Feeding of preterm infants and fortification of breast milk

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Abstract

The administration of the adequate amount of nutrients helps to improve a correct short-term linear growth and long-term neurocognitive development. To reduce the extra-uterine growth delay in very low birth weight infants (VLBW) the best strategy of nutrition (parenteral or enteral) should be established rapidly, since the first day of life. In preterm infants, nutrition can be administered parenterally and enterally. Prematurity is the most frequent indication for parenteral nutritional support due to intestinal functional immune deficiency, deficiency of digestive enzymatic systems and reduced nutritional reserve of these infants. In terms of enteral nutrition, breast milk is the first choice. In case of preterm and VLBW infants, fortifiers are used to overcome breast milk's protein and mineral deficiencies. When breast milk is not available, specific infant formula is the alternative.

Introduction

The improvement of neonatal care has led to an increase in the survival rate of very low birth weight infants (VLBW) infants (<1500 g). Nonetheless, growth failure is still a very frequent issue with incidence that ranges from 43 to 97% among various neonatal units. Thus, more aggressive nutritional strategies have been developed: first the parenteral nutrition then the enteral nutrition. Parenteral nutrition is often the only source of nutrients that can be used during the period of clinical instability.[1] Enteral nutrition must be gradually introduced as soon as possible; in presence of a good enteral tolerance, the parenteral nutrition should be rapidly discontinued, thus reducing its related side effects.[2]

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Key words: Preterm infants; Breast milk; Fortification.

Funding: Funded by Merqurio Editore S.r.l., with the unconditional contribution of Nestlè Italiana S.p.A.

Received for publication: 7 June 2017.
Accepted for publication: 21 June 2017.

La Pediatria Medica e Chirurgica 2017; 39:158
doi:10.4081/pmc.2017.158

Parenteral nutrition

Assuring an adequate nutrition to preterm infants is a real challenge, especially during the first hours after birth, when a total parenteral nutrition (TPN) is needed to meet the high nutritional requirements but it is often complicated by glucose and lipids intolerance.[3]

Parenteral nutrition (PN) is an intravenous nutritional therapy that includes the administration of fluids, electrolytes, glucose, proteins, lipids, minerals, vitamins and oligo-elements.[4] It should be started as soon as possible within the first 24 hours of life. It can be prescribed in individualized or standardized administration; PN is provided through a central catheter (umbilical vein catheter or percutaneous central catheter) or, temporarily, via a peripheral route in the case of partial parenteral solutions and low osmolar load (<600 mOsm/L).

Fluids and electrolytes

In the first week of life changes occur in the extracellular and intracellular compartments, resulting in a redistribution of fluids. This is one of the reason that explains the weight loss (5-10% of birth weight) that usually takes place during the first days of life. The fluid intake in the newborn (VLBW) and very low birth weight (ELBW) starts with 80-90 mL/kg/day and then is gradually increased by 10-20 mL/kg/day up to 160-180 and 150-160 mL/kg/day, respectively.[2,5-8] Electrolytic supplementation usually begins on the third-fourth day of life and consists of a supplementation of 2-5 mEq/kg/day of sodium and 1-2 mEq/kg/day of potassium.[2,5-8] Electrolytes must be strictly monitored because of their frequent alterations due to an immaturity of the kidney and of the neuroendocrine system.[9]

Calories

Caloric requirements are around 40-60 kcal/kg/day in the first few hours of life, reaching 85-95 kcal/kg/day within the first week,[10] because of the daily energy expenditure and the calories stored for growth.

Carbohydrates

Carbohydrates are the main source of energy in preterm infants. In VLBW infants the daily intake is of 7-9 g/kg/day in the first day and increases to a maximum of 13-15 g/kg/day; ELBW infants, instead, must have a daily intake that starts from 7-8 g/kg/day in the first 24 hours and then gradually increases to 10-14 g/kg/day at the end of the first week of life.[5] The maintenance of a correct glucose homeostasis is not easy since preterm infants are at increased risk of hypoglycemia, due to the immaturity of the organs involved in glucose metabolism, but at the same time are exposed to many risk factors for hyperglycemia (insulin resistance, sepsis, related stress, limited glucose oxidation).

Proteins

Current recommendations suggest a protein supplementation that ranges from 2.5 to 4 g/kg/day. For the VLBW infants, the intake should start with 2.5 g/kg/day in the first day, and then gradually increases to 4 g/kg/day on the fourth day; in the ELBW infants an initial dose of 3 g/kg/day is recommended and then increased to 4 g/kg/day from the third to fourth day of life. Early aminoacidic administration promotes protein synthesis, nitrogen retention, insulin secretion and glucose tolerance and albumin synthesis.[11,12]

Lipids

Lipids administration is also recommended from the first day of life (within the first 24 to 30 hours of life) in VLBW infants, starting with 2.5 g/kg/day then increasing to 3 g/kg/day from the fourth day, while in ELBW infants from 2 g/kg/day up to 3 g/kg/day on the fifth day of life.[1,5,13-16] Lipids emulsions help to reach the high caloric requirements of preterm and are the unique source of essential fatty acids. Lipids should account for 25-40% of non-protein calories.[17]

Minerals

An adequate intake of minerals must include appropriate calcium levels (*e.g.* 25-40 mg/kg/day in the first days of life; 65-100 mg/kg/day on the seventh day of life), phosphorus (*e.g.* 20-35 mg/kg/day in the first days of life; 50-80 mg/kg/day) and magnesium (*e.g.* 0 and 3 mg/kg/day in the first days; 6-12 mg/kg/day on the seventh day).[18] Minerals play an important role in bone metabolism and influence energy and immune systems. These values widely range because the absorption and bioavailability of minerals depend on more variables, so the intake should be customized for each patient. Since minerals' uptake and bioavalaibility depend on several variables, the individual intake varies from patient to patient. Thus, base-line values are widespread.

Vitamins and oligoelements

It is a standard practice to give vitamin supplements to preterm infants in pre-dosed solutions.[5] A higher dose is recommended in case of cholestasis. While zinc treatment starts on day one (*e.g.* 400 mcg/kg/day), the remaining oligoelements are usually administered after the first week. In infants with cholestasis, oligoelements should be interrupted.

Enteral nutrition

Enteral nutrition should be started as soon as the newborn is stable, but maternal colostrum should be administered within the earliest hours of life to establish an appropriate oral and gastrointestinal microflora.[3] Then, small amounts of food (*e.g* <20 mL/kg/day) are given to promote trophism and stimulate the maturation of intestinal motility. According to specific nutritional protocols (Tables 1 and 2),[19] enteral feeding must gradually increase.[20] Usually, the progression is from 15-30 mL/kg/up to enteral doses of 150-170 mL/kg/day. Breast milk is used as first choice and, when not available, human donors milk banks or premature formulas are the alternatives.

Breast milk

The American Academy of Pediatrics considers breast milk the ideal enteral feeding also for preterm infants.[21,22] Breastfeed is known to improve nutritional, immunological and developmental outcomes and it has been related to a reduction in the more frequent complications of VLBW infant such as bronchopulmonary dysplasia and necrotizing enterocolitis (NEC).[23]

Preterm infants are exposed to a higher risk of infection because of the immaturity of their immune system. In fact, they have a reduced concentration of circulating T cells, with a higher percentage of naive T cells, and less neutrophil stored in the bone marrow compared to the term infant; the immunity cells (macrophages, neutrophils, NK cells, T and B lymphocytes) show a reduced activity and there is a decreased production capacity of immunological proteins (cytokines and complement). Thus, in preterm infants, human milk provides immunological benefits through two mechanisms: direct protection through components such as lactoferrin, lysozyme, defensine and other cytokines, and stimulating action on the growth of the immune system due to its high content of growth factors and nucleotides.[24]

Despite the great scientific efforts made by pediatricians and

Table 1. Nutritional intake for preterm infants with very low birth weight during the first week of life (kg/day).

Day of life	1	2	3	4	5	6	7	>7
Volume (mL)*	80-90	100-110	120-130	130-140	140-160	160-180	160-180	160-180
Carbohydrates (g)	7-9	7-9	10-11	11-13	12-14	13-15	13-15	13-15
Lipids (g)	2.5	2.5	2.5	3,0	3.0	3.0	3.0	3.0
Aminoacids (g)	2.5	3.0	3.5	4	4	4	4	3.5-4
Na (mEq)	0	0	0	3	3	3.5	3.5-4.0	3.5-4.0
K (mEq)	0	0	0	2	2	2	2-3	2-3
Ca (mg)	25-40	30-45	40-60	50-65	55-75	65-90	70-100	80-100
P (mg)	20-30	30-40	35-50	45-55	50-60	55-70	60-80	60-80
Ca/P ratio	1-1.3	1-1.3	1-1.3	1-1.3	1-1.3	1-1.7	1.3-1.7	1.3-1.7
Mg (mEq)	0-0.25	0-0.5	0.5	0.5	0.5-1.0	0.5-1.0	1.0	1.0
kcal (tot)	61-69	61-71	76-80	87-95	91-98	95-102	90-102	93-102
Non-protein kcal	51-59	51-69	62-66	71-79	75-82	79-86	79-86	79-86

*In preterm infants with a weight ranging from 1501 to 2500 g, fluid intake should be lower than in very low birth weight infants and slightly higher than in term infants.

neonatologists, there are still many difficulties in effectively promoting breastfeeding in Neonatal Intensive Care Units. In May 2016, in Italy, the Ministry of Health published a list of recommendations aiming to increase this practice (Table 3).[25]

Donor human milk

Donor human milk represents a safe and effective alternative to breastfeed milk in NICUs. Although the processes used for pasteurization can affect the milk's macronutrients and some immunological components, it has been demonstrated that donor human milk bring benefits in preterms if compared to the use of infant formula.[26] A recent meta-analysis showed a higher incidence of NEC and dietary intolerance in infants fed with infant formula than in infants fed with human donor milk.[23] In addition, despite pasteurization, many bioactive components and anti-infective properties are still preserved.[27,28]

Human milk fortification

Breast milk alone cannot satisfy the high nutritional needs of VLBW infant. Its composition varies through time: in preterm mothers its protein content is higher in the first weeks of lactation, then it gradually decreases.[29] Moreover, milk production in mothers of preterm infants can be affected by several factors such as stress, health problems, lactation delay and distance from the infant. For these reasons, breast milk is often unable to satisfy the nutritional needs of preterm infants and its exclusive use has been correlated with growth failure. Poor weight gain can lead to worse developmental outcomes, in terms of neurological adverse events. In fact, in literature growth failure has been associated with increased risk of hearing loss, visual defects and mental retardation.[30-32]

To avoid growth retardation of preterm infants but also to maintain all the benefits provided by human milk, commercial fortifiers of human milk are now frequently used in NICUs. Fortification can be achieved through three different methods: standard, adjustable and targeted fortification.

Standard fortification: in this approach, the fortification of human milk is achieved by adding a fixed amount of fortifier during the necessary period, considering a human milk protein content of 1.5 g/dL. This is the most common technique used for the fortification of human milk. Nonetheless, this strategy does not consider the physiological modification in human milk's composition, as

Table 2. Nutritional intake for preterm infants with extremely low birth weight during the first week of life (pro kg/day).

Day of life	1	2	3	4	5	6	7	>7
Volume (mL)	80-90	90-110	110-120	120-140	140-160	150-160	150-160	150-160
Carbohydrates (g)	7-8	7-8	9	9	10	10-13	10-14	10-14
Lipids (g)	2.0	2.5	2.0-2.5	2.0-2.5	2.5-3.0	3.0	3.0	3.0-3.5
Aminoacids (g)	3.0	3.5	3.5-4.0	4.0	4.0	4.0	4.0	4.0
Na (mEq)	0	0	0	2.5	2.5	2.5	2.5	3-6
K (mEq)	0	0	0	1-2	1-2	1-2	1-2	2-3
Ca (mg)	25-40	35-50	50-60	55-65	60-80	65-90	70-100	80-100
P (mg)	25-35	35-45	40-55	50-60	55-65	55-70	60-80	60-80
Ca/P ratio	1-1.3	1-1.3	1-1.3	1-1.3	1-1.3	1.3-1.7	1.3-1.7	1.3-1.7
Mg (mEq)	0-0.25	0-0.5	0.5	0.5	0.5-1	0.5-1	1.0	1.0
kcal (tot)	58-62	65-69	68-75	70-75	78-83	83-95	83-98	83-103
Non-protein kcal	46-50	51-55	54-59	54-59	62-67	67-79	67-82	67-87

Table 3. Promotion of the use of breast milk in Neonatal Intensive Care Units and access of parents in the hospital wards.

	Suggestions
Use of breast milk in NICU and access of parents to the hospital wards	Ensuring the free access of parents to the neonatal nursing department during the hospitalization of their children by providing them with information and support, including on the use of breast milk and/or human milk
	Promote parents' staying with their children for 24 hours a day to reduce stress and facilitate feeding with breast milk
	Facilitate physical contact between parents and newborns, also by skin contact due to the positive effects on parent-child relationship and on milk production
	Facilitate the establishment of hospital-based donor human milk banks to increase the use of human milk in the absence of own breast milk, especially in preterm infants
	Help the family to participate in the care and delivery of clinical decisions concerning their son/daughter and in particular of his/her diet
	Promote the knowledge of up-to-date information about the promotion and use of human milk in the NICU among the healthcare staff, in order to prepare health-related protocols based on scientific evidence

NICU, Neonatal Intensive Care Units.

the reduction of the protein content after the first days post-delivery. Therefore, the nutritional intake provided to the infant may be insufficient or excessive in comparison with the desired target.

Adjustable fortification: in this second method, BUN (blood urea nitrogen) value – a marker of level of protein nutrition – is used to modulate the dose of the fortifier. However, this technique tends to underestimate the real protein intake.

Targeted fortification: targeted fortification has become possible thank to human milk analyzers (HMA) that analyze human milk's composition through spectroscopy. Fortifiers are added based on the real macronutrient composition. The milk is analyzed twice a week. This method is undoubtedly the most innovative and is currently considered the gold standard.[33]

Table 4. Human milk fortifiers available in Italy.

Fortifier	BMF (Aptamil)	PreNidina FM85
	per 100 g	per 100 g
Energy (kcal)	347	435
Energy (kJ)	1475	1821
Fats (g)	-	18
MCT (g)	-	12.5
LA (mg)	-	958
ALA (mg)	-	417
DHA (mg)	-	157
Carbohydrates (g)	62	32.4
Protein (g)	25	35.5
Vitamin A (mcg)	5275	9509
Vitamin D (mcg)	115	88
Vitamin E (mg)	59	107
Vitamin K (mcg)	145	187.5
Vitamin C (mg)	272	469
Vitamin B1 (mg)	3	4
Vitamin B2 (mg)	3.9	5.4
Niacin (mg)	59	40
Vitamin B6 (mg)	2.5	3.5
Folic acid (mcg)	682	937.5
Vitamin B12 (mcg)	4.5	4.7
Biotin (mcg)	57	82
Pantothenic acid (mg)	17	18.8
Sodium (mg)	795	918
Potassium (mg)	523	1210
Chloride (mg)	568	803
Calcium (mg)	1491	1890
Phosphorus (mg)	872	1095
Magnesium (mg)	117	100
Iron (mg)	-	45
Zinc (mg)	13.8	23,5
Copper (mg)	0.8	1.3
Manganese (mcg)	184	228.5
Fluoride (mcg)	-	<60
Selenium (mcg)	39	106.8
Chromium (mcg)	-	<23
Molybdenum (mcg)	-	<20
Iodine (mcg)	250	485.9
Coline (mg)	-	230.4
Inositol (mg)	-	123.7
Taurine (mg)	-	53.6
L-carnitine (mg)	-	71
Dosage (g/100 mL)	4.4	4

BMF, breast milk fortifier.

Effects of fortification

There is an agreement on the importance of fortify breast milk to meet preterm infant needs and adjust protein, calcium and phosphorus intake. Scientific evidence, however, on the effects of fortification of breast milk are still lacking. According to a recent Cochrane review, published in 2016, an increase in hospital growth rate of preterm infants fed with fortified breast milk has been demonstrated but it seems there are no consistent data on long-term benefits in neurocognitive development.[31] In a subsequent study Mimouni *et al*., agreed that new studies are needed to clear these uncertainties.[32]

Fortification products

In the U.S.A. liquid fortifiers are available. Major products are Enfamil Human milk fortifier (Mead Johnson Nutrition, Evansville, IN, USA) and Similac Human milk fortifier (Abbott Nutrition, Columbus, OH, USA), both of them are based on concentrated bovine milk. Prolacta Bioscience products on the other hand are derived from pooled human milk and contain even electrolytes and minerals. In Italy it is possible to find products that provide combined nutrients supplementation (proteins, carbohydrates, fats) or products that provide only one specific macronutrient. Here are the main components of the products that provide combined supplementation, currently marketed in Italy (Table 4).

Formula milk

When breastmilk or donor milk is not available, a specific preterm formula can be used. A preterm formula contains more proteins (2.4 g/100 mL or 3 g/100 kcal), calories (77-83 kcal/100 mL), calcium (90-120 mg/100 mL) and phosphorus (55-77 mg/100 mL) compared to infant formula for term infants. A new generation of formula with an even higher protein content (2.68-2.9 g/100 mL or 3.3-3.6 g/100 kcal) is currently available.[34]

Conclusions

Nutrition is one of the most crucial factor that influences growth and developmental outcomes of preterm infants. Even if there are still many controversies that need to be addressed, it has been demonstrated that it is fundamental to ensure a proper nutrition from the first hours of life through a well-balanced parenteral nutrition and through the early onset of enteral nutrition.[35,36]

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