosine with stable isotope techniques at various levels of threonine intake, one can exactly determine the requirement of threonine since at a certain level the body will not breakdown any proteins to match the dietary shortage of intake of threonine.

First-generation parenteral lipid emulsions are based purely on soybean oil, which is very rich in n-6 polyunsaturated fatty acids (PUFAs). PUFAs are prone to peroxidation by incorporation of an oxygen molecule into one of the unsaturated sites of the carbon backbone. Metabolites of the formed lipid peroxides, in turn, impair basal metabolism as well as

cell and organ functions. Besides, n-6 PUFA-derived eicosanoids have pro-inflammatory characteristics. Second-generation lipid emulsions have been developed that are a mixture of soybean oil and other lipids, such as medium-chain triglycerides or olive oil. The added lipids dilute the high n-6 PUFA content, potentially reducing the inflammatory consequences such as PN-as-

sociated liver disease but exert other beneficial effects as well. Third-generation lipid emulsions contain soybean oil for the supply of essential fatty acids, medium-chain triglycerides for rapid provision of energy, olive oil to reduce the n-6:n-3 ratio and to supply vitamin E, and fish oil for its anti-inflammatory effects. Beneficial effects of these mixtures on liver function and serum triglycerides have been described in various studies, including children [39, 40]. Whether they will also increase the tolerance to parenteral substrates in preterm neonates is being investigated in several ongoing trials.

Promoting Tolerance to Enteral Substrates

After premature birth, everything should be done to bring the intestine as quickly as possible in a condition that allows administration of sufficient amounts of nutrients, as adequate growth is best achieved with optimal enteral nutrition. Lack of enteral nutrition causes gut atrophy in animal models [41], with an increased risk of bacterial translocation. Increased sepsis rates

during PN might well be more related to increased bacterial translocation rather than to bacterial entrance via the inserted catheters. Moreover, early establishment of enteral nutrition will prevent or minimize the complications caused by prolonged TPN. Today, in most NICUs trophic or minimal enteral feeding (MEF) is initiated directly after birth (e.g. 12–24 ml, every 1–3 h). These small volumes of milk are insignificant to the body from a nutritional point of view but are thought to stimulate maturation of the developing gut. Infants given MEF show enhanced activity of digestive enzymes, increased digestive hormone levels, and improved gut motility when compared to infants who do not receive MEF. Several studies show that infants given MEF tolerate

full enteral feeding earlier, without an increased incidence of necrotizing enterocolitis [42]. However, several other studies show no beneficial effects [43] and these results could not be confirmed in a meta-analysis [44]. On the other hand, it is important to emphasize that the meta-analysis did not suggest any harmful effects either. Further randomized controlled trials – although potentially difficult to organize since

MEF is deeply rooted in clinical practice – are necessary to determine how the timing of introduction and rate of progression of enteral feeding affect clinical outcome. Other factors that can improve tolerance to enteral feeding might be feeding frequency. A small study showed increased tolerance to enteral nutrition when the milk was delivered as a bolus, in contrast to the widely used (semi-)continuous way [45]. Efforts to further improve the tolerance to enteral feeding are desperately needed in order to provide the preterm infant with the required amount of nutrients. Finally, although first-pass oxidation of amino acids might be higher when given as free amino acids than as intact protein [46], a hydrolysate formula might improve tolerance as well [47].

Premature infants fed own mother's milk are known to tolerate full enteral feeding earlier compared to their formula-fed peers [48] and have a reduced risk for developing necrotizing enterocolitis [49]. Factors present in human milk but not in formula, such as insulin-like growth factors 1 and 2 and endothelial growth factor, are thought to

Table 4. Subdivision of amino acids into non-essential, essential, and so-called 'conditionally' essential amino acids

Non-essential	Essential	'Conditionally' essential
alanine	valine	cysteine
serine	leucine	tyrosine
asparagine	isoleucine	glutamine
aspartate	methionine	arginine
glutamate	phenylalanine	proline
	threonine	glycine
	lysine	taurine
	histidine	
	tryptophan	

stimulate maturation of the premature gut [50]. Donor milk has been shown to exert similar effects on the premature intestine [51]. Caution should be applied when interpreting the results of these studies as they were performed in the 1980s and (feeding) practices and the quality of infant formula have changed dramatically since then. However, if this effect of donor milk can be confirmed in large randomized clinical trials, this will be an additional argument to advocate the use of donor breast milk for infants whose own mothers cannot supply (sufficient amounts of) milk.

Fig. 1. Indicator amino acid oxidation method, the preferred way to estimate individual amino acid requirements.

Fortification of Human Milk

The amount of protein and energy in mother's own or donor milk is not sufficient to supply the VLBW infant with enough substrates for optimal growth and development. Extra protein and energy, but also vitamins and minerals, are added to the milk in the form of breast milk fortifier. Recent studies show that infants fed fortified human milk often receive less protein than they actually need and less than is assumed by their physicians. The reason for this discrepancy is that manufacturers of breast milk fortifier designed their product to fortify preterm milk with an average protein content of 1.5 g/100 ml. The assumption that all preterm milk has an average protein content this high is unjustified. Although preterm milk might have a higher protein content during the first weeks of lactation this declines within a few weeks to the level of term milk, amounting on average 1.2 g/100 ml [52]. Forti-

fiers, when prepared according to the manufacturer's instructions, add on average 0.8 g of protein per 100 ml of milk. To reach the same protein levels as in preterm formula (2.5 g/100 ml), the unfortified milk must thus contain 1.7 g/100 ml, a level that will not be met in most cases. A possible solution to this problem could be titration of extra protein to human milk on the basis of regularly determined biochemical parameters such as serum urea [53]. It is debatable, however, what would be an appropriate parameter and what reference values should be used. Another solution is the bedside measurement of protein content by the use of (easy-to-operate but labor-intensive) human milk analyzers and to adjust the addition of fortifier to the necessary values. However, weight gain rates using such a personalized approach do not show a great improvement over standard fortification [53]. Also, current sources of breast milk fortification leave room for improvement. Several beneficial effects may be expected from the development of a human-milk-based fortifier, as human milk proteins are potentially better digestible compared to cow's milk protein; besides, the avoidance of cow's milk protein may be of benefit to preterm neonates.

Long-Term Consequences of Proper and Improper Feeding

Short-term consequences of under- or malnutrition are increased vulnerability to infectious diseases [54], higher susceptibility to lung injury caused by impaired tissue repair and muscle weakness [55], and decreased maturation of the intestines [56, 57]. It is increasingly acknowledged that improper feeding or hampered growth during early life has profound effects on several physiologic and metabolic aspects throughout life. The 'developmental origins of adult onset disease' theory was born after the observation that individuals who developed cardiovascular disease in later life had grown differently during fetal life and childhood compared to individuals who had not developed this disease [58]. It is suspected that several mechanisms play a role in this phenomenon. When an organism is malnourished during fetal or early postnatal life, it anticipates to receiving a low nutrient supply in later life by adjusting the setting of hormones and metabolism. This economical way of handling nutrients is an effective strategy for optimizing survival chances if the postnatal environment is truly sparse in nutrients. However, if the postnatal environment is not scarce in nutrients these adaptations become inappropriate and may make the individual more prone to diseases like obesity, diabetes and high blood pressure.

More direct mechanisms may play a role in this phenomenon (fig. 2). Early disrupted growth and decreased formation of the pancreatic islets of Langerhans are for example an easily conceivable concept that may eventually lead to diabetes mellitus. The same holds true for kidney development. A reduction in growth of the number of nephrons will ultimately lead to an increased blood pressure with concomitant health problems in later life. The detrimental effects of early undernutrition may also lead

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to poorer academic achievements in later life as the most significant part of brain growth takes place during the first 2 years of life. Brain development in the last trimester of pregnancy is characterized by neuronal differentiation, synaptogenesis and myelination. During this period the brain volume more than doubles and the cortical gray matter volume increases 4-fold. When after premature birth the continuous supply of nutrients through the umbilicus ceases, the infant is dependent on exogenous nutrient supply. If this supply falls short, brain development is hampered with permanent effects. The relationship between early intake and neurological development was for example shown by Stephens et al. [28] who retrospectively found that in extremely LBW infants, after adjusting for confounding variables related to disease, an increase of

1 g/kg per day of protein intake during the first week of life was associated with an 8-point increase in mental developmental index at 18 months corrected age. The effects of early diet on later intelligence were also strikingly shown by Lucas et al. [59]. Preterm neonates were randomized between term formula (energy: 60 kcal/100 ml, protein: 1.5 g/100 ml) and preterm formula (energy: 80 kcal/100 ml, protein: 2.0 g/100 ml). The assigned diets were fed from birth until 2-kg BW or until discharge, whichever was sooner. At 8 years of age, infants were subjected to the Wechsler Intelligence Scale for Children-III. It was shown that boys who were fed with preterm formula had a 12.2-point advantage in verbal IQ and a 6.3-point advantage in overall IQ compared to infants fed term formula [59]. Remarkably, this effect was not observed in girls, as the girls from both treatment groups had scores that were comparable to the boys that were given preterm formula. At 16 years of age, a subgroup of the study population, those born before 30 weeks of gestation, were invited again for an intelligence test and a brain MRI scan [60]. The effects of early diet were still apparent in these infants: the infants fed a high nutrient diet had a 6.9-point advantage in verbal IQ. No effects were found on performal IQ. The 2 groups showed significant differences on MRI scan in both left- and right-sided caudate volume, with the standard nutrition group showing lower caudate volumes that further correlated with IQ scores, with lower volume indicating lower verbal IQ [61].

It must also be noted that not only the quantity but also the quality of the supplied nutrients is important: the quality of the supplied building blocks will reflect the quality of the synthesized tissue. Human-milk-fed premature neonates have a lower diastolic and mean blood pressure in adolescence than individuals who received

Fig. 2. Possible mechanisms of long-term consequences of improper feeding. For example, early disrupted growth and decreased formation of the pancreatic islets of Langerhans are an easily conceivable concept that may eventually lead to diabetes mellitus.

formula [62]. This might be explained by the high amounts of essential fatty acids linoleic and α -linolenic acids present in human milk, which are precursors of long-chain PUFAs. Long-chain PUFAs are incorporated in the vascular endothelium and cardiac tissue. Furthermore, long-chain PUFAs, such as docosahexaenoic acid (DHA), are important precursors of membrane lipids and are, as such, important components of brain growth and myelination. DHA is the most abundant (n-3) fatty acid in the mammalian brain. This could explain the association found between breast feeding and intelligence in later life [63]. DHA levels in human milk vary depending on the amount of DHA in the mother's diet. Whether this justifies the prescription of fish oil capsules to mothers who are breast-feeding or expressing milk for their (preterm) infant needs to be examined.

Conclusions

Feeding preterm neonates is still extremely challenging. Optimal administration of TPN with a low incidence of complications requires a well-organized in-

frastructure with professionals from several disciplines working closely together. Furthermore, it is pivotal that hospital staff acknowledges that preterm birth is a nutritional emergency and that, when left untreated, this will result in serious short- and long-term detrimental effects. As preterm infants still end up growth restricted during NICU admission and requirements are so often not met, there remains the necessity of optimizing our feeding strategies. More research is mandatory to determine the right quantity and quality of energy and protein these infants need. In addition, we are in need of accurate parameters and reference values to monitor efficacy and safety of (parenteral) nutrition. Novel strategies to fortify human milk on an individual basis may improve the nutrient supply to enterally fed preterm neonates as well.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article. The writing of this article was supported by Nestlé Nutrition Institute.

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