Evaluation of the evidence to support current recommendations to meet the needs of premature infants: the role of human milk

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ABSTRACT
The beneficial effects of human milk extend to the feeding of premature infants, because their nutrition support must be designed to compensate for metabolic and gastrointestinal immaturity, immunologic compromise, and maternal psychosocial conditions. Significant effects on the recipient host, such as reduction in sepsis and necrotizing enterocolitis, have been reported for premature infants fed their mothers’ milk. However, nutritional concerns arise because the quantity of nutrients in breast milk may not meet the great nutrient needs of premature infants born weighing <1500 g. Human milk supplements, or fortifiers, are available to augment the nutrient content of unfortified breast milk. Host defense benefits observed in infants fed unfortified human milk also are found in premature infants fed fortified human milk. Availability of milk is an issue for mothers delivering prematurely. Donor pasteurized human milk has been suggested as a proxy for the mother’s own milk. Am J Clin Nutr 2007;85(suppl):625S–8S.

KEY WORDS Human milk, premature infants, fortified human milk

INTRODUCTION
Significant benefits to infant host defense, gastrointestinal maturation, neurodevelopment, and some aspects of nutritional status are observed when premature infants are fed human milk (1). The nutritional adequacy of mother’s milk, however, is a limiting factor in very-low-birth-weight infants weighing <1500 g at birth. Nutritional needs are determined on the basis of intrauterine rates of growth and nutrient accretion (2). To meet overall nutritional needs, infants fed their mother’s milk and who weigh <1500 g at birth receive a nutrient supplement or fortifier.

UNFORTIFIED HUMAN MILK
The nutritional adequacy of human milk for premature infants may be limited for several reasons. The nutrient content of the milk may be inadequate for the infants’ needs, and 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. Indeed, the energy and protein contents of human milk brought to the neonatal nursery vary greatly (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). Because human milk is not homogenized, as the milk stands, the fat content separates from the body of milk. Much of the variation in the energy content of milk as used in the nursery is a result of differences in or losses of fat in the unfortified milk (6, 7). Although concentrations of protein, sodium, and zinc decline through lactation, the nutrient needs of premature infants 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. The content of other nutrients (eg, calcium, phosphorus) varies less through lactation but remains too low with respect to the needs of premature infants. Technical reasons associated with the collection, storage, and delivery of milk to infants also result in a decreased quantity of available nutrients (eg, vitamin C, vitamin A, and riboflavin).

Growth and nutritional status during and after the hospital stay of premature infants are affected by the nutrient inadequacies of unfortified human milk (8, 9). Because growth rates in excess of 15 g · kg⁻¹ · d⁻¹ are desired, unfortified human milk would not meet this target. Indexes of protein nutritional status, eg, blood urea nitrogen, serum albumin, total protein, and prealbumin, are lower and continue to decline over time when premature infants are fed unfortified human milk (10). 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 (11, 12). Follow-up investigations of infants with extremely elevated serum alkaline phosphatase activity at 18 mo found an association with height, in which infants having the highest alkaline phosphatase values in the hospital had as much as a 2-cm reduction in linear growth (13). Evaluation of this cohort at 9 to 12 y of age found that the elevated neonatal serum alkaline phosphatase activity remained a significant predictor of attained height (14). These data suggest that long-term mineralization might be affected by early neonatal diet. The low milk sodium may be associated with late hyponatremia, and zinc deficiency with...
prolonged feeding of unfortified human milk has been reported (15, 16).

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 indexes of protein nutritional status, including blood urea nitrogen, serum albumin, total protein, and prealbumin (10, 17). The efficacy of only protein fortification of human milk is of short-term benefit and results in increases in weight gain and increments in length and head circumference growth (18).

Supplementation with both calcium and phosphorus results in normalization of the biochemical indexes of mineral status, including serum calcium, phosphorus, and alkaline phosphatase activity, and the urinary excretion of calcium and phosphorus (11, 19). Mineral supplementation of unfortified human milk has been associated with improved linear growth and increased bone mineralization during and beyond the neonatal period (20).

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 (20). More than 600 infants with birth weights <1850 g were included in the analyses. The addition of multinutrient fortifiers to human milk resulted in short-term improvements in weight gain, length and head circumferences, and bone mineral content during the hospital stay.

EFFECTS OF HUMAN MILK ON HOST DEFENSE

The relation between diet and the incidence of infection in premature infants shows 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 (NICU), human-milk-fed infants had a 26% incidence of documented infection compared with 49% in formula-fed infants (21).

A semi-randomized trial in the United Kingdom 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 (22). That study identified the highest risk of necrotizing enterocolitis in the group of infants born before 28 wk gestation. The receipt of human milk was associated with significant protection from necrotizing enterocolitis in all gestational age groups >27 wk. When compared with human milk feeding, the receipt of formula was associated with a 2.5-fold increase in necrotizing enterocolitis (95% CI: 1.2, 5.2; P < 0.02) for all cases and a 6.5-fold increase (95% CI: 1.9, 22; P < 0.001) for confirmed cases of necrotizing enterocolitis as identified from surgical pathology or postmortem examination. A significant 3-fold increase in necrotizing enterocolitis also was seen when a diet of exclusive formula feeding was compared with formula used as a supplement to human milk: the CI for all cases was 1.5 to 5.7 (P < 0.005) and that for confirmed cases was 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 incidences of necrotizing enterocolitis, diarrhea, and urinary tract infection and received fewer days of antibiotic treatment (23). The relation between dose of human milk and protective effect was examined post hoc from data derived in a study of 2 feeding strategies for premature infants: trophic feeding at 4 versus 14 d and continuous versus intermittent bolus tube feeding (24). The study enrolled infants born before 30 wk gestation who were stratified by diet, either mother’s milk or preterm formula. Differences between groups favored early trophic feeding at 4 d with the intermittent bolus feeding method. However, for all measured outcomes, the diet was the most important variable. Infants fed predominantly human milk (averaged as >50 mL/kg·d−1) had significantly less late-onset sepsis and necrotizing enterocolitis and a shorter hospitalization than did infants fed preterm formula. Late-onset sepsis or necrotizing enterocolitis was of greater incidence in infants receiving preterm formula, but if infants received a combination of mother’s milk and preterm formula, they had the highest risk of sepsis or necrotizing enterocolitis. The study identified a dose of human milk that might be protective. This dose of mother’s milk, >50 mL·kg−1·d−1, subsequently was shown to protect against late-onset sepsis in a 4-wk study of premature infants when compared with daily doses of 1–24 and 25–49 mL/kg (25).

A reduction in infectious morbidity in human-milk-fed premature infants was reported in nearly a dozen studies over the past 25 y (26). Unfortunately, the reports have numerous methodologic issues and are compounded by the inability to perform truly randomized trials in human-milk-fed premature infants. Several issues arise when comparing studies, such as differences in the definition of breast milk (eg, partial, exclusive, mothers’ own, or donor milk) and how the milk was treated (eg, fresh raw milk or heat treated). In addition, the measured outcome of infection was not always defined rigorously, and confounding factors were not considered uniformly. There also appear to be factors inherent in the mother’s choice to provide breast milk and differences in sociodemographic variables affecting parental contact between study groups (27, 28).

A theoretical concern with human milk fortification is that the added nutrients may affect the milk’s intrinsic host defense system. A meta-analysis comparing infants fed fortified and unfortified human milk did not identify any difference in necrotizing enterocolitis (20). One randomized trial of fortified versus unfortified human milk in premature infants indicated no increases in the incidence of either confirmed infection or necrotizing enterocolitis compared with controls (29). When the latter 2 events were combined, however, the group fed fortified human milk had more events than did the infants in the control group. The data, however, were difficult to interpret because study infants in both groups received >50% of their diet as preterm formula (30). Overall, these data suggest that by reducing infectious morbidity, feeding premature infants fortified mother’s milk might have a marked effect on reducing the cost of medical care.

EFFECTS ON NEURODEVELOPMENTAL OUTCOME

There are increasing reports that the diet in the NICU might affect long-term neurodevelopmental outcomes in premature infants. An 8-y follow-up of 300 premature infants (≈1.4 kg and 31 wk gestation at birth) observed that when factors affecting intelligence quotient (social class, maternal education, infant sex, and
duration of mechanical ventilation) were considered in a regression model, the receipt of breast milk in the NICU was associated with an 8-point advantage, slightly more than 1 SD of the mean (31). A cohort of adolescents was followed since their NICU stay as premature infants, and significant cognitive and psychomotor benefits were ascribed to the feeding of human milk (32–34). In a large study of premature infants (30 wk gestation and birth weight = 1.3 kg) fed either human milk or preterm formula, a human milk diet was associated with significantly greater scores for behavioral visual acuity at 2–6 mo corrected age than was preterm formula (35). The effect of human milk on cognitive indexes also was seen at 12 mo corrected age, and in infants with chronic lung disease, a significant benefit of a human milk diet was observed in psychomotor indexes. These observations were adjusted for HOME Inventory, maternal intelligence testing, smoking, and birth weight.

The relation between human milk intake at the hospital and neurodevelopmental outcome at 18–22 mo of age has been reported (36). When adjusted for demographic and biological confounders, there were significantly positive effects for dose of human milk intake on mental and motor development. The magnitude of the effect was greatest in the highest quintile of human-milk-fed infants (36).

MATERNAL MILK PRODUCTION

Many mothers are unable to provide sufficient milk to meet the needs of their very-low-birth-weight infants throughout the infant’s hospitalization (28). Thus, as benefits continue to be attributed to the feeding of mothers’ milk, a proxy for this milk is needed.

DONOR HUMAN MILK

The concern about transmission of infectious agents through breast milk led to the decline in donor human milk banks and to the obligatory requirement for pasteurization if donor milk is used in the United States (37). The common pasteurization process, Holder pasteurization, refers to heating milk at 62.5 °C for 30 min (38). This process results in a decrease in activity of many enzymes. The relative risk of necrotizing enterocolitis by feeding formula was 2.5 (95% CI: 1.3–4.3) (41).

The neurodevelopment of premature infants may benefit from mother’s milk, but more data are warranted in the follow-up of these infants. Studies on cognitive and motor development as well as sensory development are needed. Mother’s own milk is nutritionally adequate to meet the needs of infants weighing <1500 g at birth if it contains US human milk fortifiers. Further adjustments in nutrients are warranted. Global human milk fortifiers offer a wide range of nutrient contents, some of which do not meet recommended intakes for premature infants. There are only scant nutritional data on recommendations for premature infants weighing 1500–2000 g at birth. This is a large group of premature infants who receive unsupplemented human milk. Last, lactation strategies should be sought that increase mother’s own milk production.

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