Cognitive and Neurodevelopmental Effects of Human Milk in Preterm Infants
The Value of Human Milk in the NICU: Cognitive and Neurodevelopmental Effects of Human Milk in Preterm Infants

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Introduction

Despite improvements in neonatal and perinatal medicine, infants born prematurely have a significantly higher risk of neurological disabilities when compared to infants born at term. According to a 2002 Agency for Healthcare Research and Quality report, half of all extremely low birth weight (ELBW) infants will have at least one significant neurodevelopmental impairment. As with many neonatal outcomes, these risks are inversely proportional to the infant’s birth weight and gestational age at birth: the smaller and more preterm the infant, the greater the risk.

While many health issues of preterm infants such as, necrotizing enterocolitis and late onset sepsis are diagnosed during neonatal hospitalization, the impact of neurodevelopmental delays is greatest after discharge. Human milk reduces the incidence and severity of both acute and chronic disorders in preterm infants.

Growth and development of the human brain are quite dramatic in the last trimester of pregnancy with significant growth continuing into the first two years after birth. During this time, the placenta, followed by infant feeding, must provide essential nutrients to ensure immediate as well as long-term health outcomes.

Essential fatty acids and their derivatives docosahexanoic acid (DHA) and arachidonic acid (AA), which are naturally present in human milk are critical elements for healthy tissues, particularly those of the central nervous system, cardiovascular system and eye. Other components of human milk such as growth factors, antioxidants, hormones, anti-infective and anti-inflammatory factors as well as cholesterol are also involved in healthy human neurological development. The effects of early infant nutrition may sometimes be subtle with results not apparent for years. However, studies suggest early nutrition has the potential to influence cognition, behavior and educational performance.

In this article, we will explore evidence related to the benefits of human milk in the neurological and cognitive development of infants, particularly preterm infants. Our discussion is organized around four research articles:

- The first two articles, combined into one summary, discuss the same longitudinal study but at two points in time. These articles by Vohr and et al. investigate the effects of breastmilk on cognitive skills and behavioral ratings of extremely low birth weight infants. After reviewing the articles, we will explore challenges common to studies of cognitive development and infant feeding.

- The next article, published in 2011 by Quigley et al, also looks at the association between breastfeeding and cognitive development. The authors controlled for an extensive number of confounders and separated results for term and preterm infants. Commentary following the summary will focus on the physiology of neurological development and the beneficial role of long chain polyunsaturated fatty acids (LCPUFA) and other components in human milk.
• The last article by Isaacs et al. examines the relationship of breastmilk feedings in the NICU to brain growth later in life. Of particular interest are development of white and grey brain matter and suggested responses to a human milk diet. These differences reflect the increasingly complex interface of early infant nutrition to neurocognitive outcomes.

Key Points

• Preterm infants are at greater risk than term infants for neurodevelopmental impairments.

• Fetal brains grow dramatically in the last trimester of pregnancy. For example, an infant born at 30 weeks has approximately 30% of the brain weight of an infant born at term.³³

• Sixty percent of an infant’s brain is lipid, mostly membrane lipid, which requires specific LCPUFA, arachidonic acid (AA) and docosahexanoic acid (DHA) for growth and development.⁸

• Essential fatty acids are structural components of all cell membranes. Brain, neural, retinal, vascular and endothelial systems are especially rich in LCPUFA.

• During pregnancy, the placenta supplies LCPUFA to the fetus. Acquisition of LCPUFAs is highest in the last trimester of pregnancy and the first 6 months of life. Preterm infants are usually deficient in maternal LCPUFAs because of their shortened gestational periods.

• Human milk contains a full complement of naturally occurring LCPUFAs essential to continued growth and development of an infant’s central nervous system, eyes, cardiovascular system and other tissues.

• White brain matter is composed of glial cells and myelinated axons that transmit nerve signals. Cholesterol is an essential component of all cell membranes and the myelin sheaths of nerve cells. Human milk contains highly stable levels of cholesterol independent of maternal diet while infant formulas contain little or no cholesterol.³⁴

• Current studies lend support to the notion that breastmilk promotes brain development and that the mechanisms for this effect are probably related to the interactions between multiple, naturally occurring human milk components such a DHA, LCPUFAs, growth factors, hormones, cholesterol and others, along with neural cell growth and development.


**Background**

These studies initiated between 1999-2001 were part of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Glutamine Trial. Extremely low birth weight infants in 15 study centers were prospectively enrolled during neonatal hospitalization, with evaluations of developmental outcomes conducted at approximately 18 and 30 months corrected age.

The overall objective was to evaluate longitudinally the physical, developmental, neurological, cognitive and behavioral effects on ELBW infants of breastmilk ingested in the NICU.

Nutrition data were collected during infants’ hospitalizations. Infants fell into one of two initial groups: a Breastmilk Group or a No Breastmilk Group. Infants in the Breastmilk Group received varying amounts of breastmilk during the course of the study. To evaluate the dose effect of breastmilk feedings, the authors analyzed the volume of breastmilk feeds per day of all infants in the Breastmilk Group. Quintiles of breastmilk feedings were defined as follows:

- Infants in the <20th quintile group received ≤ 23.1 mL/kg/day;
- Infants in the 20th-40th quintile group received 23.1 - 53.0 mL/kg/day
- Infants in the 40th-60th quintile group received 53.0 - 83.2 mL/kg/day
- Infants in the 60th-80th quintile group received 83.2 - 112.45 mL/kg/day
- Infants in the > 80th quintile group received > 112.45 mL/kg/day.

Data were collected on multiple confounding variables including but not limited to socioeconomic status, maternal age, education, marital status, race/ethnicity, infant gestation, gender, and neonatal complications.

Both studies evaluated the effects of breastmilk feedings during the NICU stay on cognition and behavior as measured by Bayley Scales of Infant Development II. The Bayley Scales of Infant Development II (BSID-II) includes: the Mental Developmental Index (MDI); the Psychomotor Development Index (PDI); and the Behavior Rating Scale (BRS), which includes orientation/engagement, emotional regulation and motor quality. The authors also evaluated growth, neurologic and neurosensory findings, and the incidence of infant rehospitalizations.
The first report included results of 1035 ELBW infants followed until 18 months corrected age: 775 (74.9%) in the Breastmilk Group; 260 (25.1%) in the No Breastmilk Group.

The second report included results of 773 ELBW infants followed until 30 months corrected age: 593 (76.6%) in the Breastmilk Group; 180 (23.3%) in the No Breastmilk Group.

**Results**

Children in the combined Breastmilk Group had better outcomes at 18 and 30 months than children in the No Breastmilk Group on multiple Bayley Scales of Infant Development.

- Mean Mental Development Index scores were higher and increased between 18 and 30 months in the Breastmilk Group compared to the No Breastmilk Group. At 30 months the mean MDI scores were statistically higher in the Breastmilk Group.

- Mean Psychomotor Development Index scores, while similar in the Breastmilk Group at 18 and 30 months, were statistically higher in the Breastmilk Group compared to the No Breastmilk Group at 30 months. At 30 months, mean PDI scores had decreased in the No Breastmilk Group.

- Behavior Rating Scale scores were higher at both points in time in the Breastmilk Group.

After adjusting for confounding variables, analyses indicated that for every 10 mL/kg/day increase of breastmilk, infants demonstrated incremental improvements in MDI, PDI and BRS percentile scores and rehospitalization rates. These improvements were sustained between 18 and 30 months of age.

**Conclusions**

Positive cognitive and behavioral effects of receiving breast milk in the NICU were evident at 18 months corrected age, but not statistically significant until 30 months corrected age.

The cognitive and behavioral advantages of breastmilk feedings were dose dependent; the more human milk an infant received, the greater the benefit.

The authors speculated specific human milk components; LCPUFAs - arachidonic acid and docosahexanoic acid - along with choline, glycoproteins, phospholipids, growth factors and hormones might contribute to improved cognitive and behavioral outcomes in ELBW infants.
Commentary

These articles by Vohr and associates present compelling evidence for the dose-response benefits of human milk fed to ELBW infants during neonatal intensive care. The number of subjects at each phase of study was large and the various types of subject evaluations including nutritional, neurological, cognitive, and behavioral - were extensive. Additionally, analyses controlled for many confounders related to subjects and feedings. In this research, the dose-response benefits of human milk are demonstrated by stratification of groups into quintiles of milk volume per day over the NICU stay. Overall, any breastmilk volumes were better than none with cognitive results sustained if not improved between 18 and 30 months of age.

The cognitive/behavioral benefits of human milk have been a subject of inquiry for many years. In 1929, Heofer and Hardy evaluated the effects of infant feeding type and duration on physical and mental developmental differences in Chicago school children. Study methods and analyses differed from those seen today; however, results supported the benefits of 4-9 months of exclusive breastfeeding over infant formula feeds.

Like many clinical studies in lactation, randomization of infants to breastfeeding versus formula groups is ethically problematic. If mothers want their infants to receive their milk, these wishes should be honored if there are no medical contraindications. Lucas et al in a randomized prospective multi-center trial, compared preterm infants receiving infant formula to those receiving human donor milk. Randomization was not an issue, as all mothers had chosen not to express milk for their infants. Their findings suggested infants receiving donor human milk had higher psychomotor developmental scores than infant receiving formula.

Researchers of lactation and human neurodevelopment are challenged by the complexity of factors that influence outcomes, particularly those that influence intelligence measures. Therefore, results are not always consistent. However, recent reports strengthen the argument human milk improves mental capacity in term and preterm infants. Of note, a 2011 study by Jedrychowski et al found IQ scores of children born >36 weeks increased with duration of exclusive breastfeeding when compared to partially breastfed children. A second 2011 study by Quigley et al (summarized in the next section) found similar results. These studies followed subjects for five to seven years.

In the next section, after taking a closer look at the Quigley study we will explore the science of human neurological development in relation to infant nutrition.
Background

The purpose of this study was to evaluate the relationship between breastfeeding (including breastmilk feeds) and cognitive development in term and preterm infants.

Infants were recruited from the Child Benefi ts registers in the United Kingdom at approximately 9 months of age. In total, 11,879 infants were evaluated. Of these there were, 11,101 infants born at term (37-42 weeks), and 778 infants born preterm (28-36 weeks).

Children were assigned to groups based on breastfeeding duration. The definition of breastfeeding included receiving mother’s milk from the breast or from a feeding device.

Infant feeding was categorized as Any Breastfeeding (Partial and Exclusive), Exclusive Breastfeeding and No Breastfeeding. Any and Exclusive Breastfeeding Groups were then divided into 2-month bands for duration: <2 months; 2.0-3.9 months; ≥ 4.0 months. In the term group, there were enough subjects to continue to separate the children into additional breastfeeding durations: 4.0-5.9 months, 6.0-11.9 months and ≥12 months.

Three British Ability Scales-Second Edition (BAS II) subtests were administered at 5 years of age. These subscales assessed verbal abilities, spatial abilities and pictorial reasoning.

The authors adjusted for multiple confounders. Beyond the standard confounders such as maternal age, education, socioeconomic status, gestational age and birth weight, the study team adjusted for parents’ parenting beliefs and the child’s exposure to early learning opportunities.

Results

Analyses were conducted and reported separately on the term and preterm infant groups.

In children born at term, the authors found a 1-2 point difference on the three subtests between children who were breastfed for 4-6 months and those who were never breastfed. Translating these differences into cognitive expectations of an average 5-year-old child, the authors calculated children who breastfed were approximately 3 months ahead in pictorial reasoning and 2-3 months ahead in verbal abilities.

In children born preterm who were breastfed or received breastmilk for at least 2 months, the authors found a 4-6 point increase in pictorial reasoning and spatial abilities. Children born preterm who were breastfed for at least 4 months had a mean increase of 4 points in verbal abilities over infants who had never breastfed.

The findings also suggested children born preterm who were breastmilk fed at least 2 months were approximately 6 months ahead in pictorial reasoning and 3 months ahead in spatial abilities. Lastly, preterm children fed breastmilk for at least 4 months were 5-6 months ahead in verbal abilities.
Conclusions

Study results suggested longer durations of breastfeeding/human milk feeding have greater effects on cognitive development, particularly in children born preterm.

The authors submitted several potential mechanisms for the improved cognitive development reflected in this study. These include human milk LCPUFAs, growth factors and hormones. They also noted that the higher frequency of infant infections associated with formula feeds could affect early and later cognitive development.

Commentary

This very large study contributes significant weight to the argument that breastfeeding and human milk feeds contribute positively to infant intelligence and cognitive development. Like most studies, maternal IQ is an important variable in predicting a child’s intelligence\(^{38,42}\) and was not measured directly but inferred from maternal education and socioeconomic status. Unlike some previous reports, this study controlled for selected aspects of the home environment including parenting beliefs and exposure to educational opportunities. Additionally, comparison of outcomes in infants born term versus preterm indicates greater effects of human milk feeds on preterm infants.

Like Vohr and colleagues, Quigley et al identify components of human milk that may be involved in neurological and cognitive development, specifically, LCPUFAs, growth factors and hormones. Of these, LCPUFAs are most often associated with infant central nervous system development. Although a thorough discussion is beyond the scope of this article, an abbreviated review may be helpful.

Human milk contains a variety of medium and long chain fatty acids, including two essential fatty acids linoleic acid (LA) and α linolenic acid (ALA) the human body can’t synthesize and must, therefore, get from dietary sources. Linoleic acid is the precursor for the omega 6 polyunsaturated fatty acids; α linolenic acid is the precursor for omega 3 polyunsaturated fatty acids\(^ {43}\). Of the many fatty acids in human milk, arachidonic acid (AA) from linoleic acid and docosahexanoic acid (DHA) from linolenic acid are the LCPUFAs most associated with brain, eye and cardiovascular development\(^ {5,7-13,15,18,20-22,31,44-49}\).

During fetal development, the last 20 weeks of gestation is a critical period of human brain growth and development. Linear growth in brain weight follows a steep slope: approximately half of the brain’s volume is obtained in the last 6 weeks of a 40-week gestation. In addition, at 26 weeks gestation the brain will weigh 30% of its expected weight at 40 weeks; at 34 weeks it will weigh 65% of term weight\(^ {33}\).

Brain growth is concomitant with structural maturation and organization. During the fetal period and extending into infancy, neurogenesis, synaptogenesis, dendritic arborization and neuronal connectivity occur as axons elongate to form the cerebral cortex.\(^ {15,33}\) Of interest to the discussion at hand, 60% of infant brain is lipid, mostly membrane lipid, which requires arachidonic acid (AA) and docosahexanoic acid (DHA) for growth and development\(^ {5,8}\).
DHA and AA are integral components of brain and nervous system cell membranes. They are also abundant in retinal, endothelial and vascular cells.\textsuperscript{10,12,14,15,20,21} During pregnancy, the placenta supplies LCPUFAs to the growing fetus, but after birth, the infant is dependent on exogenous nutritional sources for continued supplies. Preterm infants by nature of their interrupted gestation have the greatest need for LCPUFAs. Human milk is a natural source rich in DHA and AA and their precursors, the essential fatty acids. Bovine milk has very few LCPUFA\textsuperscript{43} and studies of the efficacy of infant formulas with added synthetically manufactured PUFAs are inconclusive at this time.\textsuperscript{5,18,50-54}

Long chain polyunsaturated fatty acids are susceptible to oxidative degradation and the formation of eicosanoids associated with a cascade of inflammatory and immune responses. Antioxidants in human milk can suppress degradation of LCPUFAs and reduce inflammation associated with eicosanoids.\textsuperscript{10} DHA also down-regulates inflammation associated with serious diseases in preterm infants.\textsuperscript{10} These components may work in concert with other anti-inflammatory agents in human milk, for example, interleukin-10 (an anti-inflammatory cytokine), lactoferrin, and epidermal growth factor to reduce destructive up-regulated immune responses in preterm infants.\textsuperscript{55-57}

Thus far, we have discussed the benefits of human milk in infant neurological and cognitive development focusing on the role of LCPUFAs. The innate complexity of human milk rarely lends itself to consideration of just one concept. Continuing with these themes, we will next examine differences in brain matter growth and maturation as they relate to early dietary intake of preterm infants.

Background

Previous studies, like those we have just examined, have associated breastfeeding with positive child cognitive development. Other research suggests cognitive scores in preterm infants are related to head circumference and brain size. Therefore, the purpose of this study was to examine the relationship between early human milk feeding, measures of intelligence and brain growth and volume in preterm infants.

In a classic randomized clinical trial conducted between 1982-1985, Lucas and colleagues studied 502 NICU preterm infants over the first 30 days of life. All breastmilk feedings were documented then converted into percentages of infants’ total feeding intake. Their results showed a dose-response benefit from human milk feeding on infant cognitive development at nine months, 18 months, and 7-8 years of age.

The 50 subjects in this study were from the original 502 infant cohort, now in their adolescent years, mean age 15 years, 9 months (Range: 13y5m – 19y9m).

All subjects were born at or less than 30 weeks gestation and were previously determined to be neurologically normal. All subjects had received primarily expressed mothers’ breast milk in the first month of life but varied as to type of supplement: 28 received preterm infant formula; 13 received term infant formula; 9 received donor human milk.

Subjects were assessed by age appropriate Wechsler intelligence scales (verbal, performance and full-scale) and by MRI studies. MRI analysis included total brain volume as well as white matter and grey matter volumes.

Grey matter is composed of nerve cell bodies, dendrites and shorter axons. It is generally associated with mental processing and cognition.

White matter is composed of glial cells and myelinated connecting axons. Myelin is an insulator that allows for increased speed of nerve impulse transmission. White matter is usually associated with coordinating communication in the brain.

Results

Results were adjusted for maternal education and social class (as variables related to maternal intelligence) and age at time of brain MRI. Results for males and females were considered separately and together.

Mean IQ scores were close to the population average of 100 with no significant difference between girls and boys.

Boys but not girls showed a significant proportional relationship between percent expressed breastmilk and all three IQ scores. The higher the percent of expressed breastmilk, the higher the IQ scores.
Also, a significant proportional relationship existed between percent expressed breastmilk and total white matter in boys. Total white matter increased with higher percentages of expressed milk feedings.

Lastly, again only in boys, white matter volumes correlated significantly with verbal and full scale IQ scores. As white matter volumes increased, so did these IQ scores.

Conclusions

The authors concluded that, “In all subjects, but most clearly in boys, the effects of breast milk were seen more strongly on white than grey matter in the brain. These data support the hypothesis that one or more constituents of mothers’ breast milk promote brain development at a structural level.” (p.6)

The authors speculated long-chain polyunsaturated fatty acids (most notably DHA), growth factors and hormones in human milk might promote infant brain development. In preterm infants, white matter growth seems to influence total brain volumes as well as intelligence in male children.

Animal studies suggest dietary cholesterol is an important component in the development of white matter myelin membranes and glial cells; therefore, the authors suggested the presence of cholesterol in human milk might contribute to white matter development and intelligence.

Commentary

In this research, cholesterol is added to the list of breastmilk constituents that may facilitate growth of human brain cells and cognitive development. Like DHA, cholesterol is an essential structural component of cell membranes in mammals. It is also the precursor of steroid hormones. Using genetically altered mice, Saher et al demonstrated the critical role of cholesterol in white matter myelin membrane growth and glial cell maturation. In human studies, plasma cholesterol levels have been shown to progressively increase in breastfeeding infants and are higher than cholesterol levels in formula-fed infants. So in addition to brain cell development, there is speculation dietary cholesterol from human milk may program a more healthy cholesterol synthesis later in life.

This research by Isaacs and associates necessitates acknowledgement of studies that have found gender differences in brain development. Kesler and associates examined neurodevelopmental differences between twenty-nine 12 year olds born preterm compared to a control group of healthy children born at term. Their subjects included both girls and boys. MRI scans of girls born prematurely were not significantly different from scans of their term counterparts. However, male children born preterm had significantly abnormal results when compared to boys born at term. The abnormalities, detected by MRI scans, were found to be “relatively diffuse, involving multiple neural systems” (p.513). Although these researchers did not find negative cognitive outcomes in the preterm male group, other studies have identified language and reading issues in preterm children, especially males. Unfortunately, there are no dietary data in the study by Kesler et al to evaluate the effects of feeding types on neurological outcomes.

These findings, when added to those of Isaacs et al, lend support the notion that breastmilk promotes brain development and that the mechanisms for this effect are probably related to the interactions between multiple human milk components, such as DHA, LCPUFAs, growth factors, hormones, cholesterol and others with neural cell growth and development. Interestingly, at a fundamental level there seems to be differences in the neurocognitive development of preterm children determined by gender. Girls and boys have different average brain volumes, different proportions of white and grey matter and different neurodevelopmental responses to human milk feedings.
Concluding Remarks

The science of human neurodevelopment, cognition, infant nutrition and gender intersected in this discussion of the use of human milk for preterm infants. Our discussion started with an exploration of neurologic and cognitive effects of human milk in ELBW infants. These types of studies are complicated by a vast number of confounding factors as well as methodological challenges of longitudinal studies. Nevertheless, the articles by Vohr et al demonstrated neurocognitive benefits of human milk feeds in the NICU for preterm infants. These benefits increased as doses of human milk increased.

Very recent research by Quigley et al evaluated the effects of human milk on neurodevelopment of approximately 12,000 infants, both term and preterm. Their findings suggested small but notable improvements in breastmilk fed infants, especially preterm infants fed for longer durations. This study is noteworthy for the authors’ inclusion of unique confounders including parenting beliefs and the educational exposure of children. Of special interest in this discussion are the roles of LCPUFAs, especially DHA, in human milk. These substances, naturally abundant in breastmilk but not infant formula, are critical to the development of a functional central nervous system and may be involved in suppressing inflammatory processes in vulnerable infants.

Lastly, Isaacs and associates demonstrated higher IQ scores and white matter growth in preterm boys were correlated with increasing proportions of human milk feeds. Whilst there are certainly limitations to Isaac and coworker’s study, it does go part way towards showing how human milk manifests itself as an advantage for the preterm infant. It would seem that the naturally occurring neurodevelopmental building blocks provided by human milk work to increase brain volume and thus may allow for the increases in IQ and the other neurodevelopmental outcomes so elegantly shown by Vohr and colleagues, Quigley and coworkers and many others before them. Thus the studies outlined in this article add to the growing body of evidence to support the use of human milk for preterm infants and begin to provide insights as to how these benefits are conferred to the infant.


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