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Importance of human breast milk in premature infant

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ABSTRACT

Human breast milk (HBM) is considered the optimum feeding for infant nutrition. The specific composition and unique properties make HBM appropriate not only for the term but also for preterm infants. HBM feeding confers protection to preterm infants against the most serious morbidities of prematurity and decreases mortality in a dose-dependent manner. We performed a literature review, aiming to provide an update on the available evidence regarding the importance and the advantages of HBM on preterm infants' health. Our findings confirmed the several health benefits in preterm infants, including the improvement of neurodevelopmental outcomes and the protection against necrotizing enterocolitis and infections. Many more investigations will be necessary to understand the mechanisms underlying the beneficial association of HBM with neurodevelopmental outcomes and to confirm the beneficial effects of HBM on bronchopulmonary dysplasia. Based on the current evidence on the health benefit of HBM feeding, promotion and support of lactation since the immediate post-delivery should be considered a priority in preterm infants' care.

KEYWORDS

HUMAN BREAST MILK
DONOR HUMAN MILK
PRETERM INFANTS
NUTRITIONAL
BIOACTIVE FACTORS
NEURODEVELOPMENT
HEALTH BENEFITS

INTRODUCTION

Human breast milk (HBM) has been shown to be the optimum feeding for infant nutrition[1,2]. Its specific composition makes HBM appropriate not only for the term but also for preterm infants[3-8]. Feeding preterm infants with HBM confers protection against the most serious morbidities of prematurity such as necrotizing enterocolitis (NEC) and sepsis[9-14], retinopathy of prematurity (ROP)[15-17], bronchopulmonary dysplasia (BPD)[18-20], and decreases mortality in a dose-dependent manner[10]. HBM feeding improves long-term neurocognitive outcomes[21-23] and confers beneficial effects against obesity[24].

We conducted a narrative review to provide an update on the available evidence regarding the importance and the advantages of HBM on preterm infants' health. We searched the PubMed database for articles relating to HBM using specific keywords such as breastmilk, human milk, nutritional, macronutrients, micronutrient, microbiome, bioactive factors, expressed and donor human milk, neurodevelopment, bronchopulmonary dysplasia, necrotizing enterocolitis. Preference was given to the more recent published sources (within 5 years), taking also into account the milestones. We included randomized controlled trials (RCTs), cohort studies, systematic reviews, and meta-analyses as well as preclinical studies.

HUMAN BREAST MILK COMPOSITION

MACRONUTRIENTS

HBM includes many nutritional elements such as fat, carbohydrates, proteins, and HM oligosaccharides (HMOs). They all play a central role in infant growth[25]. HM is composed of water (87%-88%), and solid components such as fat (3.8%), protein (1.0%), and carbohydrates (7%). It has a specific gravity of 1.030 and an osmolarity of approximately 286 mOsm/L[26].
Usually, mature HMB contains 65-70 kcal per 100 mL of energy, and about 50% and 40% of the total energy of the milk is provided, respectively, from fat and lactose[27].
Anyhow, HBM composition fluctuates over time, adjusting itself to the child's necessities during growth[28]; it even depends on environmental aspects, maternal health and diet, mammary gland physiology[26], on prematurity, if it is foremilk or hindmilk, and if it is colostrum, transitional milk, or mature milk[29]. Colostrum indeed is high in protein (10%) and low in fat, and is relatively rich in immune-protective components, such as immunoglobulin A (IgA) and lactoferrin, which help prevent neonatal infections.

Carbohydrates

Carbohydrates are the major macronutrients in HMB and play a crucial role in infant nutrition since they are important from birth for the functionality of the gastrointestinal tract and for the preservation of the intestinal microbiota[26].
Lactose is the most abundant nutrient and the primary carbohydrate component in HBM, it is easily digested by nearly all babies[30]. However, enzymes' deficiency can induce several symptoms, such as lactose intolerance or malabsorption. Contrary to protein and fat, colostrum has moderately constant lactose over time[28,31]. The nutritional role of free glucose and other glucose metabolites in human milk is marginal because their levels are low.
The second substantial component, reaching nearly 20%, of carbohydrates in HBM is highly complex HMOs. They have a concentration of 12-14 g/L in mature milk and >20 g/L in colostrum[32]. On the contrary of lactose, which is easily digested, HMOs have limited digestion and they get into the colon in an unbroken form[6]. In early stages after birth, HMOs have an important role as prebiotics, stimulating the growth of certain strains of helpful bacteria, such as *Bifidobacterium infantis*, and defending the newborn from colonization by pathogenic bacteria producing short-chain fatty acids that can preclude, decreasing the intestinal pH, the growth of unhealthy gut microbiota[33]. HMOs can even inhibit neonatal diarrhea and respiratory tract infections[34,35]. Moreover some HMOs seem to be involved, as a second role, in regulating direct immune responses.

Proteins

Proteins are an important component of HBM as they are involved in cell regulation systems and they are crucial for growth, development and functioning of the human body.
Protein concentration at birth is about 14-16 g/L, but decreases to 8-10 g/L after 3-4 months of birth and further decreases to 7-8 g/L after 6 months[28,36]. It is not considerably influenced by maternal diet but increases with maternal body weight for height[27].
HBM includes over 400 different proteins with multiple functions and they can be divided into three groups: caseins, whey and mucin proteins[26,37].
Casein of HBM occurs as alpha, beta, gamma and kappa casein and is more likely digested in the form of looser micelles and softer curd by an enzyme called carboxypeptidase, which controls intestinal motility and helps in calcium absorption.
The whey/casein ratio varies according to the time of HBM. The whey/casein ratio in HBM fluctuates between 70/30 and 80/20 in early lactation and decreases to 50/50 in late lactation[28]. Typical whey proteins of HBM are alpha-lactalbumin, which constitutes 40% of the whey protein, lactoferrin, and secretory IgA[3]. Alpha-lactalbumin support the mammary glands in producing lactose, helps providing essential amino acids and absorption of minerals and trace elements in infants and has antibacterial properties[37]. Lactoferrin and lysozyme stop the spread of potentially harmful bacteria, and IgA protects gut mucosa and kills bacteria[27].
Lastly, nonprotein nitrogen, such as urea, creatinine, nucleotides, free amino acids and peptides, consists of about 20%-25% of HBM protein. Nearly 50% of this is urea nitrogen, which is used to produce nonessential amino acids[38].

Fat

Fat is the second largest macronutrient in HBM and its concentration is essential for infant growth, as a nutrient supply (nearly 40%-55% of the total energy of HBM) and for the development of the central nervous system. In addition, HBM fat is a carrier of taste and aroma[28,39]. It is tightly associated with maternal diet and weight gain during pregnancy; moreover, there are regional differences in food intake[28].
Colostrum fat concentration is about 15-20 g/L,

but this quantity gradually increases, and mature milk contains almost 40 g/L. Its levels are 2-3 times higher in hindmilk than in foremilk[40].
Breast milk includes over 200 fatty acids; however, many of these are present in very low quantities, with others predominant.
The major lipid fraction is triglycerides (about 95%-98% of total lipids). Approximately half of HBM fatty acids are saturated fatty acids, with 23% palmitic acid (C16:0) in total fatty acids. The oleic acid (18:1w9), a monounsaturated fatty acid, is one with the highest percentage (36%) in milk. HBM also contains two essential fatty acids, linoleic acid (LA) (C18:2w6) and alpha-linolenic acid (ALA) (C18:3w3), respectively 15% and 0.35%[36] involved, as precursors, in the synthesis of arachidonic acid (AA), the former, and eicosapentaenoic acid (EPA) further converted to docosahexaenoic acid (DHA), the latter. However, this phenomenon is limited in the fetus and neonate as a result of the premature enzyme activity. Therefore, the required amounts of AA and DHA are provided from the mother during pregnancy or from HBM shortly after birth[28]. In addition, LA and alpha-linolenic acid are important for inflammatory process, immune function, and infant growth.
Even short-chain fatty acids (SCFA) in HBM are an essential source of energy[41] and they are important for the development of the gastrointestinal tract[42].
Sphingomyelins, included in the HBM fat globule membrane, are in particular crucial for central nervous system myelination, and it has been described that they can improve the neurobehavioral development of low-birth weight infants[43].

MICRONUTRIENTS

HBM includes also micronutrients – vitamins and minerals – essential for growing and developing of preterm infants. They play a central role on infant neurodevelopment but also on muscular and soft tissues system; they are indispensable for several metabolic processes. Moreover, minerals and vitamins have anti-infection and anti-oxidant effects[44].
Resources required for the maturation of the central nervous system come not only from glucose but also from copper, iron, selenium, zinc. The structuring of the brain depends on lipids, proteins, and folate. Zinc and iodine are necessary for neural cell differentiation; myelination is influenced by cholesterol, vitamin B12, choline, iron, iodine, and copper. Calcium, phosphorus and magnesium are crucial for metabolic resources and for the skeletal and immune systems.
An inadequate intake of these micronutrients has been addressed as a risk factor for neurocognitive impairment and adverse long-term development[45].
There is a substantial variability in the composition of HBM from one mother to another, concerning micronutrients. These differences are influenced by maternal age, parity, lactation time, behavioral factors, nutritional status, and maternal diet[46]. In any case, HBM does not generally give sufficient amounts of micronutrients, and it must be supplemented, particularly when using a milk bank[47], since pasteurization and freezing processes alter vitamin functions.

HBM vitamins

Thiamin acts as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids; its deficiency causes infantile beriberi.
Riboflavin (vitamin B2) is involved in energy production and activity of glutathione, a free radical scavenger; its deficiency is responsible for poor growth, impaired iron absorption, dermatologic abnormalities and peripheral neuropathy.
Vitamin B6 acts as a cofactor of numerous enzymatic activities, and plays a role in amino acid metabolism, gluconeogenesis and glycolysis; its deficiency leads to neurological and behavior abnormalities, irritability and seizures.
Vitamin B12 acts as a cofactor in enzymatic reactions, which are essential for folate metabolism and DNA synthesis; its deficiency causes neurologic symptoms and developmental regression.
Folate is necessary for protein, DNA, and RNA biosynthesis. Choline is a precursor of acetylcholine and has also a role in the integrity of cell membranes, lipid and methyl group metabolism, brain development and trans-membranes signaling.
Vitamin C is an antioxidant agent and has also an important role in immunomodulation: augments antibody production, stimulates leukocytes, and synthesis of interferons. Vitamin C is more concentrated in preterm than in term milk.
Vitamin A appropriate concentration in HBM is important for ensuring infant development and for accumulating liver stores needed after weaning.
Vitamin D has an important role in infant bone growth, brain and immune system development.
Vitamin E is an antioxidant agent for the fetus and the newborn and stimulates the development of the immune system. Preterm delivery reduces breast milk concentration.
Vitamin K concentration is very low in HBM, and infants who do not receive at birth a prophylactic dose of Vitamin K, have a risk for hemorrhagic disease.

HBM minerals

Iron is a part of the hemoglobin chain and an essential component of different enzymes. Preterm infants are particularly susceptible to iron deficiency due to its effects on growth and brain development. Iron HBM concentration is very low and independent of maternal diet.

Copper is a cofactor for enzymes involved in cellular respiration, connective tissue synthesis and iron metabolism. Copper concentrations in HBM are not related to the maternal status, but depend on selenium concentrations.

Zinc deficiency in infants results in reduced growth and compromised immune function. Adequate intake of Zinc in preterm infants promotes growth and prevents diarrhea[48].

Calcium is an important constituent of bone and a messenger in cell-signaling pathways. HBM total calcium increases in the first week and then declines. On the contrary ionized calcium concentration is stable throughout lactation in HBM. Calcium HBM concentration is independent of maternal status and diet.

Phosphorus is a component of cell membranes and nucleic acids and is involved in acid-base balance, bone mineralization, energy production and cell signaling. HBM phosphorus concentration increases in the first week and then declines, like calcium.

Magnesium is an important constituent of bone and plays a role in essential metabolic reactions. Its concentrations are not affected by maternal factors.

Iodine is necessary for mental development, infant growth and survival. HBM iodine concentrations are higher in colostrum and after an initial decline, remain stable.

Selenium is a component of many proteins, like antioxidant glutathione peroxidases and deiodinases. HBM selenium concentrations are higher in colostrum than in mature milk.

BIOACTIVE FACTORS

HBM contains a variety of bioactive factors that have a profound role in preterm infant survival and health.

Immunological factors

HBM contains numerous soluble and cellular components with antimicrobial activity, resistant to intestinal proteolysis, which give protection to the premature infant and promote the maturation of the immune system.

HBM provides the only source of IgA for the first 4 weeks of life with the highest concentrations in colostrum and in the HBM of mothers who deliver early[27]. IgA comprises the first line of antigen-specific immune defense avoiding pathogenic microorganism adherence and penetration into intestinal epithelium.

HBM cytokines (TGF-β, IL-1B, IL-6, I-10, IL-12, TNF-α, IFN-γ, GM-CSF) can determine immune system shaping in the developing gastrointestinal system of the breastfed neonate[49].

Depending on the phase and stage of lactation, a variety of leukocytes are present in colostrum and mature milk and could. Leucocytes play a role in promoting the development of the neonatal immune response. Macrophages (55-60%) and neutrophils (30-40%) dominate over lymphocytes (5-10%).

HBM-derived macrophages are reported to have phagocytic activity and to secrete immunoregulatory factors. Additionally, milk macrophages have been reported to contain engulfed sIgA, which they could release on contact with bacteria in the gut.

Great interest concerns the presence of bioactive factors in BHM as lactoferrin and lysozymes, responsible for anti-infective and anti-inflammatory pathways giving a great contribution to neonatal immune system development. Lactoferrin has been shown to inhibit microbial adhesion to host cells and has direct cytotoxic effects against bacteria, viruses and fungi; it limits excessive immune responses by blocking many pro-inflammatory cytokines and promote the growth of probiotic bacteria, regulating intestinal homeostasis.

Finally, HBM has been shown to have its own unique microbiome; HBM is one of the main sources of bacteria in the intestine of a primarily breastfed infant. Thus, the HBM microbiota influences the acquisition and establishment of the intestinal microbiome during infancy and is thought to be a major factor involved in innate immunity during early life[50].

Lipid absorption

The presence in HBM of bile salt stimulated lipase (BSSL) and the specific stereoisomeric structure of the triglycerides allow better absorption of lipids than the formula.

BSSL appears to be a constitutive enzyme of the mammary glands as it is independent of the volume of milk. The characteristics of the enzyme (kinetics, enzymatic concentration, pH optimum, pH stability, and effect of salts biliary) are similar regardless of the duration of pregnancy or lactation. The activity in milk is constant and does not change during the day or according to diet.

BSSL hydrolyzes triglycerides without position specificity, the main products are free fatty acids which are absorbed more rapidly than monoglycerides in the presence of low intraduodenal concentrations of bile salts as in preterm births. This function allows BSSL to complete the hydrolysis of the diglyceride and monoglyceride produced by pancreatic and gastric lipase, respectively.

Another important role of BSSL is to hydrolyze the retinol esters because the efficient absorption of this vitamin requires the previous hydrolysis[51].

Antioxidant capacity

HBM contains numerous components with antioxidant activities, and feeding with exclusive HBM has been associated with a reduced accumulation of oxygen free radicals[52].

The antioxidants present in milk belong to several categories: 1. Enzymes (catalase, glutathione peroxidase, glutathione reductase); 2. Vitamins (vitamin A, vitamin C, vitamin E, coenzyme Q, β carotene); 3. Binding proteins (lactalbumin, lactoferrin, transferrin); 4. Enzymatic constituents (copper, zinc, selenium); 5. Growth factors (erythropoietin).

The premature newborn is particularly predisposed to the risk of oxidative damage as a consequence of both the increased postnatal production of oxygen radicals and the immaturity of the protective systems in limiting the reactions they induce. The excess production of free radicals is a frequent occurrence in the preterm infant and can be caused by various metabolic conditions, the most important of which are ischemia-reperfusion, phagocytic activation, the arachidonic acid cascade, metabolism of catecholamines, and mitochondrial metabolism[53].

Growth factors

HBM contains numerous growth factors acting on the growth, development, functions and maturation of the epithelium, the immune system, the nervous system, and the gastrointestinal tract[1-7]. These bioactive components belong to five categories: 1. Hormones: prolactin, oxytocin, adrenocorticotropic hormone, thyroid stimulating hormone, thyroxine, cortisol, insulin, erythropoietin; 2. Growth factors: epithelial growth factor (EGF), insulin-like growth factor I (IGF-1), hepatocyte growth factor (HGF), lactoferrin, polyamines; 3. Neuropeptides: neurotensin, somatostatin, intestinal vasoactive peptide (VIP); 4. Anti-inflammatory agents: antioxidant agents, enzymes that catalyze the destruction of inflammatory mediators, antiproliferative agents, anti-inflammatory cytokines; 5. Immunomodulatory agents: nucleotides, secretory IgA, prolactin, cytokines[54].

STEM CELLS

HBM represents a precious source of stem cells recently under research for possible therapeutic opportunities. HM-derived mesenchymal stem cells have the potential to be "reprogrammed" to generate a wide range of human tissues[55].

In vitro studies showed the ability to differentiate into adipogenic, chondrogenic, and osteogenic lines, hepatic cells, and pancreatic, nervous, and cardiomiocytic cell lines. It also seems that among stem cells ingested by newborns each day, some can pass from HBM through the neonatal gut and migrate into the brain and other organs; there, they can persist and proliferate as in a micro-chimerism, influencing the development of the involved organs.

The presence of HBM stem cells shows significant potential use in research and medical therapies as a treatment option, especially in neural damage and disorder[56].

EXPRESSED BREAST MILK AND DONOR HUMAN MILK IN PRETERM INFANTS

Breastfeeding is considered the ideal and preferred feeding for all infants, but in the case of prematurity, when breastfeeding is not possible or difficult, expressed breast milk (EBM) is the best way to provide enteral nutrition.

The process of expressing needs proper expressing equipment and a milk bottle, transferring EBM into containers for storage, refrigerating or freezing, thawing, and warming EBM, and, finally, the delivery of EBM to the infant. HBM can also be hand-expressed. If there is no delay in infants feeding after expressing, there is little to no necessity for storage, compared to the mother who makes a store for later use, requiring long-term freezing. Once refrigeration or freezing is involved in the process, subsequent defrosting and/or rewarming become involved. Each step in this process has the potential for bacterial contamination, and storing and warming may potentially degrade valuable properties of EBM, so mothers must be adequately trained in the expressing process[57].

Different scientific societies, such as AAP[1] and ESPGHAN[13] as well as Milan EMBA/ESPGHAN/AAP Joint Meeting Consensus[58] recommended that a mother's own milk (MOM) should be the first choice in the feeding of preterm infants. When MOM is not available, donor human milk (DHM) should be the alternative, and only when neither MOM nor DHM is available, preterm formula (PF) should be used.

DHM undergoes pasteurization using the Holder process, which requires heating bottles of milk in a water bath at 62.5°C for 30 min followed by rapid cooling. This is the most commonly used method of pasteurization and it is believed a good compromise between microbiological safety and nutritional

and biological quality of HBM. Indeed, heating treatment and storage of HBM reduce anti-infective properties, cellular components, growth factors, and nutrients, which may reduce its health advantages[59,60]. However, the beneficial effects of pasteurized DHM seem to remain significant, and DHM is greatly preferable to formula milk[14].

Considering the nutritional properties, HBM – and even more so DHM – does not meet the nutritional needs of preterm infants, requiring a specific fortification regimen to optimize growth[47]. HBM fortification is recommended for all preterm infants with birthweight <1800 grams[47].

HBM fortification allows the addition of proteins, energy, minerals, trace elements, vitamins and electrolytes, to meet the nutritional needs of the preterm infant. Fortification should start with standard fortification and if infant growth is not appropriate, individualized fortification is suitable[61]. The standard fortification consists of adding a fixed amount of multi-nutrient fortifier per 100 mL of HBM to achieve the recommended nutrient intake.

Individualized fortification can be targeted or adjustable. Targeted fortification is based on HBM analysis and then adding macronutrients to standard fortification to achieve recommended intakes[62,63]. Adjustable fortification is based on infant blood urea nitrogen measurements and then protein intake is adjusted based on blood urea nitrogen levels[64]. Both are suitable depending on the individual experience and expertise.

BENEFITS OF BREAST MILK IN PRETERM INFANTS

Role of HBM against infections and necrotizing enterocolitis

Infections are common among preterm infants during their hospital stay[65]. NEC, which affects the gastrointestinal (GI) tract of preterm infants, is together with infections, one of the major causes of morbidity and mortality in neonatal intensive care units (NICU)[66].

Although the exact pathogenesis of NEC is still debated and under study, it is known that higher HBM intake is associated with lower rates of neonatal NEC, highlighting the protective role of components present in HBM. HBM intake in the first few days of life is associated with reduced infections, morbidity, and mortality in very low birth weight (VLBW) infants[12,67], and it has been shown to contain high concentrations of beneficial immune mediators that provide bacterial and anti-inflammatory protection and stimulate the growth of the GI tract[50,68].

The main factors are commensal microbes, HMOs, immunoglobulins, lactoferrin[69].

The microbiome of HBM is a major source of bacteria in the gut of a predominantly breastfed infant and help shape the newborn gut microbial community[50]. The most commonly reported genera in HBM include *Staphylococcus, Streptococcus, Lactobacillus, Enterococcus, Bifidobacterium, Propionibacterium,* and the *Enterobacteriaceae* family[70]. Among all, *Bifidobacterium* is the one most strongly associated with reduced risk of NEC. Specifically, *Bifidobacterium longum* in immature human enterocytes induces a reduction in the production of pro-inflammatory mediators IL-8 and IL-6[71].

HMOs are prebiotic substances found in great abundance in HBM and possess several immunomodulatory protective mechanisms on intestinal tissue that shape its integrity[72].

HMOs possess structures that resemble cell surface glycans targeted by enteric pathogens. This similarity allows HMOs to prevent the adhesion of enteric pathogens, including *Campylobacter jejuni* and *Rotavirus*, to target cells in the intestinal epithelium. In addition, HBM glycans with a sialic acid moiety also can bind pathogenic organisms, including *Escherichia coli* and *Pseudomonas aeruginosa*[73].

HMO 2-fucosyllactose has been identified as the most abundant HMO in HBM. A preclinical study in newborn mice showed that supplementation with HMO 2-fucosyllactose reduced the severity of experimental NEC with decreased gene expression of pro-inflammatory cytokines and protected the integrity of the small intestine. In addition, a higher concentration of HMO disialylacto-N-tetraose in HBM has been shown to be associated with a lower risk of developing NEC in infants[72].

HBM is the only source of secretory IgA (sIgA) in the newborn. They help to preserve an adequate microbiota, promote tolerance and influence the development of the immune system[74].

Lactoferrin is an iron-binding glycoprotein that is abundant in HBM, with maximum concentrations in colostrum, and preterm milk tends to maintain higher levels of lactoferrin over time. It inhibits microbial adhesion to host cells and has direct cytotoxic effects against pathogens via lactoferricin formation. Concerning inflammation, lactoferricin allows excessive immune responses by blocking many pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-8, and by suppressing free radical activity[75].

Lactoferrin supplementation in infants has shown promise, and in recent years it has become the subject of many studies to evaluate its role in reducing the rates of NEC and late-onset sepsis in infants[76].

Still much to be discovered about the multifactorial etiology of NEC, but certain is that HBM components in their collective teamwork, rather than individual roles, protect against NEC.

During the first days after preterm birth, preterm infants may receive DHM or PF due to maternal milk production delay or insufficiency. Several studies[46,65,77-79] have shown that increased HBM intake, whether MOM or DHM, was associated with reduced risk of infection/NEC. Moreover, breastfed preterm infants have lower rates of intestinal infections than formula-fed babies, mainly due to the anti-infectious properties of HBM[77,79].

Beneficial role of HBM in the prevention/ treatment of bronchopulmonary dysplasia

BPD is a severe chronic lung illness that affects premature infants. Improved neonatal care, the development of non-invasive ventilation techniques and the use of antenatal steroids have increased the survival of preterm infants, but the incidence of BPD remains high[80].

Currently, there are several BPD treatment strategies, starting with delivery room management, and encompassing non-invasive mechanical ventilation, steroids, diuretics, bronchodilators, and caffeine. Furthermore, dietary support, infection management, and vasodilators are beneficial as therapy for BPD.

Optimal nutritional support is considered a cornerstone in the prevention/treatment of BPD[81,82].

In 2018, a systematic review and meta-analysis on the effects of DHM on BPD was published[83]. The authors identified 18 studies, of which 7 studies[9,11,84-88] were RCTs and 11 studies[19,89-98] were observational. Meta-analysis of 3 RCTs, which reported on the rate of oxygen-dependence at 36 weeks of PMA (BPD36), could not demonstrate that supplementation of MOM with DHM had a significant effect on BPD36 risk, when compared to supplementation with PF. On the other hand, a meta-analysis of RCTs found that supplementation with DHM significantly reduced the mean days of mechanical ventilation. Meta-analysis of 8 observational studies, which compared infants receiving MOM supplemented with DHM to infants receiving MOM supplemented with PF, showed a protective effect of DHM supplementation on BPD36 and on days of mechanical ventilation, but not on days on oxygen. Additionally, an exclusive HBM diet (i.e., MOM and/or DHM and DHM-derived fortifier) significantly reduced the risk of BPD36, when compared to a diet that included PF and/or bovine milk-based fortifier. Feeding infants raw MOM, compared to feeding them pasteurized MOM, protected against BPD36. The authors concluded that the data analyzed suggest that DHM could protect against BPD in very preterm/VLBW infants. However, the process of pasteurization appeared to reduce the beneficial properties of HBM on BPD development.

Subsequently, two more systematic reviews[99,100] were conducted and confirmed that the protective effects of HBM (MOM and/or DHM) on BPD are only observed in a meta-analysis of observational studies. Using the GRADE-system[101], the authors of these meta-analyses consider the evidence to be inconclusive.

All these systematic reviews[99,100] did not focus on the role of exclusive MOM *vs.* PF and did not study the effect of MOM separately from that of DHM.

Therefore, in 2019, Villamor-Martínez et al[102] conducted a systematic review and meta-analysis on the association between MOM/PF feeding and BPD development, without including data on DHM. These authors identified 15 studies[9,69,90,97,98,103-112] to include in the meta-analysis. Since the random allocation of infants to a group receiving PF instead of MOM is not ethical, these were only observational studies. The results of this meta-analysis showed that MOM reduced the risk of developing BPD but only when used as an exclusive diet. In contrast, a meta-analysis could not find significant changes in BPD risk when comparing infants fed mainly with MOM with those fed mainly with PF, or when comparing any MOM vs. exclusive PF. The protective effects of exclusive MOM were not affected by differences in gestational age. The results of the meta-analysis may indicate that the beneficial effects of exclusive MOM may be dose-dependent. Two previous case-control studies[104,113], not included in the meta-analysis, showed a reduction in BPD associated with increasing amounts of HBM. Fonseca et al[104] reported that a minimum amount of HBM (7 mL/kg/day) in the first 42 days was associated with a reduced incidence of BPD, and Patel et al[113] have shown a 9.5% reduction in the risk of BPD for each 10% increase in MOM received from birth to 36 weeks PMA. This may generate a reduction in BPD risk up to 63% when an exclusive MOM diet is compared with an exclusive PF diet.

There may be various explanations for how the MOM acts in influencing the reduction in the incidence of BPD. In very preterm infants, BPD development is characterized by the arrest in the alveologenesis

and vasculogenesis of the lung. Other stimuli can act on the immature lung: prenatally, when chorioamnionitis occurs, the overwhelming inflammatory cascade may further interfere with lung development; postnatally, the intensive treatments needed add an inflammatory stimulus, leading to the establishment of BPD. Moreover, the incidence of BPD increases secondary to infections and inadequate nutrition. Based on these pathogenetic considerations, MOM can act thanks to nutritional and bioactive components, counteracting oxidative stress, inflammation, and nutritional flaws[102]. Moreover, MOM is involved in the reduction of NEC and late-onset sepsis risks that are related to the BPD risk themselves.

Although failure to thrive is a known risk factor for the development of BPD[114], and lower weight gain is associated with an increased risk of BPD, this does not seem to apply to the reduced growth because of breastmilk feedings. This result emerged in the study of Spiegler et al[18]. These authors observed a reduced rate of BPD in the group of exclusively breastmilk-fed infants. As a consequence, also these authors concluded that they do not know whether more weight gain because of formula feeding compared with fortified breastmilk feeding during the neonatal course in the hospital is desirable or not[18].

Recently, Yang et al[115] published a review in which they examined the role of oxidative stress in the pathogenesis of BPD and the impact of antioxidants present in HBM on the prevention and treatment of BPD. HBM contains various antioxidants factors (glutathione, superoxide dismutase, glutathione peroxidase, short-chain fatty acids, unique HMOs, vitamins, phytochemicals, probiotics, melatonin, milk fat globule membrane) which could counteract the oxidative stress effects on normal lung development: hyperoxia causes poor lung development of the immature lungs of preterm infants, increases death of alveolar epithelial cells, and triggers pulmonary vascular remodeling. In the review, the authors examined several active compounds in HBM to define how they may ameliorate BPD oxidative stress in lung development. The mechanisms analyzed include: direct secretion of antioxidant substances able to clear free radicals and to prevent their accumulation; metal chelation; the enhancement of the antioxidant signaling pathway; the interaction with the intestinal flora; the inhibition of lipid peroxidation, and anti-inflammatory and anti-infection properties. Anyway, research about HBM antioxidants and their effects on BPD is still limited based on ethical factors and, as a consequence, only a few RCTs have been conducted. So, much research in this territory is required.

HBM and neurological outcomes

Inadequate nutrition during the critical period of brain development of preterm newborns could lead to neurocognitive impairments and permanently negative consequences[47]. Premature newborns are particularly vulnerable compared to full-term newborns as they are exposed early to the external environment in a fundamental moment for brain development. In this context, nutritional factors, including HBM, have been identified as protective[23]. Current evidence suggests that HBM is the best food for both term and preterm newborns conferring health benefits in short and long term. In particular, HBM feeding improves cognitive outcomes in preterm infants, possibly by directly protecting the preterm brain from injury and/or reducing adverse effects of injury on development[116].

First, HBM intake is associated with a lower risk of neonatal infection and NEC which are common comorbidities among preterm infants during their hospital stay[67]. These conditions can lead to systemic inflammation which, by activating the microglia in the central nervous system, can damage the oligodendrocytes and thus interfere with the development of the white matter. This has been associated with long-term changes in the brain microstructure and lower intelligence quotient [67]. Ultimately, the positive effect of HBM on neurocognitive development could be partly explained by its preventive effect on the onset of infections and NEC.

Second, HBM contains bioactive components capable of acting directly on the development and protection of the central nervous system[117]. In particular, HBM is rich in long-chain polyunsaturated fatty acids (LC-PUFAs) which are normally synthesized from LA ω6 and ALA ω3, components found exclusively in HBM. These PUFAs are essential for brain development, as brain growth continues during the first weeks of life, especially for preterm infants, the intake of LA and ALA is fundamental[46]. Moreover, HBM contains a high concentration of HMOs, which can be digested or undigested. The digestion of HMOs leads to the formation of monosaccharides, such as fucose and sialic acid, that are readily used in the synthesis of brain glycolipids, such as gangliosides, molecules of particular biological importance, which intervene in the maturation processes of the central nervous system[46]. In addition, HBM contains other nutrients such as DHA, choline, and lactoferrin that play an essential role in normal brain development and are lacking in PF[23,118].

Third, the use of HBM as the main nutrient is a marker of a greater parent presence and engagement in the NICU. The bond itself between infant and parent, such as through skin-to-skin contact, is associated with better neurological outcomes[23,119].

However, HBM does not provide sufficient nutrition for the VLBW infants leading to slow growth with the risk of neurocognitive impairments. To prevent extrauterine growth retardation, associated with poor neurocognitive outcome, nutrient fortification of HBM is necessary, mostly concerning protein intake[47].

Finally, in the last decade brain magnetic resonance imaging (MRI) has been used to investigate the influence of BHM during a vulnerable period of rapid brain development in very preterm infants. A recent review[23] aimed to investigate the presence of typical brain MRI findings, such as punctate lesions in the white matter, altered microstructure, reduced volumes of several brain regions, and decreased cortical surface area in relation to the HBM feeding. The review revealed that, in the preterm population, exposure to HBM is associated with favorable brain development outcomes, including more mature and connected cerebral white matter, less volume of diffuse white matter abnormality, less dysmaturation across multiple brain regions, including deep nuclear gray matter, hippocampus, amygdala and cerebellum, and larger regional brain volumes[23].

SUPPORT BREASTFEEDING IN NICU

Breastfeeding, especially exclusive breastfeeding, is potentially important for promoting the health of both normal and low birthweight infants. The World Health Organization and the United Nations Children's Fund recommend and propel the policy of exclusively breastfeeding for the first 6 months of life[120,121].

The provision of breastfeeding support in the NICU may assist a mother to develop a milk supply for her preterm infant. HBM offers unique benefits to this highly vulnerable population. Breastfeeding influences actual supportive behaviors and provides more consistent messages to mothers during infant admission.

Feeding at the breast for preterm infants can be conceptualized as a series of steps, including: breast pump use at the infant's bedside; skin-to-skin holding; tasting HBM (suckling after breast pump use to remove all or some of the HBM); and finally consuming full feedings at the breast. There are no data to indicate that infants must attain a threshold weight or gestational age to begin tasting HBM, and several studies reveal that preterm infants remain more physiologically stable during breast than bottle feeding.

The maintenance of lactation, usually measured by whether the infant is still receiving partial or exclusive HBM at the time of NICU discharge, remains a global problem with only a handful of best practices demonstrated to be effective.

All available evidence indicates that the NICU staff should prioritize the first 14 days post-birth, using proactive interventions to achieve maternal HBM volume. A NICU toolkit for managing these early lactation phases has been described and includes a user-friendly pumping diary (My Mom Pumps for Me!), the Coming to Volume Assessment Tool and a weekly maternal feeding goals interview tool (My Plans for Feeding my Baby at NICU discharge) that assures mothers' individual HBM feeding goals are monitored and supported[122].

Lake et al[123] theorized that better NICU nursing characteristics, as measured by nurses' qualifications (education and years of experience), staffing level, and the nursing practice environment would result in improved breastfeeding support in the NICU, where the likely causal path was through better nursing care.

Lactation consultant (LC) availability across NICUs is not as well described in the literature; however, LCs dedicated to the NICU have been shown to improve both initiation and duration rates of breastfeeding in infants who have experienced an NICU stay.

Hallowell et al used regression models to examine the importance of 2 staffing variables, the PES-NWI subscale measure (staffing and resource adequacy) and the acuity-adjusted nurse-to-patient ratio, and found that both staffing variables were significantly associated with breastfeeding support, where better staffing was associated with a higher percentage of infants receiving breastfeeding support in the NICU.

The benefits of HBM have been well described; therefore, strategies to support the use of HBM and breastfeeding should be a priority. Exploration of the activities associated with breastfeeding support in the NICU as determined by nurses and mothers, such as communicating with mothers to develop an individualized feeding plan, assisting with direct breastfeeding or providing pump supplies, and evidence-based instruction, has been demonstrated to improve care and patient satisfaction[124].

A handful of multi-institutional quality initiatives have demonstrated higher rates of HBM provision at NICU discharge by adopting multidisciplinary infant nutrition and lactation teams that incorporate clear protocols for premature infants.

Most studies addressing barriers to the initiation and maintenance of lactation in mothers of preterm infants have focused primarily on motivational and behavioral interventions such as skin-to-skin care, patterns of breast pump use and models of support. However, many breast pump-dependent mothers of preterm

infants have chronic health problems or pregnancy and birth complications that impact lactation outcomes and that may be unresponsive to current behavioral and motivational interventions. These complications, which include, preterm birth, cesarean delivery and preeclampsia, as well as prolonged bed rest and medications to treat these complications, impact the hormonal processes that regulate secretory differentiation and early lactation. However, because preterm infants require so little HBM volume in the early post-birth period, these maternal HBM volume problems can easily go unrecognized for days or weeks, which impact lactation outcomes for breast pump-dependent mothers of preterm infants, who are often ill themselves[119].

Another research priority is addressing the mothers' consistent reports about the dislike and inconvenience of breast pump use. Mothers of preterm infants are completely breast pump dependent, meaning that the breast pump regulates the lactation processes of HBM removal and mammary gland stimulation, which are critical to continued HBM production. Thus, a critical research priority for the maintenance of lactation in mothers of preterm infants is the improvement in the design of breast pumps and breast pump supplies so that they optimize efficiency and convenience, consistent with mothers' concerns.

CONCLUSIONS

Based on the current evidence, we can conclude that breastfeeding, thanks to the unique properties of HBM, may lead to several health benefits in preterm infants, including the improvement of neurodevelopmental outcomes. Further investigations are needed to understand the mechanisms and pathways underlying beneficial associations of HBM with neurodevelopmental outcomes, identifying specific HBM bioactive components with neuroprotective or neurorestorative potential. Exclusive MOM seems to reduce the risk of developing BPD and breastfeeding can ameliorate the effects of BPD. Anyway, to confirm the beneficial effects of MOM on BPD and to define the mechanisms implicated in the action of MOM in the pathogenesis of BPD, further studies are needed. These should be adequately powered to detect changes in BPD rates and adjusted for the different characteristics of infants who receive MOM and PF. Finally, HBM confers protection against NEC and infections, and decreases the overall mortality. For these reasons, promotion and support of HBM feeding since the immediate post-delivery should be considered a priority in preterm infants' care.

Conflict of Interest

The authors declare that they have no conflict of interest.

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