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Nutritional dilemmas in extremely low birth weight infants and their effects on childhood, adolescence and adulthood

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Abstract

Objective: To review the recent medical literature on nutrition of extremely low birth weight infants, focusing on nutritional dilemmas and their effects on childhood, adolescence and adulthood.

Sources of data: An extensive review of the related literature was performed using MEDLINE, the Cochrane Database of Systematic Reviews and the Best Evidence database.

Summary of the findings: There is a growing body of evidence that early nutritional practices may affect short-term growth and development outcome. In addition, these practices may play a role in determining adult health and disease. There is still much to be learned about safe and efficacious nutrient administration in preterm infants; about techniques to assess the effect of different nutritional strategies; and about the long-term effects of these regimens on development outcome, growth and disease.

Conclusion: Despite recent progress in neonatal nutrition, there is a lack of basic and clinical research to better define the nutritional requirements of preterm infants and the best way to meet these requirements, avoiding long-term undesirable consequences.

J Pediatr (Rio J). 2005;81(1 Suppl):S33-S42: Nutrition, human milk, prematurity, parenteral nutrition, enteral nutrition, nutritional programming.

Introduction

In the late 19th century and early 20th century, obstetricians of the Maternity of Paris, led by E. S. Tarnier and later on by Pierre Budin, were able to remarkably improve the survival of preterm infants. These pioneers, now regarded as the forefathers of modern neonatology, were concerned with temperature control and prevention of infections, and also put in a great deal of effort to guarantee that preterm newborns had an appropriate nutrition.[1]

More than one century later, the knowledge about the nutritional peculiarities of preterm infants has considerably developed. However, much controversy still exists over the knowledge and practices regarding the improvement of nutrition, growth and development of these infants.[2]

Ideally, the diet of preterm infants should meet their specific nutritional requirements, ensuring a growth similar to that occurring *in utero* in the same time length of time.[3-5]

Nonetheless, this goal is seldom achieved. There are factors that are inherent to infants and those which derive from neonatologists' concerns that are not always well-founded, running counter to the appropriate nutrition of newborn infants. Insufficient growth, also of the head circumference,[6-8] delayed neuropsychomotor development,[9] with late effects on the cognitive and abstraction capacity, which possibly persist up to adulthood,[10] are some of the consequences of preterm birth that have long drawn the attention of researchers. The younger the newborn infant, the worse the problems will be.

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Extremely preterm birth results in events such as low blood pressure, hypoxia, acidosis, infection, surgeries and use of drugs (e.g.: corticosteroids) that restrict growth. Additionally, there are the physiological limitations arising from the immaturity of newborn infants. Neonatologists are concerned about the fact that nutrition may cause disease, including necrotizing enterocolitis and potential toxicity to the central nervous system and other organs, resulting from high serum concentrations of amino acids, glucose, fatty acids and/or their metabolites. However, the amount and quality of nutrition are the main reasons for this growth restriction.[6,11]

The rate of intrauterine and extrauterine growth, either slow or rapid, seems to be important to the infant's future life. The largest challenge nowadays is to find the appropriate rate of growth for each infant.

Consequences of insufficient nutrition

The consequences of nutritional deficiencies have been relatively well documented. For a long time it has been known that nutritional deficiency at early stages of development causes permanent disorders in several aspects of the central nervous system development, in cognition, behavior, and somatic growth.[12,13] Bearing in mind that human growth and development represent a continuum that begins at conception, it is not surprising that neonatal nutrition exerts some impact on physiological parameters at later stages of life.

Although no animal model can simulate what actually occurs with a preterm infant, the global analysis of the available information is convincing, suggesting that the central nervous system of preterm infants is susceptible to nutritional insults. Uncertainty remains over the degree and length of malnutrition that are necessary to jeopardize the life of a preterm infant. Based on animal studies, there exists a direct relationship between the length, degree of malnutrition and compromise of development. Thus, infants suffering nutritional deficiency, but who are able to grow are at lower risk than those who do not have somatic growth.[14]

Authors have assessed the possible association between fetal malnutrition and hypertension. Interactions between nutrients and hormones have been investigated, for instance, protein deficiency and the decrease in the gene expression of IGF-I (insulin growth factor I). Another possibility is the excessive transfer of glucocorticoids from the mother to the fetus. The placenta is unable to properly metabolize these corticosteroids, due to the insufficient action of 11-beta-hydroxy-steroid dehydrogenase (11ßHSD). Thus, patients with fetal malnutrition are more susceptible to hypertension.[15]

These concepts have been reinforced by studies that show that maternal diet during gestation and an inadequate perinatal diet may affect organogenesis and, consequently organic functions in adult life. These disorders cause hypertension, cardiovascular diseases and renal disorders in adults.[16]

Nevertheless, these data were not confirmed in an analysis of 55 studies describing the association between low birthweight and hypertension. The review showed serious methodological problems in several studies. The conclusion is that birthweight might have little importance to the development of hypertension in adulthood.[17]

A special case is that of preterm infants who suffered intrauterine growth retardation. These infants have a successful fetal adaptation to intrauterine nutritional deprivation, which is an important limiting factor for growth.[2] To overcome this problem, these infants may need to readjust their metabolism and only then they will be able to tolerate a larger nutritional intake. After this adjustment, their rate of growth will be near normal, as suggested by some animal studies.[17-19]

Consequences of excessive nutrition

If nutritional deficiency can have deleterious effects, excessive nutrition can also be dangerous. If individuals at a crucial stage of development experience a period of nutritional deficiency, they can subsequently increase their rate of growth as soon as their conditions improve. This natural strategy seemingly compensates for the initial problems.

The issue is how beneficial this compensation can be to the infant. Animal studies suggest that, if on the one hand, compensatory growth can bring benefits, on the other hand, it may be associated with costs that will only be evident in adulthood. This balance between beneficial and deleterious effects of rapid growth is poorly understood and largely neglected by ecologists and biologists who investigate evolution.[20]

The available literature shows common agreement regarding the immediate benefits of rapid and compensatory growth for preterm infants. This compensation may minimize or even avoid acute disorders related to immaturity and intrauterine malnutrition.[21-23] However, animal studies have suggested that this rapid growth may also lead to nutritional programming (which will be discussed further ahead). The theory of deleterious effects of excessive growth is certainly less consistent than those effects resulting from growth deficits.

It has been suggested that infants who suffered intrauterine malnutrition hyperactivate the IGF system while trying to compensate for their impaired growth within a short period of time after birth. This system is often quiescent during intrauterine life in infants with nutritional deficiency. It is believed that such low activity is a successful adaptation to adversity, allowing the restricted supply of nutrients to be used for the survival of vital organs, instead of for growth. The hyperactivation of IGF produces metabolic adaptation with long-term effects. This causes increased insulin resistance due to secondary factors which, if associated with genetic susceptibility and/or obesity, may eventually result in non-insulin dependent diabetes.[24,25]

It has been suggested that both intrauterine environment and fetal genome may influence the number and/or function of pancreatic beta cells in early life. These alterations may have long-term implications for the development of postnatal diabetes.[26]

Evidence suggests that beta cells derive from neogenic processes in the pancreatic ductal epithelium. Murine studies show that many fetal phenotypes of beta cells are destroyed in the neonatal period. This is known as a process of apoptosis related to normal development. These cells are restored at a later stage of neogenesis, which results in islets with insulin release characteristic of postnatal life. The length and amplitude of these ontological events change with nutritional sufficiency. This may be mediated by changes in the expression of pancreatic growth factors, especially of the IGF axis. Due to the limited plasticity of beta cells after the perinatal period, a dysfunctional programming of B cell ontogeny may produce a long-term risk factor for glucose intolerance and type 2 diabetes. This critical pancreatic development window probably occurs in the third trimester of gestation, and low birthweight, premature birth and its associated nutritional disorders may change this development.[26]

The supplementation of carbohydrate-rich milk-based formula to newborn rats caused immediate hyperinsulinemia. This effect persisted during the period of dietary intervention. The animals showed an increase in insulin secretion, an increase in the gene expression of pre-proinsulin and a change in the number and size of islets. These changes are programmed and expressed in adulthood, supporting the hyperinsulinemic condition in the post-weaning period and constituting the grounds for obesity in adulthood. Another study revealed that female rats which received a carbohydrate-rich diet in the neonatal period spontaneously transfer this phenotype to their offspring. The use of a low-protein diet (8%) in pregnant and lactating rats, compared to normal diets (20% of protein), caused some changes in the number of pancreatic islets and in the release of insulin to the newborn rats, resulting in glucose intolerance in adulthood.[27] In general, dietary changes in the neonatal period may produce disorders such as chronic hyperinsulinemia and obesity in early adulthood.[28]

Following the same train of thought, it is argued that a rapid neonatal growth, resulting from aggressive parenteral and enteral nutrition, may affect the cardiovascular system later in adulthood. One speculates whether these two possibilities could be put together in one single theory, i.e., the fetal origin of adult degenerative diseases and the early acceleration of growth rate, causing the same diseases. Fetal growth restriction regarding the genetic potential of growth results in accelerated growth after birth that is deleterious to the individual. Even if it occurs for few weeks, it conditions the occurrence of cardiovascular diseases in adults and not only metabolic diseases.[29] The same group of researchers sought to confirm this tendency by assessing vascular reactivity in adolescents. Three groups were evaluated as to their neonatal conditions: 1) those who were small for gestational age and grew rapidly; 2) those who were small for gestational age and grew more slowly; 3) control group (normal growth). The results of this study demonstrated that vascular reactivity in the group with rapid growth is 4% lower than in the group with slow growth. The authors consider that 4%, albeit being apparently too low, is the same reactivity caused by tobacco, and therefore it may have a relevant impact on public health. On the other hand, the group with rapid growth showed a similar vascular reactivity to the control group, thus decreasing the impact on public health.[30]

The theory of deleterious effects of the growth rate has been fiercely criticized. Authors restate the importance of rapid growth in infants with intrauterine malnutrition, as deleterious effects can be minimized in the short run, and reinforce the criticisms by conversely showing that rapid growth reduced the incidence of coronary heart disease in Finnish male patients. Apparently, the most unfavorable growth pattern is that of preterm infants, who initially have a slow growth followed by late accelerated growth, possibly developing obesity and their complications.[22,31,32]

The choice of the amount and quality of nutrition plays a central role in the determination of short and long-term consequences.

Fetal origin of adult degenerative diseases – nutritional programming

The article by Barker et al., published in 1989,[33] was a valuable contribution as it supports the assumption that nutrition in early life may have effects on adult life. The authors introduced the principles of the fetal origin hypothesis of degenerative diseases in adult individuals. By analyzing a cohort of 64-year-old Caucasian adults, Barker et al. concluded that low birthweight is associated with a higher risk for the late development of cardiovascular disease or type 2 diabetes. Their hypothesis posited that changes in the nutrition and endocrine status of the fetuses caused development adjustments that permanently modified their structure, physiology and metabolism. Thus, these individuals were susceptible to cardiovascular, metabolic and endocrine diseases in adult life.[33] These observations were confirmed by other studies in the subsequent 10 years.[25]

Based on these observations, Alan Lucas developed the concept of nutritional programming.[34] The basic idea is that when an early stimulus or aggression occurs at a critical or sensitive stage of development, there is a long-term or permanent structural or functional change. These events occurring at the early stage of fetal development may influence or "program" evolution in three different ways: 1) by direct impairment, for instance, limb loss due to a vascular accident. 2) by induction, deletion or abnormal development of a somatic structure. 3) by a physiological "adjustment" due to a stimulus or aggression in a critical period, with long-term functional consequences. The term "programming" has been used for the latter two processes.[34]

Although "programming" has been well-documented in animals, it can only be predicted in human beings, since the hypothesis can be hardly confirmed. There is some evidence of compromised neuropsychomotor development associated

with early malnutrition. Other examples of possible programming in humans are the excessive early intake of salt associated with hypertension in adults and the association of low anthropometric indices at birth and at one year of life with the occurrence of cardiovascular disease and their risk factors in adult life.[33,34] By considering the possible mechanisms implicated in nutritional programming, some programming events may have immediate effects on structural development, while other may show these effects later on. An example of the immediate effect is the lack of fuel and raw material for the growth process. Nutritional deficiency during brain development may lead to dendritic arborization or growth of glial cells in the brain, with consequent reduction in the total number of brain cells.[34]

However, nutritional programming may not reflect only deficiency. Nutrients can act directly as critical signs or by the action on receptors of susceptible tissues causing functional changes later on. The most relevant issue is to explain how the "memory" of an event can be preserved during life, despite continuous replication and replacement of cells. A proposed mechanism is that adaptive events occur in gene expression and are therefore transferred to daughter cells. Another possibility is that early nutrition may stimulate an adaptive clonal selection. This way, all or part of a cell population of a tissue is permanently affected.[34]

No matter what these mechanisms are, retrospective and prospective epidemiological studies have shown that maternal nutrition, intrauterine environment and fetal growth restriction are associated with late degenerative disease.

Despite all the questions raised, maternal nutrition may have some effect, either quantitatively or qualitatively, on the adult life of the conceptus.[35] Low protein intake and high carbohydrate intake during gestation and lactation have been associated with the late development of obesity, increased insulin resistance, hypercholesterolemia, hyperlipidemia and diabetes in infants.[34]

Studies carried out in the United Kingdom, Sweden, Jamaica, Australia, India and China have been favorable to the hypothesis that disproportionate fetal growth restriction results in high blood pressure and increased risk of death from cardiovascular events.[15] There was an association of fetal growth restriction with diabetes, hyperlipidemia, accumulation of abdominal fat, coagulation factor disorders, combination of non-insulin dependent diabetes, hypertension and hyperlipidemia (X syndrome) and death from cardiovascular disease and chronic obstructive pulmonary disease.[35]

The body composition of preterm infants was associated with the body fat content at the ages 8 to 12 years, and could be "programmed" by early growth and nutrition. The authors speculate whether the lower body fat content may be beneficial to preterm infants. However, lower triceps/subscapular skinfold values may predict higher deposition of abdominal fat, which in its turn is associated with a higher risk for late cardiovascular diseases and diabetes.[36]

The use of the vaccine against typhoid fever revealed that intrauterine growth retardation was associated with inappropriate production of antibodies in adolescence. The authors suggest that early environmental and nutritional problems may have an impact on immunocompetence in the long run and on the risk of infectious diseases in adolescents, especially in developing countries.[37]

Therefore, we may consider that there is a strong possibility that the quality and amount of nutrients received *in utero* have long-term consequences. Perhaps, even more surprisingly, decisions taken in the neonatal period, such as breastfeeding or bottle-feeding, may have a later impact on health, which in its turn has a considerable effect on public health. It is extremely important to gather more information that can clarify the relationship between adult health and fetal and neonatal nutrition.

Some problems regarding the nutrition of preterm infants

As previously mentioned, compared to the abundant supply of nutrients received by the fetus, preterm infants are invariably submitted to some malnutrition during some time after birth. We should bear in mind that the younger the preterm infant, the more severe the situation. The great challenge is to prevent the occurrence of malnutrition and its deleterious effects. Therefore, we must ensure that the supply of nutrients that the fetus had been receiving is not interrupted after birth.

We should recall that growth and development are very vulnerable to nutritional deprivation. It is also important to bear in mind that if the extremely preterm infant were in the uterus, he/she would have a rate of growth that could never be reached outside the uterus. If we take length as an example, while an extremely preterm infant has an intrauterine growth of over 5 cm/month, a full-term newborn grows 2 to 3 cm/month. For the sake of comparison, an adolescent during the peak growth spurt does not usually ever grow 1 cm/month.[38] Theoretical calculations show that preterm infants have nutritional stores for a few days,[39]and the smaller the size of the infant at birth, the smaller the store. Preterm infants born at 24 weeks have only one day of calorie reserves.[40] Preterm infants weighing less than 1,000 g, even if they receive parenteral nutrition on the first day of life, lose 10% of their weight and take about 11 days to regain their birthweight.[41] Overcoming these problems is a great challenge.

Calorie requirements of preterm infants

Indirect calorimetric measurements show that the baseline calorie requirements of these infants range from 60 to 75 kcal/kg/day.[42] The energy expenditure with growth, the greater heat loss and evaporation due to the thin skin and the larger surface/mass ratio add to these values. Situations such as respiratory difficulty, sepsis and some drugs such as caffeine, insulin and dexamethasone also seem to increase the energy expenditure of preterm infants.[43] There is an increase of approximately 25% in the metabolic requirements of ventilated preterm infants.[44] Thus, when treating extremely preterm and ill infants, the requirement

of 110 to 150 kcal/kg/day usually predicted for preterm infants may not be enough. One should try and reach the upper limits of this recommendation, but this seldom occurs. Among the various reasons for this are the necessity for fluid restriction, intolerance to the infusion of glucose solutions and frequent periods of limited lipid intake due to the concerns with respiratory function, hyperbilirubinemia and sepsis. It is very common to delay its implementation and increase its length in order to achieve total enteral nutrition. On top of that, there are other technical problems, such as the necessity for the infusion of non-nutritive fluids together with the drugs.[45]

Glucose is the major source of energy to the fetus and preterm infants early in life. Glycogen deposits are limited in preterm infants, since the fetus does not produce glycogen. An infant weighing 1,000 g at birth has only 2% of his/her weight as fat and less than 0.5% as glycogen, compared to a full-term infant who has 15% of fat and 1.2% of glycogen.[46] A 24-week-old preterm infant has energy for less than one day of life.[40] Thus, preterm infants need a significant and continuous source of glucose for their metabolism.

A full-term newborn needs around 3 to 4 mg/kg/min (or less) of glucose to prevent hypoglycemia. For preterm infants, even immediately after birth, values between 6 and 10 mg/kg/min are recommended.[47] These values are a little bit above those recommended for full-term infants, since the ratio between the brain and body of preterm infants is large and also because of their greater energy requirements. The production of glucose via glycogenolysis and glyconeogenesis begins immediately after birth, even in preterm infants. The levels of production and use are around 6 to 8 mg/kg/min. However, the infusion of glucose greater than these values results in adipose tissue and increases the production of carbon dioxide. It is not known whether this has some clinical importance or what the consequences are in the long run.[2]

In practice, large glucose infusions are limited by the low tolerance of infants on the first days of life, who may develop hyperglycemia, with an incidence between 20 and 85%.[48] The minimum glucose levels tolerated by preterm infants have not been properly established yet, but recent evidence recommends values between 45 and 55 mg/dl.[49] It is not known whether the use of these recommended values brings benefits to infants.[2]

A common practice is to administer glucose around 4 to 6 mg/kg/min (6 to 9 g/kg/day) to preterm infants, which is often well tolerated, and then increase it on the following days up to 10 to 12 mg/kg/min (15 to 18 g/kg/day) provided that hyperglycemia does not occur. Infusions greater than 16 to 18 g/kg/day may increase the CO_2 level in the plasma.

Amino acid and protein requirements of preterm infants

The largest uptake of protein during life occurs before 32 weeks of gestation.[50] Newborns with less than 1,000 g who are fed only glucose lose around 1.2 g/kg/day of endogenous proteins. The supply of amino acids, even with a low energy intake, stores endogenous protein by increasing protein synthesis, thus reducing the difference between proteolysis and protein synthesis.[51] In general, 1.5 to 2 g/kg/day is necessary to prevent catabolism, but by offering low amounts of amino acids parenterally, such as 1.0 to 1.5 g/kg/day and 30 kcal/kg/day, one changes the protein balance from negative to zero or somewhat positive.[52] These latter values can be regarded as lower limits for the implementation of the parenteral infusion of proteins. Several studies show that this infusion can be initiated on the first day of life. A greater calorie intake reduces proteolysis and a larger intake of both protein and calorie leads to anabolism.[52] With regard to the upper limits of protein intake, if the goal is to achieve the levels of intrauterine protein aggregation, then the estimated requirements are 3.85 g/kg/day for preterm infants weighing between 700 g and 1,000 g.[53] The values are possibly a little bit greater for infants weighing less than 700 g, maybe 4 g/kg/day. Further studies are necessary to confirm and assess the limits of protein intake on the first days of life.

Even if the supply of proteins is appropriate, the limited intake of a single essential or conditionally essential amino acid may limit the use of the protein. Among these amino acids are tyrosine, cysteine, taurine, histidine, glycine, glutamine and arginine. In order to maintain the appropriate protein balance, a sufficient amount of all essential amino acids is necessary. If their amount is not sufficient, essential amino acids will be used for the production of non-essential amino acids and will thus reduce protein synthesis. Therefore, not only the quantity but also the quality of amino acids is important for appropriate growth. Whereas the content of amino acids in human milk is appropriate, their quality in milk-based formulas may be compromised. Especially in parenteral mixtures, the proportion of amino acids may be inadequate. This increases the possibility of protein imbalance on the first days of life, when enteral nutrition is limited and parenteral solutions are introduced as the only source of protein. For instance, conditionally essential amino acids such as glutamine, cystine, cysteine and tyrosine are not included in currently available amino acid mixtures.[2] Glutamine, cystine and cysteine are unstable in solution, but could be offered on a daily basis not as a mixture; however, tyrosine is insoluble. The necessary amount of these amino acids is also unknown, especially for extremely preterm infants. This is another challenge to be overcome.[54,55]

It has been clearly shown in preterm infants that with the same protein intake, a rise in energy intake increases protein aggregation up to a limit of 100 to 120 kcal/kg/day. This is however a curvilinear correlation, i.e., most of the gain from the increase in calorie intake occurs with the supply of 50 to 60 kcal/kg/day. Conversely, by increasing protein intake, there is an increase in protein aggregation in all energy ranges above 50 kcal/kg/day.[50] On the first days of extrauterine life of a preterm infant, when intolerance to energy can occur, the minimum amount of energy to metabolize proteins is still unknown. Theoretical calculations based on relatively stable infants submitted to mechanical

ventilation on the first days of life indicate the necessity of at least 50 kcal/kg/day of energy for an amino acid intake of 2 g/kg/days and 60 kcal/kg/day for an amino acid intake of 3 g/kg/day.[56] These theoretical calculations support the clinical observation that most infants have a positive protein balance, receiving 50 to 60 kcal/kg/day of energy.[56]

In the absence of protein intake, glucose is more of an effective energy substrate than lipids in the prevention of protein breakdown. When amino acids are offered, both glucose and lipids spare the protein catabolism, but the optimal glucose/lipid ratio for preterm infants is still unknown.[56]

Lipid requirements of preterm infants

Fat is essential for brain development, since it is necessary for myelination and growth of neurons, and for retinal development, constituting one of the key substances of the cell membrane. Preterm infant are especially vulnerable to the lack of lipids, since their intrauterine supply does not occur before the third trimester.

The determination of lipid requirements is restricted to the requirements of essential fatty acids, for instance, 1 to 4% of the energy ingested in the form of linoleic acid (18:2w6), and approximately 1% of the total energy ingested as alpha-linoleic acid (18:3w3).[3] There is no detailed information about the requirements of extremely preterm infants.

With regard to the minimum supply of lipids, it is imperative that linoleic and linolenic acid deficiencies be avoided, as they play a crucial role in the brain development of preterm infants. Preterm newborns may develop essential fatty acid deficiency within 72 hours if they do not receive them from an exogenous source.[55] This occurs mainly in the presence of low calorie intake when lipids are oxidized to produce energy. The deficiency of essential fatty acids can be prevented with intravenous doses of lipids between 0.5 to 1.0 g/kg/day. It is recommended that the maximum infusion of lipids be 0.25 g/kg/hour.[3] A 24-hour infusion at this rate is equivalent to the intake of 6 g/kg/day. The usual recommendation is that the supply of lipids be progressively increased up to 3 g/kg/day.[56]

The maximum amount of serum triglycerides tolerated must be less than 150 mg/dl to 200 mg/dl. Plasma clearance of supplied lipids depends on the activity of lipase in the vascular endothelium and in extrahepatic tissues, of hepatic lipase in the hepatic vascular endothelium, and of lecithin-cholesterol acyltransferase. The action of these enzymes is smaller the lower the gestational age, being especially low below 26 weeks. This also depends on the rate of lipid infusion, thus clearance is maximized if infusion is performed within 24 hours. The clearance of equivalent amounts of triglycerides is slower if solutions at 10%, instead of 20%, are used. Solutions at 10% have not been used due to the interference of phospholipids, which are found in relatively larger amounts in solutions at 10%.[57]

The infusion of parenteral lipids in preterm infants is often delayed and limited due to the concern with lipid intolerance, either because of the reduced clearance (increase in the plasma concentration of triglycerides) or reduced use (increase in the plasma concentration of free fatty acids). Both situations may have adverse effects. Among the most common concerns described are difficulty in oxygenation, impaired lung function due to abnormal ventilation/perfusion ratio, increased risk of pulmonary disease, especially bronchopulmonary dysplasia, impaired immune function and increase of free bilirubin in the plasma.[2,58,59] Parenteral lipid emulsions may cause adverse effects, secondary to the inadequate composition of fatty acids.[60]

Currently available lipid solutions contain a large amount of linoleic and linolenic acids. These solutions do not contain arachidonic acid (ARA 20:4w6) and docosahexaenoic acid (DHA 22:6w3). These fatty acids are transferred across the placenta and are found in human milk. The high concentrations of DHA in the retina and of DHA and ARA in the gray matter suggest that these fatty acids play an important role in retinal and cerebral functions. Animal studies have demonstrated that DHA depletion results in reduced visual function and learning disabilities.[61,62]

The docosahexaenoic acid can be synthesized from the alpha linolenic acid; however, it is not known whether its synthesis is enough to ensure neural and retinal development in preterm infants. The synthetic capacity of ARA from the linoleic acid is also limited. It has been suggested that supplementation with DHA reduces ARA in tissues, probably creating a conditional necessity for ARA.[61-63] The long-term effects of the low intake of arachidonic and docosahexaenoic acids on brain development are unknown and should be investigated, since they contribute a lot to brain growth and development at this early stage of development.

The requirements and metabolism of minerals will be discussed in a special article in this issue of *Jornal de Pediatria*.

Challenge of enteral nutrition of preterm infants: human milk

Enteral supply of milk is possible even in young infants.[64] In these very young infants, parenteral nutrition, which is implemented immediately after birth, is gradually replaced by enteral nutrition. Even if the intake of remarkable amounts of milk is not tolerated by the infant, one should try to maintain the minimum supply of milk between 10 to 20 ml/kg/day in order to benefit from its trophic effects provided by minimum intake. Among the advantages of minimal enteral nutrition are the promotion of intestinal motility, better food tolerance, decrease in the incidence of sepsis and induction of lactase activity.[65] These advantages have not been totally confirmed after systematic literature review.[66]

Most preterm infants born at less than 34 weeks of gestation are fed through a nasogastric or orogastric tube due to their difficulty in synchronizing sucking, swallowing, and breathing. The discussion about continuous or bolus infusion does not seem to be relevant.[67] The introduction of

milk in the presence of arterial or venous catheter did not increase the incidence of necrotizing enterocolitis.[64] During milk infusion, non-nutritive sucking was associated with a shorter hospital stay.[68]

When feeding orally preterm infants use two strategies to protect their airways: they alternate between vigorous sucking with breathing pauses and breathing periods while they interrupt the food flow.[69] Infants have difficulty in performing this technique when they are bottle-fed. Breastfeeding allows them to control the flow of milk, but this does not occur with bottle-feeding. In infants with pulmonary disorders, pulse oximetry during breastfeeding may minimize episodes of hypoxia.[70]

Cup feeding, regarded as a safe alternative for the feeding of preterm and low birthweight infants, has been described by some authors and recommended for ill and low birthweight babies by the World Health Organization, among other guidelines of the Baby Friendly Hospital Initiative.[71] In our setting, cup feeding has not shown advantages over bottle-feeding as far as an increase in breastfeeding rates is concerned.[70]

After years of discussion, the literature is almost unanimous in stating that breastmilk is the ideal type of milk for preterm babies.[72] A doubt that persisted for a long time was whether the advantages of human milk described for full-term infants are also valid for preterm infants.[73]

Neuropsychomotor development

An interesting issue is the impact of the use of human milk on neuropsychomotor development. Intriguingly enough, it has been reported that the use of nonfortified human milk in infants exclusively during their hospital stay was associated with higher intellectual scores between 7.5 and 8 years than in formula-fed infants. These data led the authors to conclude that this initial period is critical to the nutrition of preterm infants and to their neurological development.[74,75]

Obviously, current information does not ethically allow us to carry out double-blind randomized studies to investigate this issue. Thus, the available information derives from studies that provide little evidence, usually suggesting a positive impact of human milk on the development of preterm infants.[76,77] Interestingly enough, the authors concluded that besides its nutritional value, breastmilk is related to improved mood and interactive maternal behaviors, which indirectly contributes to the development of preterm infants.[78]

In a systematic review of 40 articles that sought to associate breastfeeding with the beneficial effects on intellectual functions, including studies with full-term and preterm infants, 27 (68%) concluded that breastfeeding promotes intelligence. Due to methodological problems, only two of these studies met the requirements of the meta-analysis. One concluded that the effect of breastfeeding on intelligence was significant, whereas the other pointed out that it was not. In other words, this association is not completely established.[79]

Lipid profile

The presence of long-chain fatty acids in human milk, DHA and ARA, has led researchers to assess their effects.

In terms of future consequences associated with lipids in human milk, the possibility of programming the lipoprotein profile in adolescence and adulthood was assessed by conditioning the risk of atherosclerotic disease and associated events. The largest intake of human milk by preterm infants was associated with lower LDL/HDL and apo B/apo A_1 levels. These data suggest long-term positive effects of human milk on the risk of atherosclerosis.[80]

The benefits of formula supplementation with long-chain fatty acids could not be confirmed, and there is insufficient evidence for recommending this practice.[81,82]

Anti-infectious action

In general, clinical trials have suggested a decrease in infection rates in preterm infants who are fed human milk. Specific factors such as secretory IgA (sIgA), lactoferrin, lysozyme, oligosaccharides, growth factors and cellular components seem to positively affect the defense system of preterm infants.

A systematic literature review revealed that preterm infants who received human milk had a risk three times lower for necrotizing enterocolitis and a risk four times lower risk of having this disease confirmed than did formula-fed infants.[83]

An intriguing theory posits that protective effects of human milk on preterm infants act through the immune system by the enteromammary pathway. The exposure of mothers to the environment of neonatal intensive care and skin-to-skin contact with their infants may induce them to produce specific antibodies against nosocomial pathogens. This way, there is the transfer of specific antibodies through human milk.[64,72,84]

Immunity

Human milk, especially raw milk, fed to preterm infants may play a vital role in the development of their immune system. The role of human milk cytokines in the development of wheezing in the first year of life was assessed in full-term infants. The length of breastfeeding was inversely associated with the incidence of wheezing in the infant. The authors conclude that the protective effect of breastfeeding against wheezing occurs via human milk cytokines.[85] If this also applies to preterm infants, we have one more excellent indirect action of human milk. It has been suggested that the occurrence of eczema in preterm infants is associated with the early presentation of solid foods.[86] Perhaps, this shows, once again, the adverse effects of inappropriate nutritional practices on preterm infants.

Human milk supplements

Despite the benefits of human milk to the nutrition of preterm infants, we should not forget that its use is

associated with low growth rates and nutritional deficits, during and after hospital stay. Instead of precluding the use of human milk, we should supplement it in order to provide the nutrients necessary for preterm infants. The fact that growth and nutritional deficits can be minimized with the use of nutrient supplementation renewed the interest in the use of human milk for preterm infants.[84]

Supplementations of human milk with simple additives and with multinutrients have been associated with improvement of growth in the short run and of the nutritional status of low birthweight newborns. Supplementation of calcium and phosphorus improves bone mineralization before and after the neonatal period and prevents a decrease in linear growth, resulting in the normalization of biochemical indices. Sodium supplementation results in the normalization of serum sodium levels. Supplementation with protein and energy is associated with more appropriate rates of weight gain and better protein nutritional indices. The use of multicomponent additives does not seem to be related to adverse effects. Thus, the use of multicomponent additives to human milk has been recommended for small preterm infants.[74,84,87] New studies should assess the quality of different commercially available additives.[87]

Other benefits of human milk

In addition to the described benefits,[88] special attention should be paid to the benefits for the mother, which should not be overlooked. Among them are the reduction in ovarian cancer and breast cancer before the menopause.[89] Women go back to their original status before gestation much faster and decrease the incidence of obesity. The risk of osteoporosis is minimized. Lactation stimulates calcium absorption and the production of calcitriol and parathyroid hormone.[73]

Another interesting fact is that the policy of human milk supplementation for preterm infants has brought the mother into the neonatal unit. Mothers are encouraged to actively participate in the nutrition of their infants, even during the time their babies are not being breastfed. This involvement may be a positive stimulus to the maintenance of lactation, which is extremely difficult in this population.[90]

This is a big problem that should be overcome. Quite often, there is a long period during which mother and infant are separated from each other, which may affect the mother's ability to breastfeed.[91] A possibility is to encourage skin-to-skin contact (kangaroo mother care), which showed to promote better development, growth and well-being of infants, in addition to increasing milk production and the length of breastfeeding.[92-94]

Conclusions

Despite great advances in the understanding of short and long-term effects of the nutrition of preterm infants, further investigation is necessary. However, given the currently available evidence, it is necessary to rethink the goals of nutrition in preterm infants. The intention is to obtain an appropriate growth that partly mirrors that which would occur *in utero*, but as important as that, or even more important, is that one should be concerned with the future impact of nutrition on infant development.

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