Human milk fortification for premature infants\textsuperscript{1,2}

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The article by Lucas et al (1) in this issue of The American Journal of Clinical Nutrition comes as an important follow-up to their previous large-scale, multicenter study (2). That study of premature infants reported specific benefits of feeding human milk compared with formula: a reduction in the incidence of necrotizing enterocolitis (NEC) and an increase in neurodevelopmental scores (3, 4). However, because unfortified human milk was used in that study, several adverse nutritional outcomes were observed. The infants receiving human milk during their hospitalization had more evidence of abnormal bone mineralization (high alkaline phosphatase activity, low serum phosphorus concentrations), which, beyond hospitalization, was associated with decreased linear growth through 18 mo of follow-up (5). In addition, it was concluded, in a subset of infants from the multicenter study, based on increased psychomotor developmental scores from feeding preterm rather than full-term formulas, that a greater protein intake was indicated for premature infants (6). Thus, Lucas et al paved the way for clinicians to advocate feeding human milk in neonatal intensive care units (NICUs) and, in doing so, encouraged the use of nutritional fortifiers to increase the calcium, phosphorus, and protein contents of human milk.

As the authors suggest, the article published in this issue points out the complexity of nutrient fortification of human milk for premature infants. The current study also shows the difficulties in interpreting data from intent-to-treat analyses in which the subjects cannot be kept on the assigned treatment or the treatment becomes obscured by other factors, such as the unavoidable feeding of preterm formula. This is especially the case in instances where the results will prompt changes in the clinical management of patients.

In the current study design, the groups of infants fed human milk were randomly assigned to receive either a fortifier consisting of protein, glucose polymers, sodium, potassium, calcium, phosphorus, magnesium, zinc, copper, and vitamins or a control regimen consisting of sodium, potassium, phosphorus, and vitamins. Thus, both groups received some fortification, ie, supplementation of their mothers’ milk. The question to ask is does human milk fortification benefit premature infants in terms of 1) development, 2) growth, 3) morbidity, and 4) nutritional status?

1. The investigators conclude that psychomotor indexes were not significantly different between groups. These results are of interest because of group similarities; both attained normal scores. The addition of bovine protein appeared to not impair these outcomes.

2. The fortified group had faster weight gain when human milk exceeded 50% of intake.

3. The differences in the incidence of NEC between groups was not significant. Note that the incidence was low and similar to that reported previously by the investigators for premature infants fed human milk or human milk plus formula (~4%) compared with similar formula-fed infants, in whom the incidence was 10% (3). Because the reported incidence of NEC in this study population was low, it would be difficult to design a study with sufficient sample size to show a further reduction in the incidence of this condition.

The difference in the reported rates of infection between groups is noteworthy. There is a concern that manipulating human milk—either by the mechanical means of milk expression and feeding or by the addition of fortifying nutrients—will affect the intrinsic host-defense properties of the milk. My group reported that the addition of commercial fortifier to human milk resulted in slightly greater bacterial growth after 24 h of refrigerator storage (7). Under the same conditions, we observed no changes in the total immunoglobulin A concentration of fortified human milk from 0 to 72 h (7). The results of the current study should be interpreted cautiously. There were no differences between groups in the incidence of bacteriologically proven infection. Differences between groups were observed only when clinical and laboratory data were combined with positive bacterial cultures. Thus, these results do not provide sufficient evidence to question the safety of commercial fortifiers.

4. The fortified group had better protein status. The fortified group had greater plasma urea concentrations from weeks 3 to 6 of the study (values between 2 and 3 mmol/L), greater plasma protein values at weeks 3 and 4, and, overall, fewer instances of very low plasma urea concentrations (<1 mmol/L). However, as an indication of the complexity of these findings, the fortified group also had a greater number of elevated plasma urea values than the control group. Paradoxically, the fortified group had lower plasma amino acid concentrations, although the differences were <1 SD. Does this suggest that the better growth in the fortified group was associated with more

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The consensus is that infants with a birth weight of human milk had slower growth rates than expected (8). In our study is which premature infants should receive fortification. For the subgroup analyses. No differences in developmental outcome were observed; however, the fortified group had greater weight gain than the control group. The subgroup analyses for morbidity and nutritional status were not provided. Further description of the group receiving human milk fortifiers is a logical option, identifies the complexity of the issue, and defines areas that require further investigation. The group should be applauded for successfully completing the first large-scale study of human milk fortification.

REFERENCES


utilization of amino acids? The reasons for these differences are unclear. The protein content of breast milk declines during the course of lactation. Was the decline delayed more in the fortified group? Was there any loss of fortifier by precipitation or settling out in the container or feeding syringe?

Despite differences in mean plasma calcium between groups, the mean plasma calcium and phosphorus values were in the normal range in both groups throughout the study. The fortified group had greater plasma alkaline phosphatase activity in the last 3 wk of the study. This may be associated with more rapid growth. It is difficult to interpret differences when both groups received a phosphorus supplement.

The results of this study may lead one to conclude that there was not a great benefit to premature infants from fortified human milk. Because breast milk made up only ~47% of the enteral intake, it is a concern that the use of preterm formula may have obscured subtle differences between the groups. As the investigators indicate, the interpretation becomes quite complex. It would be important to better understand why mothers stopped providing milk for their infants and whether the reasons were similar between groups. Were those infants more ill? Did they have more nutritional abnormalities or slower growth that prompted clinicians or parents to stop providing milk? Nonetheless, the basic study design tested the outcome of current practice because it is often the case that human milk-fed premature infants receive some preterm formula.

The investigators indicate that subgroup analyses were conducted on those infants who received ≥50% breast milk and <50% breast milk. No baseline comparisons were provided for the subgroup analyses. No differences in developmental outcome were observed; however, the fortified group had greater weight gain than the control group. The subgroup analyses for morbidity and nutritional status were not provided. Further description of the group receiving ≥50% breast milk might identify specific differences between groups.

There are many issues to be reconciled with the use of human milk fortifiers. One area not addressed by the current study is which premature infants should receive fortification. The consensus is that infants with a birth weight <1500 g should receive human milk fortifiers but no data exist in its support. Because the current study enrolled some larger infants, it would be of interest to compare the outcomes of larger premature infants with smaller ones.

We found that premature infants fed commercially fortified human milk had slower growth rates than expected (8). In our investigation, weight gain increased when larger volumes of milk (180–200 mL · kg⁻¹ · d⁻¹) were provided. Energy intake and weight gain also increased by using hindmilk in the feeding protocol (9). We observed normal biochemical indexes of nutritional status in premature infants fed fortified human milk compared with expected values and with values obtained in infants receiving preterm formula. We speculated that mothers may produce milk with more species-specific host defense properties if skin-to-skin care is encouraged in the NICU. The enteroenteric immune system, therefore, might be triggered to produce milk that has the capacity to inhibit the growth of bacteria common to the environment of the NICU. If such a mechanism exists in this environment, the importance of feeding human milk for host protection would receive top priority.

The study by Lucas et al (1) concludes that the use of human milk fortifiers is a logical option, identifies the complexity of the issue, and defines areas that require further investigation. The group should be applauded for successfully completing the first large-scale study of human milk fortification.