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Review

Breastfeeding the preterm infant

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Abstract

Due to its peculiar nutritional and non-nutritional contents, which include long-chain polyunsatured fatty acids (LC-PUFA), prebiotics, immunological factors, hormones and growth factors, breast milk shows significant advantages over infant formulas in nourishing preterm infants.

Better neurocognitive outcomes, which are reported to persist far beyond the early childhood, have been largely observed in breastfed preterm infants; a role of LC-PUFA in promoting neural and retinal development is assumed.

As far as the gastrointestinal tract is concerned, several evidences have reported a dose-related reduction in NEC incidence among preterm infants fed on human milk. Moreover, the higher amount of immunological factors as secretory IgA within preterm breast milk might play a remarkable role in reducing the overall infections.

Despite breastfeeding in preterm infants is generally linked with lowered growth rates which might potentially affect neurocognitive outcomes, the beneficial effects of human milk on neurodevelopment prevail.

Fortified human milk might better fulfill the particular nutritional needs of preterm infants. However, as breast milk fortification is difficult to carry out after the achievement of full oral feeding, some concerns on the nutritional adequacy of exclusive breastfeeding during hospitalization as well as after discharge have been raised.

Finally, breastfeeding also entails maternal psychological beneficial effects, as promoting the motherhood process and the mother-child relationship, which could be undermined in those women experiencing preterm delivery.

Keywords

Human milk, preterm infants, neurodevelopmental outcome, NEC, growth, maternal psychology.

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Introduction

Preterm birth still represents a major cause of mortality, morbidity [1, 2] and poor long-term outcome [3-5].

Due to its peculiar nutritional and non-nutritional contents, which include long-chain polyunsatured fatty acids (LC-PUFA), prebiotics, immunological factors, hormones and growth factors, breast milk shows significant advantages over infant formulas in decreasing the rate of neonatal mortality [6, 7] and in determining better short and long-term health outcomes [8]. Hence, there is general agreement in recognizing breastfeeding as being superior to formula feeding for the enteral nutrition of preterm or very low birth weight infants [9, 10].

Breast milk varies its composition in relation to several factors, thereby acting as a biological tissue. Time after delivery is the major determinant of breast milk contents. Colostrum, the fluid produced within the first 24-48 hours after delivery, is markedly different from both transitional and mature milk, exhibiting a higher density of nutrient, proteins and immunoglobulin levels. Preterm delivery plays as well a remarkable role on breast milk composition [11], especially within the first 4 weeks of lactation. Furthermore, higher levels of long-chain polyunsatured fatty acids (LCPUFAs), protein, electrolytes and micronutrients in preterm breast milk are reported [12, 13].

Hereunder we provide an updated overview of the evidences regarding the main beneficial effects reported in association with breastfeeding in the preterm population.

Neurodevelopmental outcomes

Significant beneficial effects of breast milk on developmental outcomes have been largely established [14-21] in the preterm population, which is known to be at higher risk of long term disability and cognitive impairment [22, 23].

An 8-point higher mental development index score at the Bayley Scales was firstly disclosed by Lucas et al. [14] in preterm infants fed on breast milk compared to those formula-fed at 18 months of corrected age (CA). When evaluated at 7.5-8 years follow-up, the same breastfed infants showed better IQ scores [15], thereby supporting the hypothesis of long-term beneficial effects. Interestingly, a major part of this cohort was followed up to adolescence: a significant association between higher verbal intelligent quotients and major percentages of expressed human milk (EHM) received in the NICU was found out. Moreover, EHM volumes showed a positive correlation with total brain volumes, especially of white matter, evaluated by magnetic resonance imaging (MRI) [16].

Ameliorative effects of human milk on neurodevelopmental outcome have been recently confirmed by Vohr et al. in large trial on extremely low birth weight (ELBW) infants who were breastfed during their NICU stay. Among these, however, the 77% stopped receiving breast milk at discharge. The breastfed group revealed significantly higher scores at the Bayley Scales of Infant Development II (BSID II) assessed at 18 months of CA follow-up [21]; a positive effect in motor and mental development was confirmed even after adjustment for confounder factors. Higher scores at developmental and behavior tests in these breastfed infants still persisted at 30 months CA [17], sustaining the hypothesis that benefits of breast milk provision during hospitalization may act far beyond the neonatal period.

Better values of developmental quotient (DQ) at 2 years follow up were additionally perceived by the EPIPAGE study group in a large cohort of very preterm babies who were breastfed at discharge [18].

Interestingly, the amount of the neuro-developmental improvements was found to have a positive correlation with the overall length of human milk feeding [19].

Thus, as the risk of abnormal sensory-neural development is significantly increased after premature birth, breast milk provision should be strongly encouraged in the preterm population.

A role of LCPUFA omega-3 fatty acid docosahexaenoic acid (DHA) and the omega-6 fatty acid arachidonic acid (AA) in determining better neurodevelopmental outcomes in breastfed infants is assumed [24-29], due to their involvement in the structural composition of retinal and neuronal membranes. With regard to preterm infants, relevant ameliorative effects on neurodevelopmental and visual outcomes have been described [24, 27, 29, 30]. Particularly, an improved retinal rod function was previously observed by Uauy et al. in association with breastfeeding and LC-PUFA supplementation [27], while we have firstly disclosed an enhanced maturation of visual evoked potentials in both breastfed infants and those on LC-PUFA supplemented formula [24]. Better visual acuity, evaluated with the Teller Acuity Card procedure, was found as well in preterm infants fed formulas supplemented with marine oil, which is rich in DHA [29].

Due to their poorer enzymatic activities, preterm babies are particularly vulnerable to LC-PUFA deficiency; as a consequence, dietary intake of LC-PUFA is crucial for this specific population to support the ongoing structural development of brain and retinal membranes.

According to these beneficial effects of LCPUFAs, which are not contained in bovine milk, the supplementation of infant formulas with a proportion of DHA between 0.2% and 0.5% of fatty acids and amounts of AA being at least equal to those of DHA has been recommended [31]. However, as shown in two recent meta-analyses of clinical trials [32, 33] LC-PUFA supplemented formula failed to demonstrate clear beneficial effects on neurodevelopment in preterm infants when compared to standard formulas, thereby supporting the advantageous role of breast milk consumption.

Infectious diseases, NEC and intestinal maturation

As far as non-nutritive constituents of breast milk are concerned, peculiar immunological properties are guaranteed by the provision of secretory IgA, oligosaccharides, leukocytes, lysozyme, interferon-γ, lactoferrin, nucleotides, cytokines [34], which play a key role in promoting gut maturation and preventing invasive infections [35-37].

Higher levels of secretory IgA, the main immunoglobulin contained in human milk, are found in preterm milk [38, 39]. Due to their immunologic immaturity, preterm infants are particularly predisposed to develop infections; therefore, the host defense factors provided through breast milk are fundamental for this specific population. As a result, a significantly lower rate of overall infections (late onset sepsis, meningitis, upper respiratory tract infections, urinary infections, diarrhea), as well as a reduction of upper respiratory symptoms during the first year of life [40], are observed in breastfed preterm infants when compared to those formula-fed [6, 41-43]. Additionally, breastfed infants had fewer hospital readmissions for illness up to 2.5 years after discharge [17, 19, 44].

Neonatal infections are known to entail poorer neurodevelopmental outcome. Hence, a possible role of a lowered rate of infective events in determining an improved neurodevelopment in human milk-fed preterms infants might be speculated [44].

The maturation of gastrointestinal tract in preterm infants is still dynamically developing.

Necrotizing enterocolitis (NEC) represents the most frightful gastrointestinal complication of prematurity, as it is burdened by a high rate of mortality.

Even though its pathogenesis is still not completely understood, NEC might ensue from an abnormal disproportion between bacterial intestinal colonization, immunological functions and inflammation, which is commonly observed in the preterm population. Preterm infants are more likely to develop a pathogenic intestinal microbiota [45]. Several antimicrobial factors contained in human milk, as immunoglobulins, cytokines, lactoferrin, and glycoproteins with antiadhesive capacity may contribute to hinder gut colonization by pathogenic organisms [34]. Additionally, the high levels of fructo-oligosaccharides within breast milk may promote intestinal colonization by Bifidobacteria sp., therefore inhibiting the pathogenic bacterial overgrowth [46] which is known to be involved in NEC pathogenesis [47].

NEC generally occurs after the beginning of enteral nutrition [48]. Indeed, preterm infant have an excessive inflammatory response to luminal stimuli, which can lead to develop gut injury. Recently, Penn et al. [49] performed an in vitro comparison between the cytotoxic effects of infant formula versus fresh breast milk on the intestinal mucosa. Due to higher levels of free fatty acids (FFA) resulting from the digestive process, digested infant formula was found to provoke a major cytotoxicity. Given the enhanced intestinal permeability of preterm infants, the absorption of cytotoxic molecules might represent a relevant trigger for intestinal inflammation and subsequent ischemia and necrosis. Hence, these findings chiefly support the protective role of breast milk towards NEC development. Furthermore, a significant, dose-related reduction of intestinal permeability has been observed in preterm infants predominantly fed on human milk [50].

One of the major clinical trials comparing the effect of breast and donor milk versus both term and preterm formula on NEC development dates back on 1990, when Lucas et al. [36] disclosed a 10-fold increase of NEC incidence in formula-fed preterm infants; the higher was the dietary intake of human milk, the lower was the risk for NEC development.

These preliminary findings have been subsequently confirmed by a large number of studies [6, 7, 35, 51-54]. Moreover, several evidences supporting the dose-response relationship between HM intake and NEC risk have been provided [43, 52, 53]. Although exclusive HM feeding was found to be the most effective [7, 51, 52], a significant protecting effect towards NEC development was observed even in those infants receiving at least 50% of human milk [52].

With regard to donor milk, the amount of immunoprotective factors may be compromised by pasteurization. However, two recent meta-analyses of data from randomized controlled trials have showed that, when compared to formula feeding, donor human milk is likewise effective in reducing NEC incidence in the preterm population [55, 56].

Due to the immaturity of gastrointestinal functions, preterm infants frequently develop an impaired feeding tolerance. As a consequence, days to achieve full enteral feeding, as well as the duration of parenteral nutrition and central line access, are often increased.

HM contains specific bioactive agents, as growth factors and hormones, that may promote the functional maturation of gastrointestinal tract. As previously ascertained in several clinical trials [21, 53, 56-58], lower rates of feeding intolerance and shorter time to gain full feeding were observed in preterm babies fed on human milk when compared with those formula-fed. The enhancement of gastric emptying, which has been reported in breastfed infants [53, 59], might partially explain the underlying mechanisms [48]. The length of both parenteral nutrition and central line access was likewise decreased [58]; a possible positive role of these findings in reducing the risk for late-onset sepsis might be postulated.

Moreover, the enzymatic activity of lipases or proteases is frequently blunted in the preterm population. Digestive enzymes contained within breast milk may allow to supply this lack, improving the digestion and absorption of nutrient and thereby leading to better feeding toleration [60, 61].

Growth and nutritional adequacy of human milk

Although the nutrient concentrations of preterm breast milk are reported to be either the same as or higher than in term milk, concerns regarding its adequacy to support the nutritional needs of preterm and VLBW infant have been raised [8].

When compared with term infants, preterm babies have limited nutrient reserves at birth. Moreover, they undergo a variety of metabolic and physiological stresses that contribute to boost their nutritional requirements. Recommended nutrient needs for preterm infants were assumed on the dogmatic concept that the optimal rate of postnatal growth should be almost the same as that of normal, uncompromised fetuses of an equivalent postmenstrual age [62]. In practice, however, target levels of nutrient intakes are rarely achieved and a relevant deficit in energy, protein, mineral and other nutrient is often accrued during NICU stay. Indeed, it has been estimated that almost 50% of preterm infants develop an extra-uterine growth restriction [63] unrelated to the previous fetal growth trend.

Breastfeeding during hospitalization and at time of discharge is shown to be associated with poorer early weight gain as well as with reduced length and head circumference growth [20, 53, 64, 65].

Worse neurodevelopmental outcome and later cognitive dysfunction have been observed in preterm infants with suboptimal early postnatal nutrition [66]. Lower neurocognitive scores and higher rates of cerebral palsy, evaluated in a large cohort of extremely preterm infants at 18 to 22 months of corrected age, were likewise found to be linked with an impaired growth during NICU hospitalization. [67]. Furthermore, a relevant association between poor head growth, higher risks of neurodevelopmental impairment and worse cognitive outcomes in later childhood was previously noticed in children born prematurely [68].

Hence, on the basis of these results, the lowered growth rates observed in breastfed preterm infants might potentially undermine the neurocognitive development. However, some reassuring evidences have been recently disclosed in two independent cohorts of preterm infants. Although these breastfed infants had a suboptimal weight gain during hospitalization, breast feeding at discharge resulted in better neurodevelopmental assessments at 2 and 5 years of age [20]. Indeed, this paradoxical observation might encourage the indication to breastfeed preterm infants during NICU stay and at discharge.

Breastfed preterm infants frequently accumulate nutritional deficits, especially in protein, calcium and phosphate [69]. The latters, particularly, might entail higher risks of low bone mineralization, metabolic bone disease and subsequent poor skeletal growth [65].

It has been largely shown that human milk fortification promotes short-term neonatal growth [53, 64, 70, 71]. Indeed, breast milk supplementation with nutrient fortifiers is a valid practice to ensure protein supply adequate for preterm infants growth as well as minerals such as calcium and phosphorus to enhance an appropriate bone mineralization [53].

During NICU stay, preterm infants generally received their own mother's milk via a gastric tube; thus, human milk fortification is easy to carry out. However, once the baby can suckle the breast or at the hospital discharge, the fortification of human milk is often discontinued, as it might interfere with the breastfeeding practice [12, 72]. As a consequence, the risk of nutritional deficit is potentially enhanced [73], thereby casting some doubts on the nutritive reliability of exclusive breastfeeding in preterm infants after hospital discharge.

Breastfeeding: the programming effects

Evidence regarding the effects of early nutrition on biological programming, which may be involved in long-term outcomes, is increasing [74]. A lowered incidence of obesity, hypertension, leptin resistance and insulin resistance, has been observed in premature infants fed on human milk [74-78]. Particularly, Singhal et al. [76-78] performed a long-term study, enrolling premature infants into two different arms depending on whether they were fed on human milk or on formula. A comparison between preterm infants fed either breast milk or donor human milk as well as preterm or term formula was carried out up to adolescence. Infants on the high nutrient density diet, which was provided by formula feeding, showed a more rapid growth during the neonatal period; as far as long-term outcomes, however, they experienced higher rates of low-density lipoprotein cholesterol, leptin resistance, insulin resistance and hypertension, whereas the group fed on human milk showed dose-response beneficial effects, despite a lowered rate of growth noticed during the neonatal age.

The linkage between breastfeeding and the development of atopic diseases is still a controversial issue. With regard to term infants, whilst previous evidences disclosed a protective effect of breastfeeding during the first 3 months of life on the incidence of both atopic dermatitis [79] and asthma [80] in children with a family history of atopy, the recent PROBIT study confirmed the efficacy of breastfeeding in reducing the rates of atopic eczema but not of other atopic diseases (i.e. asthma, hay fever) [81].

Data regarding preterm infants, however, are few. To the best of our knowledge, the only prospective randomized study comparing banked human milk versus cow milk formula was carried out in 1990 by Lucas et al. [82]. In this research, formula feeding resulted in an increased risk of atopic eczema and cow milk's allergy at 18 months of life in the subgroup of neonates with atopic heredity.

What about mothers? Psychological aspects of breastfeeding

Additionally to the well-known beneficial effects exerted on the babies, breastfeeding plays a chief part in the transitional process to motherhood [83].

The synthesis of milk components from the mammary glands of pregnant women begins before 22 weeks of gestation, so that colostrum is produced even in case of very premature delivery [84]. Mothers of preterm infants, however, face significant difficulties in establishing a proper milk expression, as a probable consequence of several negative influencing factors. Among these, the main are represented by inadequacy of nipple stimulation, failure of breast emptying [84, 85], provision of specific medications which might interfere with the lactation process, emotional stress that may negatively interfere with oxytocin release and, not least, prolonged hospitalization and infant medical complications. As a result, the rate of breastfeeding in mothers of VLBW infants remains quite low [86].

In the last years, however, it has been observed that a motivation to breastfeed, especially if provided since the beginning of pregnancy, plays a relevant predictive role on breastfeeding initiation and duration [87, 88].

The experience of breastfeeding may also yield beneficial psychological effects on mothers who experienced a premature delivery. For instance, it may contribute to reinforce the feeling of connection between the mothers and their preterm babies as well as the perception of the parental role [83, 88, 89].

Hence, breastfeeding practice should be largely motivated, not only for the beneficial observed in breastfed preterm infants, but even for its capability to encourage both the process of motherhood and the mother-child relationship in those women who had a premature delivery.

Conclusions

Benefits of breastfeeding in preterm infants are several and largely established. Among these, the main is represented by better neurocognitive outcomes, which are reported to persist far beyond the early childhood. A relevant role of LC-PUFA, especially in the improvement of visual functions, is assumed. With regard to the gastrointestinal tract, there is general agreement in reporting a dose-related reduction of NEC rate in infants fed on human milk. This beneficial effect is mainly provided by non-nutritive constituents, as growth factors, immunological factors and hormones. Additionally, the higher amount of secretory IgA within preterm breast milk might play a remarkable role in reducing the occurrence of overall infections. Although breastfed preterm infants generally show lowered growth rates, neurocognitive development is not affected, as the beneficial effects of human milk prevail. Indeed, fortified human milk might better fulfill the particular nutritional needs of preterm infants. However, once full oral feeding is reached, breast milk fortification is difficult to carry out, thereby raising some concerns on the nutritional adequacy. Finally, breastfeeding practice also entails maternal psychological beneficial effects, reinforcing the mother-child relationship which can be undermined by the preterm delivery.

Declaration of interest

The Authors declare that there is no conflict of interest.

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