New Approaches to Optimizing Early Diets

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Abstract

Most extremely low birthweight (ELBW; <1,000 g) infants will survive if cared for at a tertiary neonatal intensive care unit, and should be given optimal nutrition for brain development. Human milk confers nutritional and non-nutritional advantages over infant formula, and is started during the first hours of life. In Sweden, most ELBW infants are fed individually with mother's own milk (preferred) and banked milk, with supplementary parenteral nutrition. There is an enormous variation particularly in the fat and protein content of milk between mothers, during the day and the course of lactation. Infrared macronutrient analyses on 24-hour collections of mother's milk are performed once a week allowing for optimal protein and energy intakes. All banked milk is analyzed, and the most protein-rich milk is given to a newborn ELBW infant. After 2 weeks, the milk may be fortified if the protein or energy intakes need to be further increased, and fortification is continued throughout the tube-feeding period. Parenteral nutrition is continued until the enteral intake constitutes 75–80% of the total volume intake. Protein markers, e.g. serum urea and transthyretin, are assessed, and growth is monitored by measurements of weight, crown–heel length and head circumference.

Introduction

The increasing number of extremely preterm infants who survive with gestational ages of 23 weeks and birthweights of 400 g is a new challenge to neonatology and neonatal nutrition. The vast majority of extremely low birthweight (ELBW) infants will survive if they are born and taken care of at a hospital with a tertiary neonatal intensive care unit. Nutrition is essential over several weeks consisting of periods of intermittent ventilator
treatment, episodes of septicemia and persistent ductus arteriosus, which consistently lead to varying degrees of malnutrition upon discharge from hospital.

ELBW infants, particularly those born at 23–26 weeks of gestation, have an increased risk of school and cognitive problems and, to a limited extent, motor and vision problems [1]. There is also an epidemiologic association between low birthweight and cardiovascular disease later in life, particularly with rapid catch-up growth [2]. However, the general view is that preterm infants should be given optimal nutrition for brain growth and development [3]. Nutrition during the vulnerable preterm period, preferably based on human milk, should lead to adequate growth, at least corresponding to the intrauterine growth rate.

Feeding Systems

The best available method for nutrition of these infants during the preterm period is a combination of parenteral and enteral nutrition. Today, in Sweden most immature infants are fed according to the following scheme: (1) mother's own milk (preferred); (2) banked milk (if mother's own milk is not available); (3) preterm infant formula (only if human milk is not available), and (4) supplementary parenteral nutrition (starting at birth or immediately thereafter).

Parenteral Nutrition

There is a trend to a more ‘aggressive’ nutrition of preterm infants, i.e. initiating parenteral nutrition early after birth including starting administration of not only intravenous glucose but also amino acids and lipids immediately after birth or during the first day of life [4]. Enteral feeding with human milk is also started during the first few hours of life [5]. Parenteral nutrition is continued until the enteral intake constitutes 75–80% of the total volume intake. It has been shown that early intravenous amino acids are well tolerated and can be utilized as a substrate for protein synthesis during the first day of life [6]. The distribution of amino acids contributes to a more stable glucose homeostasis [4], and amino acids also act as precursors for the synthesis of various hormones, enzymes and neurotransmitters. Moreover, early intravenous lipids can usually be started during the first day of life as a concentrated substrate for energy. Administration of intravenous lipids also diminishes the risk of a deficiency of essential fatty acids. Total parenteral nutrition should be avoided in the immature infant and is given only in situations with intestinal malformations or severe necrotizing enterocolitis (NEC).

Parenteral nutrition can be administered as a solution containing glucose, amino acids, lipids, minerals, vitamins and trace elements. As an alternative,
the lipid solution including vitamins can be given separately. Most of the available components for parenteral solutions are not completely adequate for the special needs of ELBW infants, and there is a need for development in this area.

The ready-to-use solutions should, if not commercially available, be prepared under sterile conditions at the pharmacy.

**Enteral Nutrition**

Previously, there was a fear of causing NEC if enteral feeding was initiated early. However, it has been shown that enteral nutrition, preferably with breast milk, can be started a few hours after birth and the volumes gradually increased [5] with a low risk of developing NEC [7, 8]. After a few weeks the supplementary parenteral nutrition can usually be discontinued and the infant completely enterally fed. During the first days of life, banked milk (from another woman, preferably from another mother of a preterm infant) is given until the mother's own milk is available.

Tube feeding is mandatory until the infant can be fed by the nipple or bottle, usually at an age corresponding to 35–36 weeks of gestation. Whether the ELBW infant should be tube fed continuously or intermittently every 2nd or 3rd h is still a matter of controversy [8]. Also, there is no agreement on whether the tube should be placed by the orogastric or nasogastric route. In Sweden, most mothers manage to express their milk during the preterm period and breastfeed their infants at discharge from the hospital.

**Superiority of Human Milk**

During the last years, there is a growing body of evidence that human milk is superior to infant formula for all newborn infants including ELBW infants [9]. Human milk confers nutritional and non-nutritional advantages, and there is now a worldwide trend to using more human milk than infant formula in the feeding of preterm infants [10]. Outcome data support the improved neurological development when human milk is used [11], even if human milk intake has been limited to only a few weeks [12]. The risk of infection, retinopathy and NEC also seems to be lower if the infant is fed human milk as opposed to formula [7, 13]. Human milk is also better tolerated by the immature intestine than infant formula [3, 9].

If the mother's own milk is not available, banked human milk should be used [14]. Infant formula is used only in situations in which there is a complete lack of breast milk and, if used, only preterm formulas, not term formulas, should be given. To reduce the risk of transmission of viral and bacterial infections, banked milk is pasteurized before use (usually Holder pasteurization, 62.5°C for 30 min).
Preterm Milk

In the 1970s it was shown that the milk of mothers of preterm infants had higher concentrations of protein and fat, at least for the first weeks of lactation, but this difference may persist in some mothers for several months [15, 16].

Human Milk Macronutrient Variation

Unfortunately the misconception that human milk has a predictable and uniform composition is still widespread in many neonatal units throughout the world. However, several studies have underlined the enormous variation in the nutrient composition of human milk, particularly fat and also protein. There are variations between mothers, during the course of lactation, and during individual meals (fig. 1), and also as a consequence of the varying pumping techniques [17–20]. This has to be taken into account when using breast milk in the nutrition of ELBW infants.

Human Milk Analyses

To find a tool to determine the macronutrient content (protein, fat, carbohydrates and energy) of human milk from individual mothers, after evaluation of available chemical methods [21], we found that the most reliable method for analyzing the macronutrient content of milk is the infrared (IR) technique [18]. During the last 10–15 years, a system has been established in Sweden where most neonatal units use a centrally situated IR instrument for routine analyses [19, 22].

However, there is now a new and less expensive IR instrument available. It was originally developed for cow’s milk, but modified and calibrated for human milk against reference methods for fat, protein, lactose and total solids (Rose-Gottlieb, Kjeldahl, Luff-Schorl and drying-oven, respectively) with an accuracy of $r \geq 0.98$ (Miris AB, Uppsala, Sweden) [23]. This equipment can be used bedside in the neonatal unit allowing analyses to be run on small amounts of milk (1 ml in duplicate or triplicate) at a low cost with the results available within 1 min for immediate use.

Analysis of the protein content in milk based on a calibrated Kjeldahl method probably slightly exaggerates the amounts of nutritionally available protein, but the method yields a reasonable appreciation of the need for fortification.

Perhaps equally important is how to get a representative human milk sample for analysis [24]. Fresh milk is usually not a problem, but when using the IR technique frozen-thawed milk can give unreliable results due
to the formation of complexes and may need homogenization before being analyzed.

The enormous meal-to-meal variation, mainly in fat and protein concentrations (fig. 1), makes it useless to analyze spot samples (milk from a single collection) [20, 22]. Instead, milk should be collected preferentially over 24 h, well mixed, and a representative sample taken for analysis [19]. Such 24-hour collections analyzed once or twice a week give sufficient information on the macronutrient content of the milk for reliable estimations of the actual macronutrient intakes [22].
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Techniques to reduce the variation in nutrient intake of ELBW infants are the following.

- Mother’s own milk is given in chronological order, i.e. in the order it was pumped. As the protein content will slowly decrease during the course of lactation, the most immature infant will receive the earliest milk with a higher protein level.
- All milk is mixed in 24-hour collections before being given or frozen for later use. This will substantially reduce the day-to-day and meal-to-meal variation in nutrient content, which is likely to increase gut tolerance (fig. 1).

**Fortification of Human Milk**

The enteral nutrition of choice should always be breast milk [10]. However, the content of certain nutrients in the milk, such as protein, is not always sufficient to meet the extreme needs of ELBW infants [25, 26]. Therefore, there is usually a need to fortify the milk during the tube-feeding period.

There are various fortifiers available on the market, all of them (with one exception) of bovine origin. As there are no comparative studies, it is still unclear whether the source of energy should be carbohydrates or fat.

Various methods have been used to fortify milk for feeding of preterm infants.

*Standardized Fortification*

Standardized (blind) fortification, often started at 1 week of age, is widely used in the belief that all human milk has a uniform composition. The same amount of fortifier is added to the milk regardless of whether it is own or banked mature milk with quite different compositions. This method may cause under- or overnutrition and should be avoided [3, 19, 27, 28].

*Semiquantitative Fortification*

This seems to be a slightly better method, as the milk to be enriched is taken into account. For example, the preterm infant’s mother’s milk can be expected to have a higher protein content than the milk of a mother of a term infant after 3 months of lactation.

*Individualized Fortification*

The individualized feeding regimen is used in Lund, Sweden. This feeding system focuses firstly on protein intake, secondly on energy intake, and is used, at least in part, in most neonatal units throughout Sweden [22].

By analyzing the macronutrient content of the milk, the intake of the individual infant can be adjusted accordingly [19, 21]. Aiming initially at a daily protein intake of 3.5–4 g/kg in the ELBW infant or, later during the preterm period 3 g/kg, the milk can be individually fortified in relation to the...
gestational age of the infant. Short-term studies of the individualized feeding system indicate improved growth corresponding to the intrauterine growth rate [19, 28, 29].

**Computerized Calculations**

A computerized calculation system for nutrient intakes will increase the safety of the calculations and diminish the time required to evaluate the need for appropriate fortification. Such a system is used at our unit and is also available as part of various clinical information systems used in intensive care units.

**Individualized Fortification (table 1)**

Milk is fortified as deemed necessary (after calculating the protein intake starting at 10–14 days of age). There is no reason to start analyzing the nutrient content earlier due to the rapid changes in protein concentrations and the enhanced protein intake by the increased enteral volumes during the first weeks of life.

After fortifying the milk to achieve the desired protein intake, extra energy may be added if needed (usually using a liquid lipid preparation).

Even in situations of intestinal intolerance, try to avoid discarding the fortification completely. Instead try to diminish the amount of fortifier added to the milk.

Protein markers such as serum urea and transthyretin may be used to evaluate the metabolic capacity of the protein utilized [28, 30].

**Growth**

Growth corresponding to the intrauterine growth rate of a fetus of corresponding gestational age is the current goal in the nutrition of preterm infants [25, 26]. Not because growth itself is important but rather because poor growth is a marker of inadequate nutrition, which is associated with less favorable cognitive development [27].

**Nutritional Status**

To assess the nutritional status of the infant, the variables given in table 2, including protein markers, should be monitored continuously during the preterm period.
Conclusion

A new approach to optimizing the early diet of preterm infants is presented. The nutrition of the growing number of surviving very preterm infants is extremely important in order to diminish neurological problems, especially in infants with less than 30 weeks of gestation. Human milk is more advantageous than infant formula for the feeding of these infants. However, human milk does not have a uniform composition. Due to the huge variation in the

Table 1. Individualized nutrition of preterm infants: the Swedish model as performed in Lund, Sweden

- All preterm infants are fed human milk (mother's own milk is preferred), at least until 34 weeks of gestation
- The mother is encouraged to start pumping her milk (as soon as possible or at least within 24 h after birth) using an electric pump
- Banked milk (preferably preterm milk) is given during the first days of life, and later (rarely) if the mother's own milk is not available
- All banked milk is analyzed for macronutrient content (fat, protein, lactose and energy), and the most protein-rich milk is chosen when a new preterm infant is born
- Enteral feeding with banked milk is started within 2–4 h of life
- Parenteral nutrition with glucose and amino acids is started at birth, and lipids are initiated within the first 24 h of life. Supplementary parenteral nutrition is continued until enteral feeding constitutes 75–80% of the total volume intake
- The intake of human milk is gradually increased as tolerated (with corresponding decreased parenteral nutrition) until full amounts
- All mother's own milk (<32 weeks gestation) is analyzed for macronutrient content (24-hour collections, never spot samples) once (twice) a week, starting at 10–14 days of life
- Mother's own milk is used in chronological order to diminish the day-to-day variation in protein and particularly fat intake
- All mother’s milk is mixed in 24-hour collections before being frozen or administered to reduce the meal-to-meal variation in protein and fat content
- Using a specific calculator, macronutrient intakes and the need for fortification are regularly calculated, at least after each milk analysis
- When the milk volumes can no longer be increased and there is a need of higher protein or energy intakes, fortification with a commercial fortifier is started, aiming at daily intakes of 3.5–4 g protein (the higher protein intake in the more immature infant) and 110–120 kcal/kg (or higher if there are lung problems)
- Growth is monitored (weight every 2nd day, length and head circumference weekly), and a computerized growth curve is used
- Protein status is assessed by analyses of serum urea and transthyretin once a week
- Fortification of the milk is continued throughout the tube-feeding period, usually until 35–36 weeks of gestation when breastfeeding is initiated
- Infant formula (preterm formula) is used when there is a lack of human milk, but never <32 weeks of gestation
content of various nutrients, particularly protein and fat, there is a need to analyze the macronutrient content of the individual mother’s milk, allowing individualized fortification and nutrition including assessment of a protein marker. So far, macronutrients have been analyzed, but in the future certain minerals may also be evaluated and supplied individually.

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**References**

Discussion

Dr. Lafeber: It is very important that you have shown in this meeting that it is possible to use breast milk even for extremely small preterm infants. Nevertheless I would like to put your setting in Sweden in perspective to the rest of the world. I am
from Amsterdam, the Netherlands, and we also have an affluent society that is prepared to invest a lot of money in extremely preterm infants of 24–25 weeks gestational age. However, if you are going to promote the use of breast milk I would put more emphasis on somewhat older preterm infants. The reason for this remark is the fact that we performed several studies measuring protein turnover using stable isotope $^{13}$C-glycine in very low birthweight preterm infants with a birthweight of <1,000 g. We found that even using the maximum of fortification in breast milk, it was difficult to achieve a protein turnover of >2 g protein/kg per day. We published that about 3 years ago and using the special preterm formula we could indeed reach levels above that limit [1]. So especially in preterm infants with a gestational age of <27–28 weeks, it is important that you must be aware that we have to fortify human milk with extra protein. Another issue when giving breast milk to preterm infants is the fact that you also have to keep in mind the supplementation of calcium, phosphate, and vitamin D.

I told you yesterday after the presentation of Dr. Kalhan that we performed a study comparing the feeding of preterm infants after discharge from the hospital with a special post-discharge formula or breast milk, and what we found at 6 months corrected age was that the most important issue in very preterm infants is to add extra protein and calories until the moment of term, and from then onwards only extra protein and a normal amount of calories were given, like that in a normal standard formula [2]. We did not fortify human milk after discharge from hospital and we observed a similar growth rate compared to infants fed post-discharge formula. The only difference that we found at 6 months was that the mineral content measured by DEXA scan was lower in breastfed infants, so we might also not be sufficient in supplying enough calcium and phosphate between term age and 6 months corrected age in preterm infants fed breast milk. On the other hand the body composition at 6 months of the breastfed preterm infants showed less fat at 6 months and there was less insulin insensitivity, so I really do believe in your concept that it is very important to give breast milk to preterm infants but be aware that it is not always possible to establish the Swedish system in other countries because it is a phenomenal cost to have pasteurization and completely individualized care. The level of hygiene you need in the neonatal unit is tremendous, and to date we have not been successful in establishing that situation in the Netherlands [3].

Dr. Polberger: First a comment about the fortifiers. Today we use multicomponent fortifiers but with the individual system we rarely need full fortification. We need a separate system where we can supply extra minerals, which we actually do. So from my point of view I would in the future prefer having different fortifiers consisting of protein, some sort of energy source, and a mineral preparation which would allow us to deliver a more individualized fortification system to these infants.

Dr. De Curtis: I agree that human milk is the best food for premature infants; however, giving fresh breast milk to extremely low birthweight infants could lead to some neonatal infectious problems, such as cytomegalovirus infection. In your unit do you give the mothers' own fresh milk to all extremely low birthweight infants even if you ignore the mother's immunological status? What is the percentage of low birthweight infants breastfed at discharge in your unit? If these babies are extremely breast-fed, do you give any fortification at home to increase protein and mineral intake? Macronutrient analysis of human milk based on the infrared technique is expensive and time-consuming but it could be useful for scientific purposes. However, in clinical practice, as seen many years ago by Rigo et al. [4], the simple evaluation of growth or, if necessary, the evaluation of serum urea levels could be sufficient to estimate the adequacy of protein intake.

Dr. Polberger: For macronutrient analyses, we now have a new IR machine available which costs less than USD 20,000, and that is good enough to buy it for separate
neonatal units in Sweden. To reduce the risk of cytomegalovirus transmission from the mother's own milk, we give the milk in chronological order, and usually we freeze the milk for a few days before giving it to the baby during the preterm period. I am aware that Hamprecht et al. [5] have suggested that all milk, including mother's own milk, should be pasteurized before giving it to a baby to eradicate this risk, but so far this has not been accepted in Sweden. The final question was about breastfeeding after discharge. In our unit about 75–80% of the mothers are breastfeeding when they go home. Fortification at home is a difficult question. We usually do not fortify the milk after discharge, and at the moment we don’t know the optimal method of feeding the baby after discharge. It is much easier during the preterm period when the baby is tube-fed and the milk is easily available for analyses and fortification, but it is much harder to do that when the baby is on full breastfeeding at home. We discussed this with Dr. Lafeber the other day and there are some studies going on, among them a multicenter study in Denmark, which hopefully will give us some answers. They are actually fortifying the milk when breastfeeding by giving the baby some extra fortified milk.

Dr. Bohles: This is possibly a very provocative question. In utero the child is basically alimented intravenously, even the liver is bypassed. So why are we so reluctant in parenteral nutrition with respect to the very immature child? We are relying much more on immature digestion processes and basically we don’t really know what is finally reaching the metabolism of the child. Why don’t we further develop the intravenous route?

Dr. Polberger: That is an interesting question and there has been a lot of discussion about this. The trend at the moment is to try to reduce parenteral nutrition and start enteral nutrition as soon as possible. There are a lot of negative side effects using parenteral nutrition, for instance infections and thrombosis in the vessels being used. The risk of necrotizing enterocolitis (NEC) can actually be reduced by using human milk. So from the theoretical point of view it would be interesting to continue placental function with cord circulation but I don’t think that is realistic. Most neonatal units today are using parenteral nutrition as a supplement and an important part of the nutrition, starting at birth or very early, but then trying to proceed to enteral nutrition and withhold parenteral nutrition. Infection is a serious problem in these infants.

Anonymous: We know that once you feed very low birthweight babies very early with high calories they develop NEC. In your study how many babies with NEC did you encounter?

Dr. Polberger: We see only 1 or 2 NEC cases a year. I don’t have the exact figures but we actually see more NEC in full-term sick babies than in preterm infants. We attribute the low figures to the use of human milk and enteral feeding.

Dr. Bhattacharya: You talked about bronchopulmonary dysplasia (BPD) and high caloric intake. Do all the chronic lung disease (CLD) babies have the same benefit if they are given high calories? The second question is about protein markers, urea and transthyretin. Do you do that mainly after parenteral nutrition or before or during the course of enteral nutrition, and what about infrared counting of macronutrients?

Dr. Polberger: In babies with BPD and CLD we evaluate their growth, and as some of these infants need extra energy, we usually use a commercial fortifier to supply the amount of protein needed and, if necessary, add extra fat in a liquid preparation.

Dr. Bhattacharya: Does this improve the outcome of BPD and CLD?

Dr. Polberger: It happens that we discharge babies who are still on oxygen, usually using an oxygen concentrator for a few weeks, but that only happens a few times a year. This problem has diminished over the years with more efficient ventilation modes and is not really a big issue in our unit, fortunately. We use protein markers on a routine basis and try to analyze them once a week during the preterm period. We
start with human milk analysis mainly using the protein content of the milk and then we supply the extra fortifier needed. If in that situation we have low serum urea or transthyretin we add more protein.

**Dr. Vaidya:** So far we have been following the ESPGHAN committee recommendations for feeding our preterm infants, and we also use the same guidelines for the SGA infants. Before the metabolic syndrome, these guidelines were highly recommended in these babies. In light of the recent information, do you think these recommendations will undergo a change? With the aggressive nutrition of low birthweight babies, how is this going to affect the metabolic syndrome in the days to come? When these low birthweight and SGA infants go home, should we routinely start screening them for metabolic syndrome and at what age we should start?

**Dr. Polberger:** The metabolic syndrome may of course be a problem, but these infants are vulnerable from the cognitive point of view. During the preterm period, Lucas [6] has suggested that we have to think mainly about neurodevelopment. The protein intake cannot be decreased during these vulnerable weeks for that reason. But I am sure we have not seen the end of that discussion, and we really don't know the implications of the metabolic syndrome discussion for these tiny infants. So at the moment we try to feed them efficiently based on human milk. And your final question, we are following these infants for 5–6 years. We have no specific screening program for the metabolic syndrome, but that is an interesting question.

**Dr. Haschke:** First a comment on the device which measures protein, fat, and carbohydrates in human milk. It is definitely available in India and used by dairy companies to standardize cow's milk quality. My question is, in Sweden can you achieve intrauterine growth rates in low birthweight infants who are fed fortified breast milk or specialized formulas?

**Dr. Polberger:** As you know, all these infants are actually being discharged with some degree of malnutrition. At term they weigh almost 1 kg less than expected as compared to the in utero situation. So with our current methods we don't manage very well. We always use mother's own milk and we fortify it accordingly, and that is the best we can do right now. But there is a period, especially if you have a very sick preterm infant, when no catch-up growth occurs until sometimes 3–4 weeks of age. At the moment we have to accept that the baby is not always reaching the intrauterine growth rate. That can only be seen in the most healthy preterm infants.

**Dr. Haschke:** But to clarify this, in no case do you reach a so-called catch-up growth with your measures?

**Dr. Polberger:** We do it now and then. Usually we see catch-up growth later on. There has actually been a Swedish study where you can see catch-up growth still occurring at 11 years of age in previously preterm infants.

**References**