Outcomes of Human Milk-Fed Premature Infants

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Significant benefits to infant host defense, sensory-neural development, gastrointestinal maturation, and some aspects of nutritional status are observed when premature infants are fed their mothers’ own milk. A reduction in infection-related morbidity in human milk-fed premature infants has been reported in nearly a dozen descriptive, and a few quasi-randomized, studies in the past 25 years. Human milk-fed infants also have decreased rates of rehospitalization for illness after discharge. Studies on neurodevelopmental outcomes have reported significantly positive effects for human milk intake in the neonatal period and long-term mental and motor development, intelligence quotient, and visual acuity through adolescence. Body composition in adolescence also is associated with human milk intake in the neonatal intensive care unit. Finally, human milk intake is less associated with the development of the metabolic syndrome than infant formula feeding.

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Significant benefits to infant host defense, gastrointestinal maturation, and sensory-neural development, and the quality of their nutritional status are observed when premature infants are fed human milk.1 Nonetheless, the nutritional adequacy of mother’s milk on the basis of intrauterine rates of growth and nutrient accretion may be a limiting factor in the very low birthweight (VLBW) infant weighing <1500 g at birth.2 The overall nutritional needs of the VLBW infant are now met if a nutrient supplement, or fortifier, is added to the milk. The long-term effects of a human milk diet in the neonatal intensive care unit (NICU) recently are being appreciated. There are significant long-term benefits to this diet on improvements in host defense, neurodevelopmental outcome, nutritional status, and a reduction in the metabolic syndrome. The objective of this review is to describe the data that support these associations.

Host Defense

The relationship between diet and the incidence of infection in premature infants demonstrates that the feeding of mother’s milk mitigates the high rate of infection common to hospitalized premature infants.3 A trial in the United Kingdom reported that necrotizing enterocolitis (NEC) was reduced significantly by feeding premature infants human milk, either exclusively or partially supplemented with either formula or pasteurized donor human milk.4 That study identified the greatest risk for NEC in the group of infants born before 28 weeks’ gestation. When infants receiving a diet of human milk exclusively (mother’s own milk or donor human milk) were compared with those receiving an infant formula-only diet, there was a 6.5-fold (95% confidence interval [CI] 1.9-22, P < 0.001) increase in confirmed cases of NEC as identified from surgical pathology or postmortem examination. A significant 3-fold (95% CI 1.4-6.5, P < 0.005) increase in NEC was also reported when an exclusive infant formula diet was compared with a diet of formula used as a supplement to human milk. The relationship between the dose of human milk and the protective effect was examined post-hoc from a study of 2 feeding strategies for premature infants, trophic feeding versus no feeding (4 vs 14 days) and tube-feeding method, continuous versus intermittent bolus.5 The study enrolled infants born before 30 weeks’ gestation who were stratified in enrollment by diet, either mother’s milk or preterm formula. Differences between groups favored early trophic feeding at 4 days using the intermittent bolus feeding method. However, for all measured outcomes, the type of milk fed was the most important variable. Infants fed predominantly human milk (averaged as more than 50 mL/kg/d, approximately one-third of full milk feedings) had significantly less late-onset sepsis and/or NEC and a 2-week shorter hospitalization compared with infants fed preterm formula.

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Late-onset sepsis and/or NEC had an even greater incidence if the study infants received a combination of mother’s milk and preterm formula. The study identified a dose of human milk that potentially might be protective. This dose of mother’s milk, >50 mL/kg/d, subsequently was shown to protect against late-onset sepsis in a 4 week study of premature infants when compared with average daily doses of 1-24 and 25-49 mL/kg and was also associated with greater survival free of NEC.6,7 Similarly, a mother’s milk dose of ≥50% of enteral feeding in the first 14 days was associated with an 83% reduction in NEC (OR 0.17, 95% CI 0.04-0.68) compared with premature infants receiving <50% of enteral feedings as mother’s milk.8

NEC is a significant concern not only because of its high case-fatality ratio, but also because of implications for long-term outcome. The complications of stricture, short bowel syndrome, and cholestasis pose significant morbidity to the infant. Nutritional issues are significant because metabolism is shifted from growth to tissue repair. Therefore, long-term growth delays are noted, especially in infants with surgically-treated NEC. At follow-up between 18 and 22 months, growth was below the 10th percentile for weight in 70%, length in 48%, and head circumference in 39% of infant survivors of surgically-treated NEC.9 Neurodevelopment also may be affected in NEC survivors. More cases of cerebral palsy, mental and motor scores below 70, blindness, and deafness are reported in surgically-treated NEC survivors.9 White matter injury also is seen on magnetic resonance imaging scans in follow-up studies of premature infants surviving medically and surgically treated NEC.10

A predominantly human milk diet in the NICU is also associated with fewer hospital readmissions for illness up to 30 months after discharge in a study of over 1000 infants with mean birth weight of approximately 800 g and gestational age of 27 week.11,12 When adjusted for important confounding variables, a NICU diet comprising more than 40 mL/kg/d of human milk (more than 40th percentile of human milk intake) is associated with a reduction in this rate of hospital readmission. For every 10 mL/kg, there is a 5% reduction in the rate of hospital readmission to 2 years.12 Other studies report that infants receiving the most human milk in the NICU also had fewer readmissions to the hospital after discharge.13 A smaller study reported that upper respiratory tract symptoms for their first year after discharge were less in those infants who received human milk in the NICU but who had a declining pattern of human milk feeding over the year.14 Thus, a human milk diet in the NICU is associated with a reduction in acute infection-related illnesses and also has persistent effects for at least 3 years after discharge.

### Effects on Neurodevelopmental Outcome

The long-term neurodevelopment of premature infants is a concern and recent evidence suggests that the NICU diet may affect this outcome. An 8-year follow-up of 300 premature infants (approximately 1.4 kg and 31 weeks’ gestation at birth) observed that even when factors affecting intelligence quotient (social class, maternal education, infant gender, and duration of mechanical ventilation) were considered in a regression model, the receipt of human milk in the NICU was associated with an 8-point IQ advantage, slightly more than 1 standard deviation of the mean.15 When followed to adolescence, this cohort was found to have verbal intelligence quotients that correlated positively with the percentage of expressed human milk they received as infants in the NICU.16 Furthermore, the percentage of expressed human milk received in the NICU also correlated significantly with total and white matter brain volumes measured by magnetic resonance imaging scans.16

Other cohorts of adolescents followed since their NICU stay as premature infants were reported to have significant cognitive and psychomotor benefits ascribed to the feeding of human milk in the NICU.17-19 In a large study of premature infants who were 30 weeks’ gestation with a birth weight approximately 1.3-kg who were fed either human milk or preterm formula, a human milk diet was associated with significantly greater scores in behavioral visual acuity at 2-6 months corrected age compared with those fed a diet of preterm formula.13 The effect of human milk on cognitive indexes was also seen at 12 months corrected age and, in infants with chronic lung disease, a significant benefit of a human milk diet was observed for psychomotor indexes. Importantly, these observations were adjusted for Home Inventory, maternal intelligence testing, smoking, and birth weight.

A large multicenter follow-up study of 1035 extremely low birth weight infants who had extensive nutritional data collected during their hospitalization was conducted to determine the relationship between human milk intake in-hospital and neurodevelopmental outcome at 18-22 months of age.11 Neonatal birth weight, gestational age, intraventricular hemorrhage status, sepsis, bronchopulmonary dysplasia, and hospital stay were similar between those never receiving (25% of cohort) and those who received human milk (75% of cohort) during their hospitalization. There were differences in socioeconomic variables, race and ethnicity, educational attainment, and parity between groups. When adjusted for these variables as well as biological confounders, there were significantly positive effects for human milk intake on mental and motor development. The study found fewer infants with low mental and motor developmental scores and higher behavior rating score in the group receiving any human milk in the NICU. The magnitude of the effect was greatest in the highest-quintile (>80th percentile) group, which averaged a human milk intake of 110 mL/kg/d. The impact of feeding 100 mL/kg/d of human milk was an increase in the Bayley Mental Development Index score of 5 points (one-third of an SD) and an increase in Psychomotor Development Index of 6 points.11 Others have reported that even the 5-point difference on the Mental Development Index would have a significantly meaningful effect on the outcome of extremely low birth weight infants.20 These important observations on neurodevelopmental outcome at 18-22 months have been reported to persist to 30 months.12
The antioxidant effects of human milk may be associated with lower rates of retinopathy of prematurity (ROP) in premature infants. Fewer infants with severe ROP were fed predominantly human milk. We found significantly less stage III ROP in extremely preterm infants fed their own mother’s milk (5.6%) compared with pasteurized donor human milk (19%) or preterm formula (14%), \( P = 0.05 \). In Japan, extremely preterm infants, 24 weeks’ gestation and birth weights 600-700 g, with advanced ROP and retinal detachment, were less likely to have received human milk.

There are many factors that might explain the associations between human milk feeding in premature infants and improved neurodevelopmental outcome. Many of the analyses were adjusted for important sociodemographic and parenting confounding variables. Few infants were actually breastfed, making the milk composition itself contributory to these outcomes. The combination of bioactive factors in human milk, rather than an individual factor, may account for the outcomes described. In addition, because human milk-fed premature infants experience fewer infection-related events, their better health likely contributes to the positive effects on neurodevelopmental outcome. Thus, because abnormal sensory-neural development is a significant long-term risk after premature birth, the use of mother’s milk should be strongly encouraged in this population.

**Nutritional Status and Growth**

A large variation in the energy and protein contents of human milk brought to the NICU by the mother has been reported. Although the concentrations of protein, sodium, and zinc decline through lactation, the nutrient needs of the premature infant remain higher than those of term infants until sometime after term postmenstrual age. Indexes of protein nutritional status are lower and continue to decline over time when premature infants are fed unfortified human milk. Protein and energy supplementation are associated with improved rates of weight gain, nitrogen balance, and indexes of protein nutritional status. Protein supplementation is important to improve short-term growth and long-term neurodevelopmental outcome. The absolute nutrient content of calcium and phosphorus in human milk is also inadequate for extremely premature infants. As a consequence of the low intakes of calcium and phosphorus, infants fed unfortified human milk have progressive decreases in serum phosphorus, increases in serum calcium, and increases in serum alkaline phosphatase activity compared with infants fed preterm formula containing adequate calcium and phosphorus. Follow-up investigations of infants with extremely elevated serum alkaline phosphatase activity in the NICU found that at 18 months there was an inversely relationship to linear growth, infants having the highest alkaline phosphatase values had as much as a 2-cm reduction in linear growth. Evaluation of this cohort at 9-12 years of age found that the elevated neonatal serum alkaline phosphatase activity remained a significant predictor of attained height in adolescence. These data suggest that long-term mineralization might be affected by early neonatal diet. Supplementation with both calcium and phosphorus results in normalization of biochemical indexes of mineral status and improved linear growth and increased bone mineralization during and beyond the neonatal period.

As fortifiers adjust for nutrient inadequacies, the rates of growth in the NICU do increase. Moreover, the rate of growth in the NICU is significantly associated with long-term neurodevelopmental outcome.

**Metabolic Syndrome**

There is increasing evidence that early nutrition programs long-term outcomes. Human milk feeding reduces the chance that premature infants will develop the metabolic syndrome, characterized by hypertension, obesity, and leptin and insulin resistance. A long-term study of premature infants was conducted in the United Kingdom. Infants were enrolled into 1 of 2 arms if their mothers elected not to provide breast milk. The study compared infants fed either donor human milk or preterm formula, diets characterized as low nutrient density vs high nutrient density. The infants had more rapid growth in neonatal period if fed the high nutrient density diet. Investigators found, however, that the high nutrient density diet was associated with significant deleterious long-term effects. There was a dose response benefit through adolescence for those given human milk (low nutrient density), with lower rates of obesity, hypertension, low-density lipoprotein cholesterol, leptin resistance, and insulin resistance. These data must be interpreted cautiously because, despite slow growth in the human milk-fed infants, they had “improved” brain development compared with infants receiving the greater nutrient density diets. Therefore, the goal should be to promote careful nutrition support but not excessive growth or nutrient intake. The optimal regimen(s) remain to be identified but will surely include predominantly, if not exclusively, some form of supplemented human milk.

**Conclusions**

There are significant host defense benefits from the feeding of mothers’ own milk for premature infants, even extremely premature infants. It is unclear how much milk is protective or at what postnatal age the protective effects are maximal. The benefits of a human milk diet in the NICU are seen in fewer hospital readmissions for illness, improved growth and body composition, improved long-term sensory-neural development, and lower risk of metabolic syndrome. The mechanisms for these long-term beneficial effects remain the subject of speculation. The various explanations certainly include the beneficial effects of maternal infant interaction and selection “bias” imposed by mother’s choice to provide milk. The stimulatory effect of a nonhomogenous diet with variable taste and odor may affect sensory development. Specific nutrients may be associated with improved outcomes. The highly bioavailable
unsaturated fatty acids have been implicated in improved

protein in human milk may be responsible.11 The cholesterol in human milk may be responsible for long-term regulation of cholesterol metabolism or even myelin synthesis.42,43 Polyunsaturated fatty acids have been implicated in improved brain and visual function.44 The long-chain oligosaccharide sugars have implications for host defense and gastrointestinal maturation, and improved neurodevelopmental outcome.45 The immunomodulation components of cells, immunoglobulins, cytokines, and growth factors also may play a role.24

Importantly, although there have been studies and suggestions to isolate single components from human milk to demonstrate a biological outcome, more likely it is the multiplicity of components in the milk that act together to protect and stimulate the infant host (Table 1).

References


Table 1 Likely Reasons Why Human Milk Promotes Improved Long-Term Outcomes

| Unknown |
| Maternal—infant interactions |
| Selection of breastfeeding (mother’s choice) |
| Nonhomogeneity of milk composition |
| Taste, odor of milk |
| Specific nutrients |
| Polyunsaturated fatty acids (i.e., long-chain polyunsaturated fatty acids) |
| Docosahexaenoic acid |
| Arachidonic acid |
| Cholesterol |
| Protein quality, quantity |
| Taurine, glutamine |
| Oligosaccharides, “Prebiotics” |
| Enzymes |
| Bile salt-stimulated lipase |
| Acetylhydrolase |
| Micronutrients (iodine, iron, zinc, selenium) |
| Specific factors |
| Immunoglobulin A, G |
| Lactoferrin |
| Lysozyme |
| Nucleotides |
| Antioxidants |
| Growth factors (nerve growth factor, insulin-like growth factor) |
| Cytokines (e.g., interleukin-10) |
| Better host defense |


