Low protein intake from human milk fortified in a routine fashion is the main cause of postnatal growth restriction

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Meeting the Nutritional Needs of the Low-Birth-Weight Infant

by Ekhard E. Ziegler

Key insights

This article reviews the current knowledge regarding the nutritional needs of a preterm infant in the first few days of life. It explains why and how to increase nutrient intake to support normal growth, with the benefits and risks, as well as the extra efforts needed in resource-poor environments.

Current knowledge

The gastrointestinal tract of a preterm infant is immature. Yet, inadequate nutrition most likely causes postnatal growth restriction, which is associated with poor neurocognitive development in a dose-dependent fashion. Factorial and empirical studies on the nutritional requirements appear consistent.

Practical implications

Adequate intake of proteins is rarely achieved in practice. At a minimum, nutrients need to be administered as soon as possible after delivery. Parenteral nutrition should be started early and combined with a small amount of trophic feeding to quicken gut maturation. Targeted or adjustable protein fortification in clinical practice may be useful.

Recommended reading

Ziegler EE, Carlson SJ: Early nutrition of very low birth weight infants. *J Matern Fetal Neonatal Med* 2009;22:191–197.

Preterm infant

- incomplete absorption
- accretion
- energy cost of growth

Protein/energy ratio needed to achieve fetal weight gain (adapted from table 1). A preterm infant fed parentally and/or enterally should mimic the growth rate of a fetus; however, additional variables make this challenging (see text for details).

Meeting the Nutritional Needs of the Low-Birth-Weight Infant

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Key Messages

- Growth failure is associated with impaired neurocognitive development. It can be avoided or minimized by improved nutrient intakes.
- Parenteral nutrition is required initially because of immaturity of the gastrointestinal tract.
- Initial small (trophic) feedings aim to mature the gastrointestinal tract. Human milk does this efficiently while minimizing the risk of necrotizing enterocolitis and sepsis.
- Human milk must be fortified with nutrients in order to enable adequate growth.

Key Words

Human milk fortification • Mother's milk • Nutrient requirements • Parenteral nutrition • Trophic feeding

Abstract

Delivering adequate amounts of nutrients to premature infants at all times is challenging because the infant's immature gastrointestinal tract is initially unable to accept feedings, necessitating the use of parenteral nutrition. In the past, inadequate amounts of nutrients have commonly been given to premature infants because the administration of nutrients was thought to be hazardous. Inadequate nutrient

intakes have resulted in widespread postnatal growth restriction. Now that it is known that postnatal growth restriction is associated with poor neurocognitive development, efforts are made to increase nutrient intakes. In this review, nutrient requirements of premature infants that have been determined by the factorial and empirical methods are reviewed. Current good practices regarding parenteral nutrition are discussed, as are guidelines for the introduction and advancement of enteral feedings. Because of its trophic effects on the gastrointestinal tract and its anti-infectious effects, human milk is strongly preferred as the early feeding of choice for premature infants. Human milk also protects infants against necrotizing enterocolitis. Once full feeding is achieved, the challenge is to provide nutrients in amounts that support the infant's growth like that of the fetus. In the case of the infant fed his/her mother's milk or banked donor milk, nutrient fortification is necessary and is generally practiced. However, adequate intakes of protein are seldom achieved with routine fortification and methods of providing additional fortification are discussed.

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Introduction

When an infant is born prematurely, the rich supply of nutrients that has supported the growth and development of the fetus up to this point is interrupted. It is, in principle, widely agreed that the supply of nutrients should be restored promptly and that nutrients should be

provided in amounts that allow the premature infant to grow like the fetus in both velocity as well as body composition [1]. In reality, however, a supply of nutrients below the fetal supply is common at least for some time after birth. As a result, infants fail to grow like the fetus and almost always show postnatal growth restriction by the time they leave the hospital. The reason(s) for the low nutrient supply are not easily ascertained because they are not documented in the literature. However, it is certain that a main reason has been that the administration of nutrients, whether parenterally or enterally, has been considered hazardous and, as a result, nutrients have been provided hesitatingly. There has also been the tacit assumption that growth restriction, even of a severe degree, was innocuous, notwithstanding the fact that animal studies, most famously those by Widdowson and McCance [2], had clearly shown that undernutrition during critical periods in early life has irreversible effects on the size, structure, and function of the central nervous system.

All this has changed in the last decade as a number of studies have established beyond any doubt that postnatal growth restriction in premature infants is associated with impaired neurocognitive development. Of particular importance has proven to be the immediate postnatal period, where the long-time practice of near-total starvation has now been shown to have marked deleterious effects on neurocognitive development [3]. In response, there have been broad efforts to improve nutrient intakes. Considerable progress has been made; in 2010, based on anecdotal reports, nutrient intakes are higher than they were just 10 years ago and postnatal growth restriction is not as severe as it used to be. This does not mean that nutrient intakes are adequate now and are so at all times. Much remains to be done until the inadequacy of nutrient intake ceases to be a preventable cause of compromised neurodevelopment in premature infants.

In what follows, postnatal growth restriction is reviewed briefly as is the evidence of its association with poor neurocognitive development. Documentation of inadequate nutrient intakes is reviewed and, where available, its correlation with growth velocity. Nutrient requirements are discussed in some detail, as a good understanding of the nutrient requirements is a prerequisite for efforts to ameliorate inadequate intakes. Finally, current

methods for providing nutritional support are explored, including areas where improvement is still possible and indeed necessary.

Postnatal Growth Restriction

Although postnatal growth restriction has been present for a long time, recognition of its extent and, especially, its implications for subsequent development are of relatively recent origin. An essential step in the recognition

was the juxtaposition of premature infant growth and fetal growth (fig. 1) [4, 5]. This direct comparison illustrated in unequivocal fashion the fact that growth of premature infants was far from being like that of the fetus. Subsequent reports

have further documented the extent and the severity of postnatal growth restriction [6, 7].

The Cause of Growth Restriction

Inadequate nutrition has long been suspected to be the cause of the observed growth restriction [8]. After all, a close relationship between protein intake and growth had been demonstrated in studies designed to determine the protein requirement of premature infants. In a number of observational studies, a relation-

Much remains to be done until the inadequacy of nutrient intake ceases to be a preventable cause of compromised neurodevelopment in premature infants.

Fig. 1. Postnatal growth restriction in the LBW infant (adapted from Ehrenkranz et al. [5]). — = Reference intrauterine growth (percentile); - - - = 24–25 weeks; = 26–27 weeks; . . . = 28–29 weeks.

ship between slow weight gain and low protein intake among premature infants has been documented [4, 9–15]. Without exception, these reports show that protein intakes are considerably less than required intakes, with intakes of energy tending to be more close to or even above requirements.

The Consequences of Growth Restriction

A considerable number of follow-up studies of premature infants have shown that impaired neurocognitive development is a common finding. Several of the studies have shown associations of developmental outcome with slow growth during the neonatal period and are thus particularly important from a nutritional point of view [16–21]. Among this latter group of studies, the age at follow-up ranged from 1 to 19 years and the number of subjects also varied greatly. Two of the studies [19, 21], which both involved large numbers of subjects, carry special weight. The study by Ehrenkranz et al. [19] is important because it provided detailed data regarding growth from regained birth weight to discharge, and the study by Weisglas-Kuperus et al. [21] because of the length of follow-up (19 years). These studies establish

beyond any doubt that postnatal growth restriction is associated with impairment of neurocognitive development in a dose-dependent fashion. What the studies cannot tell us (because these infants were born in the 1980s and 1990s) is what impact, if any, today's milder degrees of growth restriction have on neurocognitive development.

It must be emphasized that the association between growth failure and late cognitive outcome does not necessarily mean that growth failure per se is the cause of impaired cognitive development. It is far more likely that growth failure and impaired development share a common cause that explains both. That common cause most likely is inadequate nutrition.

There has been only one study that linked neurodevelopmental outcome directly to nutrient intakes rather than to growth failure [3]. In 2009, Stephens et al. [3] showed that low intakes of protein and energy during the first week of life markedly impaired neurocognitive development (Bayley scores) at 18–22 months of age. These findings have provided the major impetus for the adoption of vastly improved parenteral nutrition regimens in the days immediately following birth.

Table 1. Protein and energy intakes needed to achieve fetal weight gain

	Body weight					
	500–700 g	700–900 g	900–1,200 g	1,200–1,500 g	1,500–1,800 g	1,800–2,200 g
Fetal weight gain, g/day	13	16	20	24	26	29
Fetal weight gain, g/kg/day	21	20	19	18	16	14
<i>Protein, g/kg/day</i>						
Loss	1.0	1.0	1.0	1.0	1.0	1.0
Growth (accretion)	2.5	2.5	2.5	2.4	2.2	2.0
Required intake						
Parenteral	3.5	3.5	3.5	3.4	3.2	3.0
Enteral	4.0	4.0	4.0	3.9	3.6	3.4
<i>Energy, kcal/kg/day</i>						
Loss	60	60	65	70	70	70
Resting expenditure	45	45	50	50	50	50
Other expenditure	15	15	15	20	20	20
Growth (accretion)	29	32	36	38	39	41
Required intake						
Parenteral	89	192	101	108	109	111
Enteral	105	118	119	127	128	131
<i>Protein/energy, g/100 kcal</i>						
Parenteral	3.9	3.8	3.5	3.1	2.9	2.7
Enteral	3.8	3.7	3.4	3.1	2.8	2.6

Nutrient Requirements

Nutrient requirements of the premature infant have been determined by two methods, the factorial method and the empirical method. The former uses the fetal model to derive necessary intakes of protein, energy, and many other nutrients. Because nutrient accretion accounts for a large proportion of required intakes, the factorial approach is particularly well suited for the premature infant. In the other method, the empirical approach, the intake of growth-limiting nutrients (energy or protein) is manipulated and the growth response is observed. It is important for caretakers of premature infants to understand that growth like that in the fetus is not possible unless requirements for protein and energy are met. With the current routine feeding methods, protein requirements are not always met and fetal rates of growth are difficult to achieve.

Factorial Approach

In the factorial approach, fetal accretion of body components is used as a starting point. Underlying the factorial approach is the assumption that body composition of the premature infant resembles that of the fetus and that growth should proceed at the same rate as it would have in utero. Although body water spaces are somewhat decreased in the premature baby compared to the fetus, the fetal model holds for all other body components (nutrients). The chemical composition of the human fetus is well documented in the literature, and Sparks [22] and Forbes [23] have provided comprehensive summaries of the data. Ziegler et al. [24] used the data to construct a 'reference fetus'. Using the factorial method, it was first realized in 1977 by Fomon et al. [25] that the nutrient needs of the premature infant are much higher than those of the term infant and cannot be met by breast milk. More detailed estimates of nutrient requirements based on the factorial method were presented in 1981 [26].

Table 1 summarizes the derivation of requirements for protein and energy by the factorial approach. Fetal accretion rates in table 1 are a composite of values from the different models [22–24] in combination with contempo-

rary fetal growth data. Energy accretion values include the energy cost of growth of 10 kcal/kg/day. Required parenteral intakes are obtained from accretion rates after correction for inevitable losses and for inefficiency of conversion of dietary protein to body protein. Inevitable losses of nitrogen are assumed to be 160 mg/kg/day (27 mg/kg/day via the skin [27] and 133 mg/kg/day via the urine [28]), equivalent to 1.0 g/kg/day of protein. Resting energy expenditure is assumed to be 45 kcal/kg/day in infants <900 g and 50 kcal/kg/day in larger infants, and expenditures for occasional cold exposure and physical activity are assumed to be 15 kcal/kg/day in infants <1,200 g and 20 kcal/kg/day in larger infants [29, 30]. Enteral requirements are obtained from parenteral requirements by applying corrections for incomplete absorption of protein (88%) and energy (85%).

Required intakes of major minerals and electrolytes derived by the factorial method are summarized in table 2. There is uncertainty regarding the minimum urinary losses of electrolytes and phosphorus, the intestinal absorption of calcium is variable, and it is not known what minimum amounts of Ca and P must be accrued in order to maintain bone health. In view of

these uncertainties, the estimates in table 2 are set to be conservative. It is therefore possible that somewhat lesser intakes could suffice, but how much less is not possible to state.

Empirical Approach

Protein

The empirical approach utilizes feedings (formulas or human milk) with varying energy and/or protein content and uses growth and/or nitrogen balance as outcome. Empirical estimates pertain mostly to infants weighing >1,200 g. Analysis of data from studies published before 1986 showed that weight gain (g/day) increases with increasing protein intake up to 3.6 g/kg/day, the highest intake studied [31]. Kashyap et al. [32, 33] performed a series of growth and metabolic balance studies with feedings (human milk/formulas) that varied in protein and energy content over a wide range. The data, as summa-

Table 2. Requirements for major minerals and electrolytes determined by the factorial method (per kg/day)

	Body weight					
	500–1,000 g		1,000–1,500 g		1,500–2,000 g	
	accretion	required intake	accretion	required intake	accretion	required intake
Ca, mg	102	184	99	178	96	173
P, mg	66	126	65	124	63	120
Mg, mg	2.8	6.9	2.7	6.7	2.5	6.4
Na, mEq	1.54	3.3	1.37	3.0	1.06	2.6
K, mEq	0.78	2.4	0.72	2.3	0.63	2.2
Cl, mEq	2.26	2.8	0.99	2.7	0.74	2.5

rized by the authors [34], show that weight gain increases linearly with increasing protein intakes up to about 4.2 g/kg/day. The authors estimated that the protein intake necessary for infants weighing >1,200 g to grow like the fetus was about 3.0 g/kg/day, but also realized that such

Nutrients, at a minimum, need to be provided at a level that maintains the anabolic state in which the fetus was kept until the time of delivery.

an intake would probably not be optimal as it does not yield optimal markers of protein nutrition, such as serum albumin concentration. Rigo [35] used growth, body composition, and nitrogen balance as endpoints and estimated protein requirement of infants born at 26–30 weeks of gestation at 3.8–4.2 g/kg/day (3.3 g/100 kcal) and that of infants born at 30–36 weeks of gestation at 3.4–3.6 g/kg/day (2.8 g/100 kcal).

The controlled studies of Kashyap and Heird [34] led to the conclusion that each gram per kilogram of additional protein increases weight gain by 3.44 g/kg/day. It is interesting that this value is similar to values derived from recent observational studies. In the study by Olsen et al. [11], a single gram per kilogram of additional protein was associated with an increment of weight gain of 4.1 g/kg/day and in the study by Ernst et al. [12], each gram per kilogram of protein was associated with weight gain of 6.5 g/day (equivalent to 4.3 g/kg/day if weight is assumed to be 1.5 kg).

Energy

In empirical studies, valid estimates of energy requirements are difficult to obtain because of the overwhelming effect of protein intake. However, in an elegant analysis of data from a number of empirical trials, Micheli et al. [36] were able to establish that energy needs for growth of lean body mass are no more than 90–100 kcal/kg/day. Above that intake level, energy is presumably stored in adipose tissue but is no longer limiting for growth of lean body mass.

Recommended Intakes

Table 3 provides a summary of the various estimates of requirements and of official recommendations. The Life Sciences Research Office concluded that the minimum protein intake of premature infants (weight not specified) was 3.4 g/kg/day with a protein/energy ratio of

2.5 g/100 kcal at the maximum energy intake of 135 kcal/kg/day [37], and that a protein intake of 4.3 g/kg/day (with a protein/energy ratio of 3.6 g/100 kcal) was without adverse consequences, whereas intakes >5.0 g/kg/day were thought to be undesirable. In 2010, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [38] issued recommendations for nutrient intakes of premature infants. Their recommendations for protein intakes of infants weighing <1.0 kg are the highest official recommendations to date, possibly reflecting the notion that most infants benefit from catch-up after having fallen behind in the early days and weeks of life.

Nutrient Delivery

As the fetus transitions to become a premature infant, the flow of nutrients is inevitably interrupted when the cord is clamped. There is consensus that the interruption should be kept as short as is technically feasible. In practical terms, this means that parenteral nutrition should be initiated quickly after birth. When the flow of nutrients is resumed after only a brief hiatus, much of the deleterious starvation response is avoided, including glucose

Table 3. Protein requirements and recommended intakes

	Weight <1,200 g		Weight >1,200 g	
	g/kg/day	g/100 kcal	g/kg/day	g/100 kcal
Ziegler (table 1)	4.0	3.7	3.6	2.8
Kashyap and Heird [34]	–	–	3.0	2.5
Rigo [35]	3.8–4.2	3.3	3.4–3.6	2.8
LSRO [37]	3.4–4.3	2.5–3.6	3.4–4.3	2.5–3.6
ESPGHAN 2010 [38]	4.0–4.5	3.6–4.1	3.5–4.0	3.2–3.6

LSRO = Life Sciences Research Office; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology and Nutrition.

intolerance. Nutrients, at a minimum, need to be provided at a level that maintains the anabolic state in which the fetus was kept until the time of delivery. Needless to say, because of the immaturity of the gastrointestinal tract, the administration of nutrients initially has to rely exclusively on the parenteral route.

While nutrients are provided parenterally, trophic feedings are initiated with the objective of fostering maturation of the immature intestinal tract. When maturation has advanced to the point where full feeding can be administered, parenteral nutrition is terminated, mark-

Fig. 2. Early parenteral nutrition: strategies and approximate timeline.

ing the beginning of the late feeding period during which enteral feeding is the sole source of nutrients. Developments and recommendations have recently been summarized [39].

Parenteral Nutrition

The infant is initially dependent on receiving nutrients parenterally because the immaturity of the gastrointestinal tract precludes the digestion and absorption of meaningful amounts of nutrients. However, until recently, the parenteral administration of nutrients (except for some energy in the form of glucose) was withheld for several days because it was considered unsafe, and when parenteral nutrition was started, amino acids and lipids were provided in small amounts that were advanced only hesitatingly. Thus, for many years, infants have been subjected to more or less complete starvation for some time after birth. Two key developments have brought about a dramatic change in practice. One has been the demonstration that parenteral nutrition beginning within 2 h of

birth at substantial amino acid doses (about 2.5 g/kg/day), besides being efficacious, is perfectly safe [40, 41]. The other key development has been the demonstration that failure to provide adequate intakes of protein and energy during the first week of life has profound negative effects on later neurocognitive development [3]. This finding has provided a compelling impetus for initiating nutrition promptly after birth.

But how soon after birth and in what dose must parenteral nutrition begin? Two considerations have led to the conclusion that parenteral nutrition should commence at birth (i.e. for practical reasons, within 2 h). (1) There is no imaginable benefit to the infant from an absence of nutrients for hours, let alone days. The cessation of nutrition should therefore be kept as short as technically feasible. (2) The early administration of parenteral nutrition has been demonstrated to be safe and efficacious [40, 41], and safety concerns are therefore no longer a reason for withholding nutrition. Also, as had been observed in a number of earlier studies, early administration of amino acids enables administration of greater

amounts of energy than was possible without amino acids [39].

At what dose should parenteral nutrition start? We know that the infant requires 3.5 g amino acids/kg/day for normal growth (table 1). However, as in the first few days after birth, energy intakes required for normal growth of lean body mass can typically not be achieved and amino acid intakes <3.5 g/kg/day are temporarily acceptable (but not mandatory). The initial dose of amino acids should be no less than 2.0 g/kg/day. A dose of 3.0 g/kg/day appears to be the most widely used starting dose. Within 2–4 days, the dose should be increased to 3.5 g/kg/day.

Energy intakes need to be 90–100 kcal/kg/day for optimal growth, but such an intake can usually not be achieved for several days after birth. Until it can be achieved, it is recommended to provide the maximum amount of energy that can be given without incurring hyperglycemia (fig. 2). One strategy is to start glucose infusion at birth at a rate of about 4 mg/kg/min and to in-

life simplified parenteral nutrient solutions (so-called starter solutions) that provide – besides amino acids and glucose – only calcium, magnesium, and phosphorus are acceptable.

Promptly initiated delivery of adequate amounts of nutrients via the parenteral route relieves the pressure to provide nutrients via the immature gastrointestinal tract. As the gut matures and feedings are advanced, parenteral nutrient intakes can be reduced gradually, but parenteral nutrition should always be continued until enteral feedings provide at least 90% of the required intakes.

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Table 4. Effects of early feeding of human milk

May reduce the incidence of NEC [46]
Trophic effects of human milk on the immature gastrointestinal tract [47, 48]
• reduces intestinal permeability [49]
• stimulates cell proliferation [50]
• enhances gastric emptying [51]
• facilitates earlier achievement of full feedings [52]

crease the rate daily or more frequently as long as euglycemia is maintained. In this context, euglycemia is most often defined as <120 mg/dl (6.7 mmol/l), but sometimes concentrations as high as 150 mg/dl (8.3 mmol/l) are tolerated during this period. The other source of energy, lipids, should be started on day 1 or at the latest on day 2 at a dose of 1.0 g/kg/day. The maximum dose of lipids ranges from 2.0 to 3.0 g/kg/day from soy-oil-based emulsions. It should be remembered that, besides being a source of energy, lipid emulsions deliver modest amounts of the essential long-chain polyunsaturated fatty acids, e.g. docosahexaenoic acid and arachidonic acid. As a concession to the practicalities of providing parenteral nutrition right from the time of birth, during the first 24–36 h of

Enteral Nutrition

Early Enteral (Trophic) Feeding

At birth, the gastrointestinal tract of the premature infant is immature both morphologically and functionally and is highly permeable. It often lacks a microbiota entirely or harbors an abnormal microbiota. Its motility is immature, which has its clinical correlate in gastric residuals of varying size that are not infrequently bile stained. The most important manifestation of intestinal immaturity is susceptibility to necrotizing enterocolitis (NEC).

The immature gastrointestinal tract is capable of undergoing maturation in response to stimulation by feeding. The sole objective of early feeding is thus to stimulate the immature intestinal tract to undergo maturation. Early feedings are therefore often referred to as trophic feedings. Until maturation occurs, the immature gut is not able to digest and absorb meaningful amounts of nutrients, hence, the universal need for parenteral nutrition.

In the past when it was believed that feedings cause NEC, the introduction of feedings was delayed, often for prolonged periods, and subsequently feedings were advanced slowly. Feedings were also often interrupted and withheld for prolonged periods in response to large gastric residuals, which were interpreted to indicate incipient NEC. Today, any role of the timing of feedings and their rate of advancement in the causation of NEC has been disproved [42]. The emphasis has shifted to initiating the process of gut maturation without delay and to avoid disrupting the process. Gastric residuals serve as markers of gastrointestinal immaturity and, as such, are recorded and followed. The benefits of achieving early gut maturation include, besides a need for less parenteral nutrition, a reduced risk of late-onset sepsis [43, 44].

Good practice today consists in starting trophic feedings on day 1 or 2 of life in small amounts. As maturation of the gut is the purpose of trophic feedings, there is no conceivable advantage from delaying the initiation of feedings. There also is no evidence that physiologic instability, such as low systemic blood pressure, necessitates a delay in introducing trophic feedings. With consistent stimulation, maturation usually occurs in less than 2 weeks [13]. It is recommended that each neonatal unit develops and uses guidelines for the initiation and standardized advancement of early feedings [45], as such guidelines help to avoid unnecessary withholding of feedings and thereby shorten the time to full feeds and may even reduce the incidence of NEC [46].

Some of the trophic effects of human milk on the gastrointestinal tract are listed in table 4. Human milk keeps the risk of NEC to a minimum and is therefore the preferred feeding for premature infants. Because it usually takes some days for maternal milk to become available, donor milk is often used as initial trophic feeding in order to start gut stimulation in a timely manner, i.e. on the first day of life. As maternal milk becomes available, it then replaces donor milk. Gastric residuals need to be monitored and their size taken into account in decisions about advancing feedings. It is probably prudent to keep the volume of trophic feedings low (<10 ml/kg/day) until gastric residuals are substantially diminished. But there is no consensus whether feedings should be kept at trophic levels for a fixed number of days or whether cautious ad-

Special formulas designed for premature infants provide most nutrients in adequate amounts.

vancement should begin sooner. Vigilance for signs of NEC must be maintained at all times. However, large gastric residuals without other signs of NEC should not trigger withholding of feedings. The practice of withholding feedings in response to large residuals is not of proven value in reducing the risk of NEC, but it unnecessarily prolongs the time needed to reach full feedings.

At some point, fortification of human milk must be initiated. An enteral feeding volume of 100 ml/kg/day seems to be the most widely used point at which addition of human milk fortifier (HMF) is initiated. However, earlier introduction of HMF is also practiced; however, evidence favoring one practice over another is lacking.

Sometimes when HMF is started, gastric residuals increase in size, or reappear if they had ceased earlier. Gastric residuals are not a reason for discontinuing HMF.

Fig. 3. Effects of HMF.

Late Enteral Nutrition

When full feedings have been reached and parenteral nutrition has been phased out, enteral feedings assume full responsibility for providing all nutrients in amounts needed to support normal growth. Special formulas designed for premature infants provide most nutrients in adequate amounts, the only exception being protein which is provided in amounts that are limiting for the growth of small infants. Human milk remains the preferred feeding, despite its low nutrient content, because it affords the infant relative protection against sepsis [53–55] and NEC [54, 56, 57]. Human milk provides many nutrients in amounts far below those required by premature infants, hence, the need to fortify human milk, i.e. to increase its concentrations of nutrients, including protein, minerals, and vitamins. If infants are fed unfortified human milk they show slow growth [58], and slow growth carries the risk of impaired neurocognitive development (fig. 3). In addition, premature infants can develop specific deficiency diseases, such as calcium-phosphorus deficiency (osteopenia) or zinc deficiency. Commercially available HMFs have been developed over the years and continue to evolve. They provide protein, energy, and the necessary minerals and vitamins. The amounts of minerals and vitamins help to meet or exceed, together with the nutrients intrinsically present in human milk, the nutrient needs of premature infants. Fortifiers provide energy in the form of carbohydrates and lipids, which enables to meet energy needs while keeping feeding volumes low.

Fortifiers provide protein from bovine milk in amounts of 1.0–1.1 g/100 ml of human milk. Unfortunately, these amounts of protein are insufficient to meet the needs of premature infants except when the protein content of human milk is high, i.e. during the first 1–2 weeks of lactation. As the protein content of human milk decreases with the duration of lactation, protein intake from fortified human milk becomes progressively more inadequate. Low protein intake from human milk fortified in a routine fashion is the main cause of postnatal growth restriction. Achieving adequate protein fortification presents somewhat of a challenge as the protein content of expressed human milk continues to decrease for weeks after birth and shows considerable random variation. The protein content of banked donor milk is less variable but lower (0.8–0.9 g/dl) than that of expressed maternal milk. Adequate protein intakes can be achieved by measuring the protein content of human milk and adding protein in amounts designed to achieve adequate intakes. This ‘targeted fortification’ has been shown to be effective in achieving adequate intakes and avoiding unnecessarily high intakes of protein [59]. But targeted fortification is somewhat labor intensive and requires specialized equipment, which is presumably the reason for its limited use. Another method for achieving adequate protein intake is ‘adjustable fortification’ [60, 61]. In this method, extra protein is added to human milk (in addition to standard fortification) in a stepwise fashion with monitoring of blood urea nitrogen in order to avoid excessively high protein intakes. Adjustable fortification has been shown to be effective in achieving higher protein intakes and improved growth [60, 61].

Recognizing the need for additional protein fortification (i.e. beyond standard fortification), protein is some-

There is, however, no question that the amount of protein provided by commercial fortifiers is inadequate and that additional protein must be provided in some form.

times also being added blindly, that is, without the benefit of knowing the protein content of the human milk being fortified. Sometimes a higher protein intake is achieved by adding more than the standard amount of HMF. The amount of protein that is being added ranges from 0.5 to 1.0 g/100 ml of milk. This practice aims to

raise the protein content of milk with the lowest possible protein content to an adequate level and accepts that the protein content of milk with higher protein content is fortified to a level that provides somewhat more protein than is necessary. Although this is a reasonable practice that seems to be working, there are no published reports providing evidence of its efficacy or its safety. There is no consensus regarding which of these methods is preferred. There is, however, no question that the amount of protein provided by commercial fortifiers is inadequate and that additional protein must be provided in some form. A fortifier based on human milk protein has recently been shown to provide, if used in conjunction with banked donor milk, better protection against NEC than a fortifier based on bovine milk protein used in conjunction with formula [62].

Managing Premature Infants in a Resource-Poor Environment

Parenteral nutrition is technically demanding and expensive and, in a resource-poor environment, it is often fraught with high rates of line infection. Parenteral nutrition is therefore not always utilized in resource-poor situations. With enteral feeding being the sole source of nutrients, it is especially important that gut maturation be achieved as quickly as possible. The proven agent to bring about gut maturation efficiently and in a safe fashion is human milk. Special efforts are therefore necessary to ensure that all mothers of premature infants express milk. Mother’s milk must be used as trophic feeding as soon as available. Given the absence of parenteral nutrition, infants are likely to incur substantive nutrient deficits before full feedings are reached. Nutrient fortification of mother’s milk should in this situation be initiated well before full feeds are reached. If commercially prepared HMFs are not available, skim milk powder is an acceptable substitute. It may be added in the amount of 2.5 g/100 ml to mother’s milk.

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