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Review

The evidence for the benefits from breast milk in the neurodevelopment of premature babies – a literature review

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Abstract

Introduction. The brain in preterm babies is usually not fully developed and therefore early post-term events can have long-lasting neurodevelopment and cognitive outcomes. It is known that cerebral white matter connectivity is important for later intact cognitive functioning amongst children born very preterm and that breast milk imparts neurotrophic factors. The relationship between breastfeeding and child development is a long and well-studied area, and the evidence in support of breast milk is already substantial. Here we review the recent literature on the topic to establish whether additional evidence is available to strengthen the view that breast milk is superior in maximizing neurological development in premature infants. *Materials and Methods.* A search was undertaken of PubMed, limited to the last 10 years and humans. No language restrictions were imposed. *Results.* The search yielded 45 articles, of which 12 included all three elements of breast milk, neurological/cognitive development and preterm babies; 10 were reviewed. The gestation period and birth weight (either or both were reported) ranged from 23 to 36 weeks and from 580g to <1500g. Studies were heterogeneous in methodology. In addition to two systematic reviews and a review of the literature, other studies focused particularly on the effects of certain key components within breast milk on neurological development. They generally found evidence to support the beneficial effects of breast milk on brain, visual, and cognitive development in Preterm infants. Studies focusing on how breast milk intake affects the preterm infant brain are limited. We found only two studies published in the last 2 years in relation to brain volume in breast fed preterm infants. Both used magnetic resonance imaging (MRI) to examine the brains of breast-fed babies born prematurely. These studies found that preterm infants fed more breast milk had larger brain volumes (cortical surface) compared to those fed little/no breast milk. The timing of the nutritional intervention and the dose of the nutrient/supplement have been found to be relevant factors. However, not all studies have been conclusively positive. *Conclusions.* Although the profile of preterm infants is a wide one, from the limited but recent evidence, it is reasonable to conclude that breast milk contributes positively to neurological development.

Keywords : preterm, premature, babies, breast milk, neurological development, cognitive development

Highlights

- ✓ Contribution of breast milk in relation to neurological development of premature babies is generally positive.
- ✓ Regarding cognitive development, conclusions are less clear since outcomes are generally confounded by other factors.

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Introduction

The relationship between breastfeeding and child development is a long and well-studied field. Evidence in support of breast milk is already substantial, and the World Health Organization (WHO) recommends breast milk exclusively for six months and breastfeeding to form part of a baby's diet up to two years of age (1). 'Babies who are breastfed are less likely to suffer from a wide range of illnesses when compared to those fed on infant formula. Gastro-intestinal, respiratory, urinary tract and ear infections are less common in breastfed babies. They are also less likely to become obese in later childhood.' In 2012 a report commissioned by UNICEF (2) found in addition, that three conditions – cognitive ability, childhood obesity, and Sudden Infant Death Syndrome (SIDS) could be improved with 'moderate increases in breastfeeding rates, with millions in potential annual savings to health services.

In the case of preterm babies, the brain is less fully developed and the subsequent effect on neurodevelopment and cognitive outcomes can be sustained into later life. Indeed, preterm birth is a leading cause of neurological problems in children and has been linked to psychiatric disorders which are often only detected from school age. Since breast milk has been shown to be beneficial in other areas of development, it has been hypothesized that breast milk might also benefit neurological development in babies born before their due date.

Breast milk is known to have neurotrophic factors. It promotes structural changes in the brain, including increased brain volume and white matter (3). Key elements thought to help improve cognitive development are long-chain polyunsaturated fatty acids, including docosahexaenoic acid (DHA) and arachidonic acid (AA). These are important for retinal and cortical brain development and accumulate in the brain and retina during the last trimester of pregnancy and the first months after birth. Breastfed infants have higher concentrations of these fatty acids (4).

However, advocating breast milk as superior for prematurely born infants' development is still controversial. Neurologically, preterm infants, especially very low birth weight, show decreased cortical grey matter volumes (5-7), alterations in subcortical structures, and decreased microstructural connectivity (6, 8, 9). It is known that cerebral white matter connectivity is important for later intact cognitive functioning among children born very preterm. Preterm children without cerebral white matter abnormalities (MRI at term) appear to be spared many of the cognitive impairments commonly associated with preterm birth (10). Volume and growth rate of critical brain structures measured in the first weeks of preterm birth could predict subsequent neurodevelopmental outcomes (11).

We aimed to review the most recent literature in order to establish whether additional evidence was now available to strengthen the position that breast milk is superior in maximizing neurological development in premature infants.

Materials and Methods

A search was undertaken of PubMed using the criteria: neurological and/or cognitive development in preterm or premature babies and breast milk or breast feeding (MeSH Terms: ("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields]) AND ("Cogn Dev"[Journal] OR ("cognitive"[All Fields] AND "development"[All Fields]) OR "cognitive development"[All Fields]) AND ("premature birth" [MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR "premature"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "babies"[All Fields]). "milk, human"[MeSH Terms] OR ("milk"[All Fields] AND "human"[All Fields]) OR "human milk"[All Fields] OR ("breast"[All Fields] AND "milk"[All Fields]) OR "breast milk"[All Fields]) AND neurological[All Fields] AND ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "development"[All Fields]) AND preterm[All Fields) The search was limited to the last 10 years and humans. No language restrictions were imposed.

References from relevant articles were searched for possible additional studies.

Results

The search yielded 45 articles (after removal of duplicates), of which 12 included all three elements of breast milk, neurological/cognitive development, and preterm babies. 10 were reviewed. Gestation period and birth weight (either or both were reported) ranged from 23 to <36 weeks and from 580g to <1500g.

Notably, in the last 4 years, two systematic reviews have been conducted (12, 13) with differing conclusions. After reviewing 7 studies between 2001 and 2011, Koo et al (12) could only conclude that the studies available were not sufficiently homogeneous nor of sufficient rigor to provide conclusive evidence to

support a positive role for breast milk in the neurodevelopment and cognitive function of babies born prematurely. This systematic review focused on neurodevelopment in very low birth weight (VLBW) infants fed human milk. ('In all studies, VLBW children without neurological impairment fed HM achieved normal or low normal scores on standardized tests of neurodevelopment or cognitive function').

A more recent review undertaken by Lechner et al (13) also looked at neurodevelopment in preterm infants fed human milk. However, the authors concluded that there is evidence to support the beneficial effects of breast milk on brain, visual, and cognitive development from infancy to adolescence in preterm infants.

A further detailed and more recent review of the literature (14) had been conducted in relation to early nutritional interventions for brain and cognitive development in preterm infants. It concluded that in general, mother's breast milk was reported to be better for preterm infants' neurodevelopment compared to infant formula. The authors reported that differences in methodologies made it difficult to conclude any effects of interventions with individual nutrients. In addition to the type of infant nutrition, the timing of the nutritional intervention and the dose of the nutrient/supplement were found to be relevant factors.

A longitudinal cohort study conducted by Sammallahti et al (15) focused on nutrition after preterm birth and adult neurocognitive outcomes, but although published in 2017, it was discounted as it relied on nutritional data from 1978-1985 in order to assess cognitive ability at 25 years.

In addition to the systematic and literature reviews, our search yielded a number of smaller studies conducted between 2008 and 2013 (three of which were also mentioned by Schneider et al, 16-18) which focused particularly on the effects of certain key components within breast milk on neurological development. Following from a meta-analysis by Anderson et al (19) (1999) which concluded that the presence of DHA and AA fatty acids in breast milk resulted in greater neurodevelopment benefits for preterm infants than formula, a randomized controlled double blind trial undertaken by Henriksen et al (17) in 2008 (and previously reported on by Koo et al and Lechner et al) concluded that supplementation with DHA (32mg/100ml) and AA(31mg/100ml) for very preterm infants fed milk of human in the early neonatal period was often associated with better recognition memory and with higher problem-solving scores at 6 months. The following year, Lapillonne et al (20) also recommended increasing the DHA content of human milk either by providing the mothers with a DHA supplement (DHA content above 1% total fatty acids) or by adding DHA directly to the milk to fulfil the specific DHA requirement of preterm infants and to possibly enhance neurological development, particularly that of infants with a birth weight below 1250 g. ('Enterally fed premature infants exhibit daily DHA deficit of 20mg/kg/d, representing 44% of the DHA that should have been accumulated').

Early finding from a study undertaken in 2010 by Lundqvist-Perrson et al (16) showed omega-3 fatty acids concentrations in breast milk were positively associated with the early neurological development in preterm infants (24-36 weeks) and in 2012 Biasini et al, (18) in a trial on extremely low birth rate infants (580-1250 g) born between 23 and 32 weeks, reported that the group fed human/maternal milk with additional protein levels (4,8 g Kg-1 per day) showed higher scores (p 0.04) in the lowest birth weight infants (580-980g) than the control group at 3 and 12 months corrected age using the Griffith Development Mental Score and (p 0,03) on Hearing/Language items.

Underwood (21) undertook a comprehensive study examining the composition of mother's, donor, and formula milk for preterm infants on the premise that human milk is recommended for preterm infants, but does not by itself provide optimal nutrition (a view supported by the American Academy of Paediatrics). The composition of breast milk differs from preterm to full term, with higher levels of some elements such as protein, fat, and amino acids which decrease in a matter of weeks, and insufficient or varying levels of other elements, in particular oligosaccharides which have been linked to neurodevelopment. The study concludes that 'mother's own milk improves growth and neurodevelopment (and decreases the risk of necrotizing enterocolitis and late-onset sepsis) and should therefore be the primary enteral diet of premature infants.

A population observational study (22) previously excluded by Koo, examining neurodevelopmental assessment (and weight gain) of very preterm (22-32 weeks) infants as a sub group of 2 large cohorts, was dismissed as it relied on data from infants born between 1997 and 2008.

Studies focusing on how breast milk intake affects the preterm infant brain are limited. We found only two previously-unreported studies published in the last 2 years in relation to brain volume in breast fed preterm infants.

The first and most complete was a longitudinal cohort study undertaken by Belfort et al. (23) The study used magnetic resonance imaging (MRI) to examine the brains of 180 breast fed babies (born under 30 weeks) at term equivalent as well as their neurodevelopmental and cognitive outcomes at 2 and 7 years of age. They found that babies that received at least 50% breast milk within the first 28 days of life had an increased brain development in certain specific areas by time their original due date arrived, and when it was measured again later in childhood, compared to those who received less breast milk. Specifically, the authors stated these babies had 'larger deep nuclear volume of gray matter (an area that is important for processing and transmitting neural signals to other parts within the brain) and hippocampus (important for memory and learning) at term equivalent age.' By age 7, they performed better on tests of IQ, math skills, language, reading, working memory, attention and motor function. The authors found that little evidence of associations between average daily breast milk intake and other regional brain volumes.

A similar, smaller cohort study - 77 babies at an average of 26 weeks gestation - undertaken by Reynolds et al (24) also demonstrated, through use of MRI scans, that babies fed 50% or more breast milk had larger brain volumes (cortical surface) compared to preterm babies fed little/no breast milk. The scans were taken at the point of the preterm infant's expected full-term due date.

Discussion

Premature infants are a heterogeneous group facing different challenges and needs in relation to their gestation period and birth weight. "Preterm" is defined by WHO as an infant born before 37 weeks of pregnancy are completed, with further categorization into "extremely preterm" (<28 weeks), "very preterm" (28 to <32 weeks) and "moderate to late preterm" (32 to <37 weeks) and subgroups: very low birth weight (less than 1500 g) and extremely low birth weight (less than 1000 g). The range of issues present in premature infant development is reflected in the diversity of studies available in the literature, with nutrition being key among them.

Generally, the relationship between neurodevelopmental outcomes and breast feeding has been controversial, although it has been implied that improved outcomes might be related more to improved care, higher maternal education, and higher socioeconomic status rather than to nutrients found in breast milk (4, 13). Even when advocating breast milk, the need for fortification is generally acknowledged. Extremely/very low birth rate/preterm have additional issues, one of which is the ability to suckle. Maternal sensitivity is associated with better neurodevelopment (25). Since breast feeding is positively associated with maternal-infant bonding, the ensuing interruption can lead to maternal and infant stress and therefore potentially impact neuro- and later cognitive development. Although such factors are hypothesized as contributing, they are nevertheless difficult to quantify.

Furthermore, it is important to highlight the difference between neurological development (development of the nervous system/development of neurological pathways) that influences performance or functioning such as intellectual functioning, reading ability, social skills, memory, attention or focus skills, and cognitive development, the construction of thought processes, including but not limited to remembering, problem solving, and decision-making process, from childhood through adolescence to adulthood. Even infants with different patterns of neuronal activation do not necessarily have cognitive delays later in life, as the developing brain is still plastic and shows impressive compensatory abilities (7). In our review, we found those that tested for later cognitive ability were largely assuming that better performance was linked to better neurological development as a result largely of breast milk. The studies that attempted to look at the longer-term correlation between breastfeeding and cognitive development not only excluded social confounding factors but also ran the risk of having less accurate or less complete data in relation to initial breast-feeding patterns, being mainly retrospective observational studies. It should be noted that all 10 studies we included evaluated preterm infants with no neurological impairments.

Two other important limitations of the most recent studies reviewed were that no distinction was made in data when preterm formula was used if a mother's own breast milk was unavailable or in short supply (23); and no differentiation between outcomes was made between milk that came from the babies' own mothers and donor breast milk (24). Furthermore, in both studies, neither volumes of milk nor other associated factors which could contribute/confound, were measured post discharge, which is generally an issue with most studies. It should be noted that the full details of the study conducted by Reynolds et al were not available at the time of writing this article, so information was taken from a paper released by Washington University School

of Medicine; therefore it was not possible to compare it to the apparently similar study by Belfort et al.

Breast milk has been shown to have some disadvantages as well as advantages over formula. Lundqvist et al (16) found the major omega-6 fatty acids and Mead acid were negatively associated with early neurological development.

The increased risk of neonatal complications in preterm infants should be mentioned, as the association between breast milk and positive cognitive development is reduced in these circumstances. In a study undertaken by Goelz et al (26) it seems possible that breast milk-acquired cytomegalovirus infection has a detrimental influence on the cognitive development of preterm infants.

Not all studies have been conclusively positive. A recent Australian study (27) found no associations of human milk intake during the neonatal hospitalization with neurodevelopment at 18 mouths corrected age, concluding that 'the effect of human milk intake on neurodevelopment in preterm infants is uncertain'.

It could be seen as a limitation of this paper that we did not address the implications in relation to donor milk (fortified or not), enriched/non-enriched formula, and mother's own milk. We have only reported where these were controls for other studies. These issues have been discussed at length by three studies (14, 21, 28), two already mentioned (14, 21). Neither did we evaluate the level of bias or quality of the studies used. However, the strength of this review is that it focuses on the most recent information available and does not overlap significantly with other recent reviews.

Conclusions

Although the profile of preterm infants is a wide one, from the limited but recent evidence it is reasonable to conclude that the contribution of breast milk in relation to neurological development is generally positive. In the area of cognitive development, conclusions are less clear since outcomes are confounded by other factors. More data are needed in relation to feeding patterns and volumes post discharge. Finally, it should be remembered that the implications of breast feeding are wider than the composition of milk and we should not detract from the unquantifiable benefits that this has.

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