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Human Milk and Clinical Outcomes in VLBW Infants: How Compelling Is the Evidence of Benefit?

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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. Studies on neurodevelopmental outcomes have reported significantly positive effects for human milk intake on mental and motor development, intelligence quotient, and visual acuity compared with the feeding of formula. Human milk-fed infants also have decreased rates of re-hospitalization after discharge. It is unclear how much human milk is needed to provide protection or at what postnatal age the protective effects maximize. More data are warranted to elucidate these questions. Despite the significant benefits of mothers' own milk, nutritional adequacy may be a limiting factor in the infant weighing less than 1500 g at birth. The overall nutritional needs of these infants can be supported with a nutrient supplement, or fortifier, added to the milk.
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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 human milk.[1] Nutritional adequacy of mother's milk, however, may be a limiting factor in the very low birth weight (VLBW) infant weighing less than 1500 g at birth. Nutritional needs are determined based on intrauterine rates of growth and nutrient accretion.[2] The overall nutritional needs of the VLBW infant are met if a nutrient supplement, or fortifier, is added to the milk.

Unfortified Human Milk

The nutritional adequacy of human milk for premature infants may be limited for several reasons. The absolute nutrient content may be inadequate for their needs, such as calcium and phosphorus, which remain too low with respect to the needs of the premature infant. In addition, the variability in nutrient content results in unpredictable nutrient intakes for an infant who cannot feed ad libitum. The variability in nutrient composition is both inherent to milk and imposed by circumstances of collection, storage, and distribution. A large variation in the energy and protein contents of human milk brought to the neonatal nursery by the mother is reported.[3] The most variable nutrient in human milk is fat, the content of which differs during lactation, throughout the day, from mother to mother, and within a single milk expression.[4,5] As human milk is not homogenized, on standing, the fat content separates from the body of milk. Much of the variation in energy content of milk as used in the nursery is a result of differences in and/or losses of fat in the unfortified milk.[6,7] Although 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. Therefore, the decline in milk concentration precedes the reduction in nutrient needs and results in an inadequate nutrient supply from human milk for the premature infant. Technical issues associated with collection, storage, and delivery of milk to the infant also result in a decreased quantity of available nutrients (eg, vitamin C, vitamin A, riboflavin).

Growth and nutritional status of premature infants during and after hospital stay are affected by the nutrient inadequacies of unfortified human milk.[8-10] As growth rates in excess of 15 g/kg/d are desired, unfortified human milk would not

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meet this target.[11] Indices of protein nutritional status, eg, blood urea nitrogen, serum albumin, total protein, and transthyretin (prealbumin), are lower and continue to decline over time when premature infants are fed unfortified human milk.[12] 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.[13,14] Follow-up investigations of infants with extremely elevated serum alkaline phosphatase activity at 18 months found an association with linear growth, infants having the highest alkaline phosphatase values in-hospital had as much as a 2 cm reduction in linear growth.[15] Evaluation of this cohort at 9 to 12 year of age found that the elevated neonatal serum alkaline phosphatase activity remained a significant predictor of attained height.[16] These data suggest that long-term mineralization might be affected by early neonatal diet. With respect to the greater needs of the VLBW infant, the declining sodium and zinc contents of mother's milk may be associated with late hyponatremia and zinc deficiency.[17,18]

Human milk has not been rigorously studied in minimal enteral nutrition trials. The benefits observed for minimal enteral nutrition have been identified for infants fed human milk or formula. However, full enteral feeding is achieved significantly earlier with human milk than formula.[19] In addition, if human milk is used in early minimal enteral nutrition, infants receive more of their mothers' milk, probably because mothers initiate and sustain lactation more readily than those whose infants are not receiving their milk in the first 2 weeks.[20] Thus, although the data are limited, it seems appropriate to use human milk in minimal enteral nutrition.

Human Milk Fortification

The nutrient deficits that arise from feeding unfortified human milk can be corrected with nutrient supplementation.[1] Protein and energy supplementation are associated with improved rates of weight gain, nitrogen balance, and indices of protein nutritional status: blood urea nitrogen, serum albumin, total protein, and transthyretin.[12,21] The efficacy of only protein fortification of human milk was of short-term benefit resulting in increases in weight gain, and increments in length and head circumference growth.[22]

Supplementation with both calcium and phosphorus results in normalization of biochemical indices of mineral status: serum calcium, phosphorus, and alkaline phosphatase activity, and urinary excretion of calcium and phosphorus.[13,23] Mineral supplementation of unfortified human milk has been associated with improved linear growth and increased bone mineralization during and beyond the neonatal period.[24]

A systematic review that addressed multinutrient fortification of human milk included a meta-analysis of controlled trials of human milk fortification compared with the feeding of unfortified human milk.[24] More than 600 infants with birth weights less than 1850 g were included in the analyses. The addition of multinutrient fortifiers to human milk resulted in short-term improvements in weight gain, increments in length and head circumference, and bone mineral content during hospital stay.

A theoretical concern with human milk fortification is that the added nutrients may affect the intrinsic host defense system of the milk. The Cochrane review of fortified versus unfortified human milk did not identify any differences in NEC.[24] One randomized trial of multi-nutrient fortified human milk versus human milk supplemented only with phosphorus and vitamins in premature infants indicated no increases in the incidence of either confirmed infection or necrotizing enterocolitis.[25] When the latter two events were combined, however, the group fed fortified human milk had more events than infants in the control group. The data, however, were difficult to interpret because study infants in both groups received more than 50% of their diet as preterm formula.[26] Moreover, as indicated below, most contemporary studies demonstrated protective effects of mother's own milk and the milk studied was multi-nutrient fortified human milk. Thus, the practice of human milk fortification might have a marked effect on reducing the cost of medical care.

Effects of Human Milk on 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. In a retrospective review of medical records in a Washington DC neonatal intensive care unit, human milk-fed infants had a 26% incidence of documented infection compared with 49% in formula-fed infants.[27]

A semirandomized trial in the U.K. reported that necrotizing enterocolitis was reduced significantly by feeding premature infants human milk, either exclusively or partially supplemented with either formula or pasteurized donor human milk.[28] That study identified the highest risk for NEC in the group of infants born before 28 weeks gestation. The receipt of human milk was associated with significant protection from NEC in infants more than 27 weeks gestation. When compared with exclusive human milk feeding (mother's own milk or donor human milk), the receipt of only formula was associated with a 6.5-fold increase (95% confidence interval = 1.9 to 22, $P < 0.001$) in confirmed cases of NEC as identified from surgical pathology or postmortem examination. A significant threefold increase in NEC also was seen when a diet of exclusive formula feeding was compared with formula used as a supplement to human milk (confidence interval for confirmed cases 1.4 to 6.5, $P < 0.005$).

In a randomized comparison in a NICU in Mexico City, premature infants receiving human milk had markedly lower rates of NEC, diarrhea, and urinary tract infection and received fewer days of antibiotic treatment than infants fed formula.[29]

The relationship between dose of human milk and protective effect was examined posthoc from data derived in a study