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Review

Neurodevelopmental outcomes and nutritional strategies in very low birth weight infants

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SUMMARY

The developing brain of the very low birth weight (VLBW) infant is highly sensitive to effects of the nutritional milieu during the neonatal hospitalization and after discharge. Strategies to optimize nutritional care play an important role in reducing long-term neurodevelopmental morbidities in this population. Currently available interventions to ensure that the unique nutrient requirements of the VLBW infant are met include various dietary fortification strategies and parenteral nutrition. In this article, we review evidence regarding nutritional strategies and their beneficial effects on neurodevelopment in VLBW infants. We also highlight gaps in current knowledge and areas of current investigation that hold promise for improving nutritional care and long-term outcomes.

1. Introduction

Although growth of hospitalized preterm infants has improved substantially in the past two decades, poor weight gain remains the most frequent morbidity seen in very low birth weight (VLBW, <1500 g) infants. For example, epidemiologic data from across the USA demonstrate that in 2013, over half of VLBW infants left the neonatal intensive care unit (NICU) with a weight below the 10th percentile for gestational age [1]. Another recent study from 132 California NICUs reported that VLBW infants lose on average almost a full standard deviation in weight-for-age from birth to discharge [2], demonstrating extrauterine growth that lags behind the growth that would have occurred in utero. Taken together, these findings suggest that despite the current emphasis on intense early nutritional support, undernutrition remains an important problem for hospitalized VLBW infants.

Another frequently occurring morbidity seen in VLBW infants is neurodevelopmental impairment. VLBW infants demonstrate difficulties across a wide range of domains, including cognitive, motor, language, and behavioral functioning [3,4]. These difficulties burden children and their families, and incur large societal costs related to early intervention and special education services [5]. Notably, links between neurodevelopment impairment and early nutrition are well established [6], and are explained by the sensitivity of the developing brain to nutrition [7].

For the VLBW infant, developmental processes that normally take place in utero instead occur after birth, in the NICU environment. Magnetic resonance imaging (MRI) studies provide a window into the rapid growth and development of the preterm brain that occur during this time. From 29 weeks of postmenstrual age (PMA) to term equivalent, the preterm brain increases in volume from 150 to 400 mL, reflecting a rapid expansion of both the white and gray matter [8]. Structurally, the brain surface transforms from being largely smooth at 25 weeks of gestation to demonstrating a nearly-mature pattern of sulci and gyri by term equivalent age (Fig. 1) [9,10]. On a microstructural and cellular level, the predominant developmental processes immediately after very preterm birth include dendritic and axonal growth and differentiation of the myelin-producing oligodendrocytes. Close to term equivalent age and into the first year of life, synaptic pruning and myelination become prominent [11].

Certain developmental processes may be more or less vulnerable to undernutrition, thus the timing of the limitation in nutritional support is an important determinant of its long-term impact. Also, although the potential for recovery after a period of undernutrition exists, certain aspects of brain development may be permanently altered by a limited nutritional exposure during a critical period. Clinicians who care for very preterm infants must therefore understand the key role that nutritional care plays in optimizing the neurodevelopmental outcomes of their patients.

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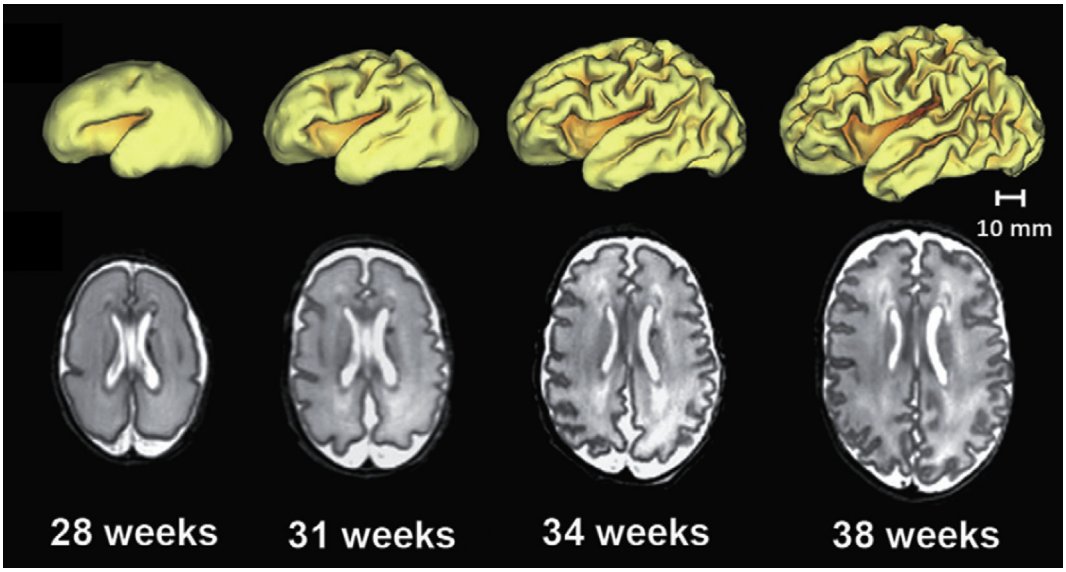

Fig. 1. Growth and development of the preterm brain. These images were obtained from a single infant at 28, 31, 34, and 38 weeks of postmenstrual age, and demonstrate the marked increase in brain size and complexity of cortical folding over this time period. From Smyser et al. [10].

During the neonatal hospitalization, although the optimal rate of growth is unknown, the goal is to match the rate of growth and body composition of the in-utero fetus [12]. Available interventions include enteral and parenteral feeding strategies, as well as micronutrient and fatty acid supplementation. The first year after hospital discharge provides an opportunity to address nutrient and growth deficits that may have accrued during the hospitalization, with the potential to ameliorate adverse long-term effects. Interventions include specialized formulas and fortification of human milk. In this article, we review the evidence base behind nutritional strategies during and after the neonatal hospitalization, with a focus on interventions that show promise to improve neurodevelopmental outcomes (Table 1). We point out both key practice points and areas requiring additional research.

2. Nutritional strategies during the NICU hospitalization

Clinicians in the NICU play a critical role in ensuring that VLBW infants receive nutritional care that is targeted to their unique needs. In reviewing the evidence base behind nutritional practices in neonatal intensive care, it is notable that many nutritional intervention studies have focused on short-term growth outcomes, whereas relatively few have determined longer-term effects of nutritional interventions on neurodevelopment. To fill this gap, longitudinal observational studies provide information that complements data from randomized trials. Clinicians should recognize that knowledge alone is not sufficient to ensure the effectiveness of nutritional interventions; implementation requires processes of care that support consistent care and attention to nutritional priorities [13]. In this section, we review enteral and parenteral nutrition strategies with a specific focus on the evidence base that established their effects on somatic growth and neurodevelopment (Table 1).

2.1. Fortified preterm formula

Seminal research by Lucas and colleagues conducted in the 1980s established that providing a formula enriched with

Table 1
Evidence for effects of nutritional strategies on growth and neurodevelopmental outcomes in very low birth weight infants.

	Weight gain and/or linear growth	Head growth	Neurodevelopmental outcomes
During the NICU hospitalization			
Fortified preterm vs term formula	+	+	+
Modifications to preterm formula			
Higher protein	+	↔	?
Long chain polyunsaturated fatty acids	↔	↔	+/↔
Bile salt-stimulated lipase	↔	↔	?
Human milk vs formula	−	−	+
Human milk fortification vs no fortification	+	+	+
Adjuncts to human milk fortifier			
Added protein	+	+	?
Human milk cream	+	+	?
Maternal DHA supplementation during lactation	↔	↔	+
Parenteral nutrition (early vs late)	+	↔	↔
Iron supplementation	↔	↔	↔
After NICU discharge			
Transitional (post-discharge) vs term formula	+	↔	↔
In-hospital preterm vs term formula	+	+	↔
Human milk fortification	+	+	+/?

+, positive association; −, negative association; ↔, no association; ?, little or no evidence; NICU, neonatal intensive care unit; DHA, docosahexaenoic acid.

macronutrients, minerals, and micronutrients for as little as three weeks after birth improved early weight gain (15.8 vs 13.3 g/kg/day), as compared with feeding a standard term formula [14]. In that study, formula was provided either as the sole diet or as a supplement to human milk. Weight gain benefits of the preterm formula were more pronounced in infants who received formula as their sole diet (no human milk). Additionally, in infants who received formula as their sole diet, not only was weight gain improved, but head growth was also substantially faster in the preterm formula group (1.53 vs 1.21 mm/day). This finding is notable given the strong correlation ($r = 0.68$) between head circumference and brain size [15], and the association of greater head circumference with better later neurodevelopmental outcome [16,17].

Follow-up of study participants at 18 months of age confirmed beneficial effects of the preterm formula on neurodevelopment [14]. Specifically, motor scores were about one-third of a standard deviation higher in the infants who received preterm formula as compared with standard formula when all infants (formula as sole diet plus formula as supplement to human milk) were combined. A benefit to social maturity was also seen. Whereas cognitive function was also better in the preterm formula-fed infants, the difference was smaller in magnitude than the motor and social maturity benefits, and not statistically significant. Mirroring results for early growth outcomes, benefits were generally more pronounced in the infants who received formula as their sole diet, without any human milk. For example, motor function was a full standard deviation better in the infants fed preterm formula only, whereas no benefit was detected in infants fed preterm formula as a supplement to their mother's milk.

Because neurodevelopmental outcomes in infancy are only modestly predictive of later abilities [18], longer-term follow-up is required to demonstrate sustained benefits of a nutritional intervention. Lucas' study comparing preterm vs term formula is unique in that testing of neurodevelopment was conducted not just in infancy, but also again at school age. This follow-up revealed that at 7–8 years of age, the odds of having a low IQ (<85) were about three-fold higher in children randomly assigned to the standard term formula [19] Additionally, in children who received the preterm formula, verbal IQ was about one-third of a standard deviation higher, although the difference was not statistically significant. A sex-specific benefit was noted, with an almost full standard deviation advantage for boys who received preterm formula, seen only in the group who received formula as the sole diet.

The strong evidence provided by those early studies led to widespread adoption of preterm formula during the 1990s. However, as noted above, slow postnatal weight gain remains frequent, despite the routine use of preterm formula. Further, observational studies of contemporary cohorts fed fortified diets reveal associations of faster somatic growth with greater brain maturation [20] and better neurodevelopmental outcomes [16,21,22]. These findings suggest additional room for improvement in nutritional care to optimize support for brain growth and development.

2.2. Further opportunities to improve preterm infant formula

While the question of whether or not to use preterm formula has already been answered, more work remains to identify the composition of formula that optimally supports the brain development of growing preterm infants. Some clinical trials have evaluated incremental improvements in the macronutrient composition of formula, for example higher versus lower protein content [23], but those studies have focused primarily on short-term benefits such as weight gain and have not assessed longer-term benefits to neurodevelopment. Other research has investigated the benefits of adding long chain polyunsaturated fatty acids (LC-PUFAs) to preterm infant formula. Whereas a few studies have noted neurophysiologic benefits, assessed with visual evoked potentials, and improved performance on a measure of infant attention (Fagan test), meta-analysis of studies that used a standard neurodevelopmental test (Bayley Scales) at 18 months revealed no benefit [24]. Nonetheless, current commercially available preterm formulas typically contain added LC-PUFAs such as docosahexaenoic acid (DHA) and arachidonic acid (ARA), and this practice appears to be safe. Current research in this area focuses on optimizing fatty acid balance [25] and other aspects of fatty acid composition, as discussed elsewhere in this issue.

In addition to nutritional improvements to infant formula, recent research has focused on the addition to formula of non-nutrient bioactive factors that are naturally present in human milk and which may improve digestion and absorption, thereby indirectly improving the infant's nutritional status. For example, bile salt-stimulated lipase (BSSL) is a lipolytic enzyme secreted by the mammary gland into human milk. BSSL assists with digestion and absorption of fat, which is of particular importance given the relative pancreatic immaturity of the preterm infant. Although an initial clinical study was promising [26], a recently published Phase III trial [27] did not find evidence of improved growth velocity, except in the subgroup of infants born small for gestational age. Neurodevelopmental testing was conducted at 12 months of age as a “safety” measure and the authors reported that there was no difference between groups, but did not include those data in the published paper.

Taken together, the available evidence supports the use of preterm formula over standard term formula for hospitalized preterm infants. Beneficial effects include more rapid somatic growth during the NICU hospitalization, as well as improved neurodevelopmental outcomes, with effects that persist at least to school age. Other widespread practices, such as the supplementation of formula with high doses of protein, or the addition of LC-PUFAs, are not based on any clear-cut evidence for neurodevelopmental benefits. Future research is expected to focus not just on nutritional modifications to preterm infant formula, but also on non-nutritional factors that may aid in digestion and absorption.

2.3. Human milk use as a strategy to improve neurodevelopmental outcomes

The previous section focused on evidence regarding the use of preterm formula rather than standard term formula. However, recent practice has moved toward an increased use of human milk rather than formula to feed VLBW infants [28], based largely on the protective effects of human milk against necrotizing enterocolitis [29]. This increased use of human milk is relevant to neurodevelopmental outcomes for two main reasons. First, human milk-fed preterm infants gain less weight during the NICU hospitalization than formula-fed infants [30], suggesting relative undernutrition that could adversely affect neurodevelopment. Second, some observational evidence suggests that human milk rather than formula-feeding is associated with better neurodevelopmental outcomes in preterm infant populations [31], which contradicts what one would expect given concerns for undernutrition in human milk-fed infants. In this section, we review the evidence behind the neurodevelopmental benefits of human milk feeding as a nutritional strategy.

Several studies have evaluated the extent to which feeding human milk (as compared with formula) to VLBW infants in the NICU is associated with better neurodevelopmental outcomes [32]. Whereas some studies have demonstrated beneficial effects of human milk on outcomes assessed in infancy and beyond [33–35],

others have shown minimal or no benefit [36,37]. Socio-economic factors differ between mothers who do and do not provide milk for their VLBW infants, and also track closely with neurodevelopmental outcomes. Thus, it is likely that at least some of the observed benefit is explained by confounding due to these social factors.

By design, randomized trials can overcome the problem of confounding inherent in observational studies of human milk and neurodevelopment. Although it is not ethical to randomize mothers to provide their own milk to their infants or not, it is possible to randomly assign infants to receive either donor milk or formula as a supplement when their own mother's milk is not available. In such studies, social factors are evenly distributed between groups, and results can shed some light on the direct neurodevelopmental benefits of human milk itself. A limitation of this approach is that donor milk does not retain all the potentially beneficial nutrient and non-nutrient factors that are present in mother's own milk, due to pasteurization and freezing processes, as well as differences in lactation stage between milk donors and mothers of preterm infants [38].

Lucas and colleagues led an early trial in which preterm infants were randomized to receive donor milk or standard term formula, either as their sole diet or as a supplement to mother's own milk. Weight gain was slower in the infants fed donor milk, suggesting relative undernutrition, but developmental outcomes were equivalent at age 18 months [39]. This finding was unexpected given the strong links between early nutritional status and neurodevelopmental outcome. It is possible that beneficial factors in donor milk itself offset the harmful effects of relative undernutrition. An important limitation of that early study is the fact that it was carried out prior to the routine use of human milk fortifiers (discussed in the next section). The question of whether fortified donor milk or preterm formula is superior in terms of early growth and/or neurodevelopment is the subject of two trials currently underway [40,41].

Overall, recommendations emphasizing a preference for the use of human milk over preterm formula [28] are based predominantly on health benefits. Observational studies suggest that human milk feeding may also benefit neurodevelopmental outcomes, but firm conclusions are difficult due to concerns about undernutrition and socio-economic differences that explain both feeding choices and outcomes. Ongoing randomized trials are expected to determine the extent of neurodevelopmental benefits contributed by fortified donor milk, and guide clinical practice regarding nutritional strategies for human milk use that optimally supports neurodevelopment in VLBW infants [40,41].

2.4. Human milk fortification

Evolutionary factors have optimized the composition of human milk to meet the nutritional needs of full-term infants [42]. However, VLBW infants have different nutritional requirements than full-term infants because VLBW infants must match fetal accretion rates, compensate for deficits that accrue prenatally and postnatally, and meet excess needs due to illness. Requirements for protein, energy, fatty acids such as DHA, minerals including calcium and phosphorus, and micronutrients (e.g. iron, zinc) are all higher for the VLBW infant than for the newborn healthy full-term infant [43], and all of these nutrients play a role in supporting brain growth and development. Thus, the extent to which human milk-fed VLBW infants are able to meet these requirements is likely to influence their neurodevelopmental outcomes.

A widely used strategy to address the special nutritional needs of the VLBW infant is to add a multi-component human milk fortifier to mother's own and donor milk before feeding it to VLBW infants. Fortifying human milk increases weight gain, linear growth, and head growth during the neonatal hospitalization, as compared with feeding unfortified milk [44], suggesting that nutritional requirements are being met more effectively. However, very little is known about the neurodevelopmental benefits of human milk fortification, as only one study [45] has examined these outcomes. That study found a 2–3 point advantage in Bayley Scales at 18 months for infants randomly assigned to multi-component human milk fortifier, but the differences were not statistically significant, and confidence intervals could not exclude clinically important differences. Additionally, a 6 point (approximately one-third standard deviation) advantage was noted in males who received the fortifier, suggesting a possible sex-specific effect. No study has examined outcomes later in childhood in relation to human milk fortification.

Moving beyond the question of whether or not to fortify human milk for VLBW infants, subsequent investigations have focused on how strategies for human milk fortification may be further optimized. For example, although standard fortifiers contain protein, providing even more protein targeted to biochemical markers of nitrogen utilization promotes greater weight gain and head growth [46]. Products for modular protein fortification are commercially available and facilitate easy adjustment of protein intake, for example in response to slow weight gain in human milk-fed infants. Regarding fat, a human milk-based cream product has been shown to improve weight gain, linear growth, and head growth [47], although this product is not yet in widespread clinical use. Initiating fortification sooner after birth and reaching higher target levels of multiple macronutrients than usual care also appears to increase weight gain. Although all of these studies demonstrate strategies for human milk fortification that are effective in improving early weight gain, one frequent limitation is lack of neurodevelopmental data, without which the magnitude of benefit to these longer-term outcomes cannot be estimated.

Besides fortifying human milk directly, another strategy to optimize the composition of human milk for human milk-fed VLBW infants is to provide nutritional supplementation to lactating mothers. This approach has been studied in relation to DHA. A large, multi-center trial in Australia randomized very preterm infants to high (~1% of total fatty acids) versus standard DHA intake, which was achieved via maternal supplementation with tuna oil capsules or placebo. At 18 months of corrected age, neurodevelopmental outcomes were similar between study groups, but subgroup analyses revealed a small benefit of maternal DHA supplementation to girls and to infants <1250 g birth weight (approximately one-third standard deviation advantage for both subgroups) [48]. Follow-up of >90% of study participants at 7 years of age revealed no between-group differences in IQ or in performance on measures of attention, executive function, behavior, visual–spatial perceptual skills, educational progress, and quality of life [49].

In addition to optimizing the composition of human milk fortifier and the maternal diet, to fully support preterm brain development, clinicians may also need to address the challenges posed by the wide variation in the macronutrient content of human milk. For example, one study [50] of 736 maternal milk samples reported a five-fold range in protein (0.61–2.96 g/dL) and 10-fold range in fat (0.66–6.35 g/dL). Donor milk is similarly variable in its macronutrient content, and has even lower average protein levels than mother's own milk [51]. Because human milk fortifiers are designed to be mixed with “typical” human milk (e.g. milk containing protein 1.2 g/dL and fat 3.5 g/dL), whenever the actual macronutrient content is less than “typical,” nutrient deficits accumulate [52]. Current research is investigating the use of bedside milk analyzers to facilitate individualized targeting of

human milk fortification based on the actual macronutrient content of the milk [53]. If this approach is successful in improving the early nutritional status of human milk-fed VLBW infants, it may also benefit neurodevelopment.

In sum, to meet the nutritional requirements of human milk-fed VLBW infants, fortifiers must be added to milk prior to feeding. Fortification of human milk clearly benefits early growth outcomes, but evidence regarding direct effects on neurodevelopment is limited. Maternal dietary supplementation during lactation is another available strategy to optimize the nutritional composition of maternal milk that is fed to VLBW infants. Providing DHA in this way may lead to improved neurodevelopmental outcomes in infancy, but longer-term benefits were not apparent. Current research is focused both on revising the "one size fits all" strategies for milk fortification, as well as developing new strategies to analyze human milk and target fortification, thereby addressing the wide variation in human milk composition and allowing individual patient nutritional needs to be met more consistently.

2.5. Parenteral nutrition

Due to gastrointestinal immaturity as well as frequent clinical instability, clinicians caring for VLBW infants typically start enteral feedings at a low volume, then increase the volume incrementally and add fortifiers over a period of one to two weeks. To fill the gap between the time of birth and the establishment of full-volume fortified enteral feedings, parenteral nutrition is a useful strategy to administer protein, fat, and other nutrients. Similar to many studies of enteral nutrition, randomized trials of parenteral nutrition have generally focused on short term benefits, such as nitrogen retention and weight gain. However, virtually no direct experimental evidence exists regarding neurodevelopmental benefits of providing parenteral nutrition, nor of specific strategies for delivering parenteral nutrition [54]. One of the few studies examining longer-term outcomes compared targeting 2.5 vs 4 g/kg/day of parenteral amino acids shortly after birth [55]. Although metabolic endpoints were more favorable in the higher-dose group, neurodevelopmental outcomes were indistinguishable. Despite limitations of the available evidence regarding neurodevelopmental outcomes, administering parenteral nutrition – particularly amino acids and glucose – as soon as possible after birth is a widespread practice in neonatal intensive care, and appears to be effective in reducing nutritional deficits and improving early weight gain.

2.6. Micronutrient supplementation

In addition to macronutrients such as protein and fat, VLBW infants have greater requirements for several micronutrients, as compared with full-term infants. This difference is especially important for micronutrients that are normally transferred in large amounts from mother to infant during the third trimester of pregnancy, such as iron. In addition to its hematologic functions, iron plays an important role in brain development. Of studies investigating the effects of different iron supplementation strategies for VLBW infants after birth, only a few have examined potential neurodevelopmental benefits, and none has identified a clinically or statistically significant benefit or harm [56].

3. Catching up: nutritional strategies after NICU discharge

After a period of weight gain that is slow relative to the gestational age equivalent fetus, VLBW infants often experience an acceleration of growth in the early months after NICU discharge, usually catching up to their full-term peers by preschool age [57]. This period of time provides an opportunity to compensate for nutritional deficits that have accumulated during the NICU stay, and is driven both by a greater intake volume of human milk or formula in the setting of increasingly mature oral feeding abilities, and also by clinical interventions to increase nutrient intake, for example specialized formulas and continued human milk fortification. More rapid weight gain after term equivalent age is associated with better neurodevelopmental outcomes both in infancy [16] and school age [58], but these apparent benefits may be explained in part by reverse causation or confounding, with sicker infants showing both slower weight gain (e.g. due to feeding difficulties) and poorer outcomes [59]. Fortunately, randomized trials provide more definitive evidence regarding specific strategies for post-discharge nutrition that are effective in improving neurodevelopmental outcomes (Table 1).

3.1. Fortification of formula with energy and nutrients

Strategies to provide energy and nutrient fortification after NICU discharge include (1) continuing the in-hospital preterm formula for a period of time after discharge, or (2) providing a "transitional" or "post-discharge" formula, which is enriched with more energy and nutrients than standard term formula, but less than typical in-hospital preterm formulas. Overall, little evidence exists for beneficial effects of transitional formulas as compared with standard term formula on early growth; only one study examined 18-month neurodevelopmental outcomes and found no effect [60]. Continuing in-hospital formula after discharge does appear to improve weight gain and head growth, but limited data do not support a benefit to neurodevelopment [60].

One possible explanation for the relative lack of benefit of post-discharge nutrient fortification – in contrast to the benefits of using preterm formula during the NICU hospitalization – is that the infant's appetite and therefore intake is downregulated in response to the nutrient enrichment, reducing the effectiveness of the intervention. Another possibility is that the brain is more sensitive to the effects of nutrition in the period of time before NICU discharge (e.g. before term equivalent age) than after discharge. Despite this lack of strong evidence for neurodevelopmental benefits, the use of transitional formula is widespread, and may be especially appropriate for infants with nutritional deficits present at the time of NICU discharge and/or limited oral intake. Although the evidence in favor of continuing in-hospital preterm formula is stronger than for transitional formula, in-hospital formula is generally not available in the community setting, so is not typically used.

3.2. Human milk fortification after NICU discharge

Fortifying human milk after NICU discharge is a strategy to provide extra nutrients required for catch-up growth, while also allowing for continued breastfeeding according to maternal preference. The benefits of this strategy must be weighed against the logistical difficulties of expressing and fortifying milk in the home environment. Overall, there is some evidence that continued human milk fortification after NICU discharge is advantageous. In a small ($n = 39$) study [61], infants <33 weeks of gestation receiving predominantly (≥80%) human milk at the time of discharge were randomly assigned to fortify half the daily feedings versus no fortification. At 12 weeks, infants in the fortification group were longer and had larger head circumferences [62], and at age 1 year the Bayley Mental Development Index was 9 points (approximately two-thirds standard deviation) higher for infants who received fortification. Although clinically important, this difference was not statistically significant due to the small sample size. A larger ($n = 207$) four-center Danish study [63] randomized infants to fortify one feeding daily versus no fortification, finding no benefits

to growth or neurodevelopment. The lack of benefit in this study may be attributable to the lower intensity of the intervention (fortification of just one versus half of all human milk feedings). More research is needed to determine the optimal frequency and duration of human milk fortification after NICU discharge.

4. Conclusions

The preterm brain is highly sensitive to the nutritional milieu. Thus, strategies for nutritional care are critical to improving neurodevelopmental outcomes for VLBW infants. Providing a nutrient-enriched diet during the NICU hospitalization is effective in improving early growth and long-term neurodevelopmental outcomes. The period of time after NICU discharge provides an opportunity to compensate for deficits that accumulated during the NICU stay, and continuing to provide a nutrient-enriched diet during this time may be beneficial. Further work is needed to elucidate the composition of preterm formula and human milk fortifier that supports optimal growth and brain development. More research is also needed to determine optimal feeding strategies after NICU discharge.

Practice points

- Providing a nutrient-enriched diet during the NICU hospitalization is effective in improving early growth and long-term neurodevelopmental outcomes.
- Feeding human milk rather than formula has some health advantages, but fortification during the NICU hospitalization is required to ensure that nutrient requirements specific to the VLBW infant are met.
- The neurodevelopmental benefits of continuing a nutrient-enriched diet after NICU discharge are less certain, but may be of benefit, especially for human milk-fed infants and those who have accumulated substantial deficits during the NICU hospitalization.

Research directions

- The optimal approach to addressing the wide variation in human milk macronutrient content and resulting potential for undernutrition in human milk-fed infants.
- Effective strategies for ensuring adequate nutrient intake after NICU discharge for both formula-fed and breastfeeding infants.

Conflict of interest statement

None declared.

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