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Review

Benefits of human milk in preterm infant feeding

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Abstract

Mother's own milk is widely recognized as the optimal feeding not only for term but also for preterm infants. Evidence documents short and long-term metabolic, immunologic and neurodevelopmental advantages of breastfeeding when compared to formula. Moreover benefits of breastfeeding on psychological and relational aspects have to be considered.

In order to meet the unique nutritional requirements of preterm infants and preserve the singular benefit of breastfeeding, human milk should be fortified to allow adequate growth and bone mineralization. Best fortification models are still object of research, in order to obtain a balance between the risk of undernutrition and the metabolic risks of a too rapid catch-up growth.

When mother milk is unavailable or in short supply, donor milk (DM) represents the second best alternative and although some nutritional elements are inactivated by the pasteurization process, it still has documented advantages compared to formula. The demonstrated benefits of human milk (HM) highlight the importance of health care professional education in the support of breastfeeding.

Keywords

Human milk, preterm infants, fortification, donor milk.

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Introduction

It is universally recognized that breastfeeding is the normative standard for feeding and nutrition of infants born at term until 6 months of age followed by a complementary feeding and continued, if possible, well beyond 1 year of life. Emerging evidence in the last decades has confirmed substantial benefits of the use of human milk (HM) also for sick and preterm infants in Neonatal Intensive Care Units (NICUs). Feeding preterm infants HM decreases the rates of infection, necrotizing enterocolitis (NEC), and mortality, while improving neurocognitive and cardiovascular outcomes at the long-term. Mother's own milk is the first choice for all neonates including preterm infants, when it is not available or not sufficient, despite significant lactation support, donor human milk is a valid alternative [1-3].

Biological aspects

Human milk can be considered a species specific biological "dynamic" system. Particular attention is given to specific bioactive and immunomodulatory factors, such as gastrointestinal hormones, immunoglobulins, lactoferrin, lysozyme, oligosaccharides, nucleotides, growth factors, enzymes, antioxidants and cellular components that can not only ensure adequate host defense against infections, but also actively modulate the immune response and modify the intestinal bacterial flora [4-6].

Among these factors oligosaccharides have a relevant role. Originally described as a prebiotic "bifidus factor" that serves as a metabolic substrate for desired bacteria and shapes an intestinal microbiota composition with health benefits for the breast-fed neonate, today oligosaccharides are known to be more than just "food for bugs": literature shows that oligosaccharides also directly act preventing pathogen adhesion to infant mucosal surfaces, lowering the risk for infections, and modulate epithelial and immune cell responses [7]. Qualitatively and quantitatively, their presence in milk is strictly related to the expression of the mother's *Se* and/or *Le* genes: on these basis 4 different milk groups have been described. Substantial differences in oligosaccharide contents were found within the groups and were strictly related to the presence or absence of specific fucosyl-oligosaccharides. A recent study performed by our group reported new data on oligosaccharide concentrations in the 4 milk groups. These differences might exert an influence on several biological functions that are important for preterm infants and currently are attributed to milk oligosaccharides. But what was more striking was the higher concentrations of Human Milk Oligosaccharides (HMOs) in preterm compared with term milk (**Fig. 1**). This highlights the relevant role of breastfeeding for preterm infants, who, because of the immaturity of their organs and systems, are at greater risk of contracting infectious illnesses. The different HMOs concentrations in preterm and term milk might represent a programmed adaptation of milk composition to the specific needs of the infants. Lower lactose concentrations in preterm milk compared with term milk were also described (**Fig. 2**). Low lactose concentrations in milk might have positive effects in preterm nutrition, because lactose contributes to lower milk osmolality. Low levels also might represent lower substrate levels for the well-known lactase deficiency that is common among these newborns [8].

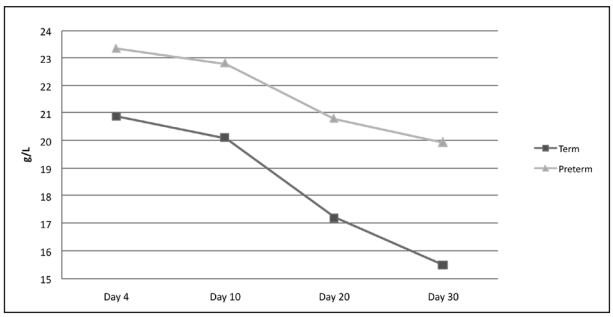

Figure 1. Oligosaccharides concentrations in term human milk versus preterm human milk.

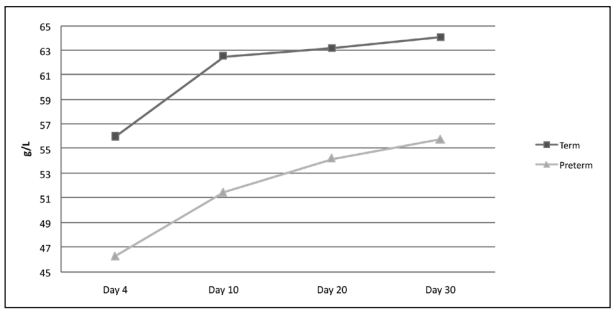

Figure 2. Lactose concentrations in term human milk versus preterm human milk.

Nutritional aspects

For its nutritional qualitative advantages, HM is nowadays universally recognized as the optimal

feeding choice for every infant [6]. However, in order to meet the unique nutritional requirements of preterm infants and preserve the singular benefit of breastfeeding, human milk should be fortified to allow adequate growth and bone mineralization [9]. Kuschel and Mc Cormick, in two recent Cochrane reviews, agree with the fact that fortification of HM with more than one nutritional component is associated with short-term improvements in weight gain, linear and head growth. Despite the lack of data on long-term outcomes, it is unlikely that further studies evaluating fortification of human milk versus no supplementation will be performed. Further research should be directed toward comparisons between different fortifiers, evaluating both short-term and long-term outcomes and adverse effects, to achieve the "optimal" composition of fortifiers [10, 11].

The optimal method for HM fortification still remains to be determined and a great variety of protocols are currently used in neonatal units. It has been observed that HM protein content after standard fortification fails to meet the recommended intake for preterm infants in approximately half of the cases [12]. Low protein intake has been proven to be the primary limiting factor responsible for preterm infants growth failure. The main reason of protein undernutrition despite fortification is that usually fortification is based on the customary assumptions about the composition of HM. However, the protein concentration of preterm HM is variable and decreases with the duration of lactation. Recently, good results have been obtained with individual fortification of human milk that compensates for the high variability of expressed breast milk composition, especially for protein and fat content. There are two models of individualization: the "adjustable fortification" based on the infant's metabolic response and the "targeted fortification" based on the analysis of human milk and on its fortification in such a way that each infant always receives the amount of needed nutrients [13].

Clinical aspects

Necrotizing Enterocolitis (NEC)

NEC remains one of the most critical morbidities of preterm babies. Although no individual randomized controlled trial have been sufficiently powered to examine the effect of breast milk on the incidence of NEC in preterm babies, two meta analysis suggest a reduced incidence of NEC in infants fed with human milk [14, 15].

The two meta-analysis from randomized controlled trials compare formula milk with donor breast milk: since maternal breast milk contains higher levels of immunoprotective factors than donor breast milk, feeding with maternal breast milk has also a protective effect, as observed in observational studies [16-18].

Neurodevelopmental outcome

Neurodevelopmental outcome of preterm infants is improved by the feeding with human milk.

Long-term studies at 8 years of age through adolescence suggest that intelligence test results, white matter and total brain volumes are greater in subjects who had received human milk as infants in the NICU. Extremely preterm infants who receive the greatest proportion of human milk in the NICU had significantly greater scores for mental, motor, and behavior ratings at ages 18 months and 30 months. These data remain significant after adjustment for confounding factors, such as maternal age, education, marital status, race, and infant morbidities [1].

It is noteworthy that in O'Connor's study the best neurodevelopmental and motor outcomes in very low birth weight infants (VLBWI) fed with fortified breast milk occurs during the first year of corrected age despite a reduced growth of these infants occurring in this period of life [19]. This observation draws attention to qualitative growth aspects obtained with breast milk versus formula in preterm infants that had already been observed by Lucas in his trial: in this work no differences in neurological development were observed despite an higher growth in infants fed with preterm formula [20]. Both studies suggest that human milk may have an independent effect on the development of preterm infants, not only for nutrient intakes.

Infections

In a systematic review published in 2004 on Archives of Childhood Disease, de Silva focused on three randomized controlled trials and six observational studies regarding the relationship between nutrition, infection and human milk in preterm VLBWI. Even if methodological problems in the included studies are pointed out

by the Authors, they conclude that human milk compared with formula has a protective effect to the onset of infections [21]. In February 2005, a large prospective study about extremely low birth weight infants or infants with less than 28 weeks gestational age at birth was published on Pediatrics highlighting the risk of late onset sepsis is significantly reduced by an early enteral feeding with human milk [22].

Feeding tolerance

There are a few of experimental studies about feeding tolerance, especially as concern mother's own milk. The meta-analysis of Henderson concluded that there are no data from randomized controlled trials to determine whether feeding preterm or low birth weight infants with formula milk versus maternal breast milk affects growth, development, or other clinically important outcomes [23] This is likely to be due to reluctance of researchers and consumers assess an intervention that results in infants not receiving the non-nutritional benefits of breast milk.

However in his meta-analysis of data from randomized controlled trials Boyde indicates that feeding with formula milk, compared with donor breast milk (DM), leads to higher rates of feed intolerance and necrotising enterocolitis in preterm infants [14].

There are several non-experimental studies indicating that clinical feeding tolerance is improved, and the attainment of full enteral feeding is made quicker by a diet of human milk. A recent international survey on enteral feeding practices in VLBWI has shown that when neonatal units would usually delay onset of enteral feeding the unavailability of both mother's own milk or donor human milk has an important role (between 55-89% of cases). This study demonstrates marked variability in neonatal feeding practices in four geographical regions. This variability is partly explained by differences in access to donor human milk. Moreover the study observed that most of the units with access to donor human milk commenced enteral feeding on the first day of life, even in the most immature infants, and advanced more rapidly than units without access to DM. Units without access to DM frequently delayed the introduction of enteral feeds until mother's own milk was available [24]. These data are supporting the beneficial effects of donor milk in feeding tolerance.

Metabolic outcome

Long-term studies of preterm infants also suggest that human milk feeding is associated with lower rates of metabolic syndrome and in adolescence it is associated with lower blood pressures and low-density lipoprotein concentrations as well as a lower risk of insulin resistance [1, 2].

Psychological and relational aspects

In case of premature birth, mother's sense of guilt and defeat of not having been able to carry the pregnancy until term and the concern of not being able to take care of such a small and fragile creature is also associated with stress and health concerns. For this purpose, free access to the ward for parents is essential. In this case, they are encouraged in helping in the care of their own baby, touching and feeding the infants by themselves. Breastfeeding creates a great emotional involvement and a sense of gratification in mothers. In this case benefits of breastfeeding outweigh the purely nutritional aspects and they can be considered part of the neonatal and the NIDCAP care [25, 26].

Donor human milk

American Academy of Pediatrics in its last policy statement on breastfeeding recommends that pasteurized DM, appropriately fortified, should be used if mother's own milk is unavailable or its use is contraindicated [1].

Pasteurization is necessary to inactivate most of viral and bacterial agents but partially affects nutritional and immunological properties of breast milk, however it is well recognized that pasteurized milk maintains some of the mother's milk beneficial and protective effects [2].

The main benefit deriving from the use of donor human milk (vs. formula) in preterm infant feeding is the reduction of the NEC incidence as indicated in three recent meta-analyses [14, 15, 27].

A reduction in the incidence of sepsis and of bronchopulmonary dysplasia as well as an enhanced feeding tolerance have also been observed [2]. However further studies are necessary to confirm these data.

Moreover, according to Quigley [15], additional randomized controlled trials are needed to compare feeding with formula versus nutrient-

fortified donor breast milk. Separate comparisons of formula versus DM as supplements to maternal milk rather than as sole diet are also warranted, since their effects may be different [15]. Analysis of costs and an evaluation of acceptability are also required, in particular research is needed to explore different cultural, religious and social attitudes to DM [28, 29].

Specific Guidelines have been prepared as a tool to optimize the functioning of existing Human Milk Banks by uniforming the organization, management and procedures in these Banks and to determine the minimal essential requirements to establish a new Human Milk Bank [2].

DM banks are not only meant to collect, process and store donated milk, but they also represent an instrument for breastfeeding promotion and support. In Italy, data from the Italian Neonatal Network show that in NICUs, exclusive breastfeeding at discharge is achieved for nearly 30% of neonates when banked milk is available during hospitalization and only for 16% of neonates when it is not [30].

Promotion

A recent Multicenter Italian Study observed limited breastfeeding and use of human milk among the NICU infants at discharge. At discharge, 28% of all infants were fed exclusively with human milk: 31%, 25%, 22% and 33% respectively in the < 1,500 g, 1,500-2,000 g, 2,000-2,499 g and 2,500 g birth weight categories. The proportion of infants not fed with human milk varied from 6 to 82% across different centers [31].

The role of health care workers, including pediatricians, is to protect, promote, and support breast-feeding. Health care workers should be trained in breast-feeding issues and counseling, and they should encourage practices that do not undermine breast-feeding. It is a health care paradox that breastfeeding is not adequately promoted and supported in the population of newborn infants admitted to NICUs.

Lack of feeding with breast milk for preterm infants is an important and costly problem that, if addressed successfully, has the potential to contribute to addressing inequalities in health [32].

Conclusions

So far the ideal model of postnatal growth of VLBWI has not been clearly defined. The importance of nutrition in the early period of life is now well known, and the term "programming" has been proposed to emphasize that early nutrition should be considered not simply in terms of meeting immediate nutritional needs, but also for its potentially long-lasting or life-long biological effects [9]. The target is to achieve VLBWI's growth potential and to ensure their good health and a normal neurological development. However by now we do not know what is the most suitable "path" we can follow. In this regard Thureen and Heird said: "Although a higher protein intake undoubtedly will improve growth and possibly reduce neurodevelopmental deficits, recent data suggest that rapid early growth may result in unfavourable markers of cardiovascular risk at 13-16 years of age. Some of these unfavourable effects appear to be related to feeding formula versus human milk" [33].

Declaration of interest

No conflicts of interest exist.

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