Growth, Efficacy, and Safety of Feeding an Iron-Fortified Human Milk Fortifier

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ABSTRACT. Objective. Survival rates for preterm infants who weigh between 501 and 1500 g at birth have continued to improve over time. In response to this continuing decrease in birth weight of surviving preterm infants, Enfamil Human Milk Fortifier has recently been reformulated to meet the nutritional requirements of these smaller, more rapidly growing infants. It now provides an increased protein level of 1.1 g/58 kJ, a decreased carbohydrate level of 0.2 g/58 kJ, and a combined linoleic and α-linolenic fatty acid content of 157 mg/58 kJ. As these very small preterm infants have an increased requirement for dietary iron, the fortifier has been supplemented with 1.44 mg/58 kJ of iron, an amount of iron similar to that provided in a typical iron-fortified term infant formula. An iron-fortified product obviates the need for administration of an iron supplement, a hyperosmolar-inducing intervention. The purpose of this prospective, double-blind, randomized, controlled study was to evaluate growth, safety, and efficacy in a population of very low birth weight (VLBW) preterm infants who received human milk fortified with either the reformulated iron-fortified powdered human milk fortifier test product (HMF-T) or a powdered commercially available human milk fortifier control product (HMF-C).

Methods. Infants who weighed ≤1500 g, had a gestational age ≤33 weeks postmenstrual age, and had an enteral intake of at least 100 mL/kg per day of unfortified human milk were stratified by gender and birth weight and randomized to receive HMF-T or HMF-C product from study day 1 to study day 28, hospital discharge, or the termination of human milk feedings, whichever came first. Unless medically indicated, investigators were not to administer iron supplements from study days 1 to 14. Infants were assessed serially for growth; enteral and parenteral intake; serum chemistry and hematologic values; clinical histories, including the administration of blood transfusions; feeding tolerance; respiratory outcomes; and morbidities, including adverse events.

Results. Of the 181 participating infants in this study, 96 received HMF-T and 85 received HMF-C. At randomization, there were no significant differences in infant characteristics between the fortifier groups. The percentage of participants who remained in the study for 28 days was similar between fortifier groups (57% HMF-T, 46% HMF-C). For both fortifier groups, the most frequent reasons for discontinuing the study before study day 28 were unavailability of human milk and hospital discharge. Rate of weight gain was similar between the fortifier groups (17.5 ± 0.53 g/kg per day for HMF-T and 17.3 ± 0.59 g/kg per day for HMF-C). Mean achieved weight, length, and head circumference were comparable between groups across the 28-day study period. Total protein intake from enteral and parenteral nutrition was significantly greater for the HMF-T fortifier group; however, this difference did not result in any difference in growth between the 2 fortifier groups. An analysis of the growth and energy intake data of a subset of the intent-to-treat population who adhered more strictly to the study feeding protocol yielded results similar to those seen for the intent-to-treat population. There were no clinically significant differences in the results of laboratory studies between the groups at study days 0, 14, and 28. Anemia of prematurity was prevalent in both study groups; by study day 28, median hematocrit levels were 27.0% (interquartile range [IQR]: 24.0%–29.6%) for the HMF-T group and 26.0% (IQR: 24.0%–31.0%) for the HMF-C group. Median ferritin levels were 77.0 ng/mL (IQR: 37-155 ng/ml) for HMF-T and 92.0 ng/mL (IQR: 33-110 ng/mL) for HMF-C. There were no significant differences between the study fortifier groups in regard to the receipt of medically indicated iron supplements on or before study day 14 or in the administration of blood transfusions before study day 0 or from study days 0 through 14. However, from study day 15 to study day 28, fewer HMF-T infants (n = 12) required a blood transfusion than did HMF-C infants (n = 20). Although the higher levels of iron in the HMF-T fortifier (1.44 mg vs 0.35 mg for HMF-C per 4 packets of powdered fortifier) did not prevent anemia per se, it did reduce the frequency of one of the most serious outcomes of anemia: the need for a blood transfusion. There was no statistically significant difference between fortifier groups in regard to feeding tolerance. Rates of suspected sepsis (26% HMF-T vs 31% HMF-C) and confirmed sepsis (5% HMF-T, 7% HMF-C) were low as were the rates of suspected necrotizing enterocolitis (NEC) 6% HMF-T and 5% HMF-C and confirmed Bell’s stage 2 or more NEC (1% HMF-T and 1% HMF-C). There were no statistically significant differences between the study fortifier groups in regard to the incidence of confirmed and suspected sepsis and NEC.

Conclusion. Both human milk fortifiers studied are safe, are well tolerated, and facilitate comparable good growth; however, using the iron-fortified product may reduce the need for blood transfusions in VLBW infants. The similar low rates of suspected and confirmed NEC and sepsis seen in both fortifier groups in this study refutes the premise that the inclusion of iron in fortifiers will increase the incidence of sepsis and NEC. Indeed,
the incidence for NEC and sepsis for both groups in this study was lower than is reported for VLBW infants and similar to that seen for infants who are fed human milk. Pediatrics 2004;114:699–706. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0911; growth, human milk, premature infants, fortifier, iron.

ABBREVIATIONS. HMF, human milk fortifier; VLBW, very low birth weight; HMF-C, control human milk fortifier; HMF-T, test human milk fortifier; NEC, necrotizing enterocolitis.

Survival rates for preterm infants who weigh between 501 and 1500 g at birth have continued to improve over time.1 In response to this continuing decrease in the birth weight of surviving preterm infants, Enfamil Human Milk Fortifier (HMF) has been reformulated several times to meet the nutritional requirements of these smaller, more rapidly growing infants. The most recent reformulation included increasing the protein content, decreasing the carbohydrate content, and increasing the fatty acid content, including that for linoleic and α-linolenic fatty acids. For improving the acceptance and tolerance of the most recently reformulated product, the incremental osmolality was reduced to 35 mOsm/kg H2O.

Iron-fortified term infant formulas. Using an iron-fortified term infant formulas obviates the need for the administration of separate iron supplements, a hyperosmolar product (HMF-C).

The purpose of this study was to evaluate growth, safety, and efficacy in a population of very low birth weight (VLBW) preterm infants who received human milk fortified with either this reformulated fortifier test product (HMF-T) or another commercially available fortifier control product (HMF-C).

METHODS

Study Population

Infants with a birth weight ≤1500 g, a gestational age ≤33 weeks postmenstrual age, and an enteral intake of at least 100 mL/kg per day of unfortified human milk were considered eligible for the study. Infants were excluded when they had (1) an underlying disease or a congenital malformation that was likely to interfere with growth or tolerance of fortified human milk; (2) a 5-minute APGAR score ≤4; (3) undergone major surgery or received a diagnosis of grade 3 or 4 intraventricular hemorrhage before or on study day 0; (4) received pharmacologic doses of glucocorticoids on >4 different days before study day 0 or on or within 72 hours of study day 0; (5) consumed any marketed HMF before or on study day 0; (6) a feeding intolerance to human milk; (7) received erythropoietin therapy, oral vitamin D, minerals, or iron on study day 0; or (8) ventilator dependence on study day 0 (>40% fraction of inspired supplemental oxygen and/or nasal continuous positive airway pressure were allowed).

The Institutional Review Board at each site reviewed and approved the protocol and procedures. The parent(s) or guardian(s) of each infant provided written informed consent.

Design

Infants were enrolled into this prospective, randomized, double-blind, multicenter study from December 2001 to January 2003. After achieving an enteral intake of 100 mL/kg per day of unfortified human milk, eligible premature infants were stratified by gender and birth weight (≤1000 g or >1000 g) and randomized on study day 0 to receive either the iron-fortified HMF-T or the HMF-C, mixed as a supplement to their human milk feedings. A randomization schedule was provided to each site to maintain a balance at each site in the number of infants who were randomized to each fortifier group within each stratification level (gender, birth weight ≤1000 g or >1000 g). Nutrient content of the study fortifiers and their fortified products are in Table 1. It was recommended that the first fortifier be fed at an initial fortifier additive strength of 1/2 strength, ie, 2 packets of study fortifier added to 100 mL of human milk and at full strength (4 packets of study fortifier per 100 mL of human milk) for the remaining days of the study. However, deviations from this schedule were allowed if the investigator deemed it appropriate. Likewise, the frequency and the volume of feedings were determined by the medical team responsible for the care of the participant. Infants were assessed serially for growth, enteral and parenteral intake, serum chemistry and hematologic values, clinical histories, feeding tolerance, respiratory outcomes, and morbidities.

Anthropometric Measurements

Daily weights of the participants were assessed using electronically calibrated scales. Length and head circumference were measured on a weekly basis by trained personnel. Body length was measured with the infant in a recumbent position using a preterm infant lengthboard. A flexible, nonstretchable cloth or vinyl tape measure was used to assess head circumference.

Enteral and Parenteral Intakes

Enteral and parenteral intakes were documented from the bedside charts used in the neonatal intensive care unit. Enteral intake documented included the daily total amount of nonbreastfed human milk consumed (fed from a bottle or nasogastric tube), an indication of whether any human milk had been fed directly from the breast; the strength of study fortifier used; and the amount of any infant formula or supplement, such as medium-chain triglycerides, ingested. The amount and the type of any parenteral nutrition was also documented.

Acceptance and Feeding Tolerance

Reasons for discontinuation from the study were recorded. Feeding tolerance, the occurrences of abdominal distention, emesis that was considered to be clinically significant by the investigators at the site, the presence of guaiac-positive stools, and the number of feedings withheld were assessed daily.

Respiratory Outcomes, Morbidity, and Adverse Events

The respiratory status of each participant was assessed daily. The incidence of apnea or bradycardia or the need for supplemental oxygen and/or mechanical ventilation was documented. All reports of suspected or confirmed septic infections were documented as were all incidents of presumed or confirmed necrotizing enterocolitis (NEC), classified according to Bell’s staging criteria.4 Participants were monitored for any requirement for positive pressure ventilation, reintubation as a result of a worsened condition, surgery of any kind, and the occurrence of serious adverse events.

Laboratory Studies

On study days 0, 14, and 28, blood samples were drawn from the participants by venipuncture. A small portion of the sample was used by the laboratory at the site to determine the hematocrit. The remainder of the sample was frozen and later processed at a single laboratory for determination of albumin, transthyretin, alkaline phosphatase, blood urea nitrogen, triglycerides, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, zinc, copper, ferritin, and vitamin D.

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The remaining continuous variables were analyzed using analysis of variance; categorical variables were analyzed using Fisher exact test.

Statistical comparison of rate of weight gain was based on a 1-tailed test; all other tests were 2-tailed. All testing was conducted at an α level of .05 using SAS version 8.1 software.

**RESULTS**

**Study Population**

A total of 185 preterm infants were enrolled and randomized into this study. Four of these infants never received study fortifier. Of the remaining 181 participants, 96 received human milk fortified with the HMF-T and 85 received human milk fortified with the HMF-C. Fifty-five (57%) of the HMF-T infants and 39 (46%) of the HMF-C infants remained in the study for 28 days. Of the 87 participants who did not remain in the study for 28 days, 63 discontinued because in-hospital human milk fortification with study fortifier was no longer possible because of (1) a lack or insufficient supply of human milk (\( n = 28 \)), (2) discharge from the hospital before day 28 \( (n = 34) \), or (3) transfer to a nonstudy hospital \( (n = 1) \). There was no statistically significant difference between the study groups in regard to the percentage of infants who did not remain in the study for 28 days.

Characteristics of the infants are summarized in Table 2. There were no statistically significant differences between study groups with respect to any infant characteristic at entry to the study.
subset analyses, there was no trend for the HMF-T group to have a higher energy intake from the total enteral and parenteral nutrition, and protein intake from fortified human milk was significantly greater for the HMF-T group than for those who received human milk fortified with HMF-C (Table 3).

Subset Analysis

Infant growth and energy intake parameters were also analyzed for a subset of the overall study population who met more strict criteria. This subset included data for only those study infants who (1) received 80% of their energy intake from human milk fortified with study fortifier for at least the first 2 weeks of the study and who received nothing by mouth for <3 days during this period; (2) ingested study fortifier at full strength on study day 3; (3) received no glucocorticoid therapy during the study; and (4) had no diseases that affected growth. Results from these analyses were very similar to those obtained for the overall study population (weight gain [g/kg per day]: 17.4 ± 0.60 HMF-T, 17.6 ± 0.63 HMF-C, \( P = .35 \); energy intake (kJ/kg per day) from fortified human milk: 116 ± 2 HMF-T, 114 ± 2 HMF-C, \( P = .25 \); energy intake (kJ/kg per day) from parenteral intake: 0.6 ± 0.2 HMF-T, 0.4 ± 0.2 HMF-C, \( P = .20 \); energy intake (kJ/kg per day) from total enteral and parenteral intake: 118 ± 1 HMF-T, 117 ± 1 HMF-C, \( P = .34 \); protein intake (g/kg per day) from fortified human milk: 3.9 ± 0.1 HMF-T, 3.7 ± 0.1 HMF-C, \( P < .001 \); protein intake (g/kg per day) from parenteral intake: 0.03 ± 0.01 HMF-T, 0.02 ± 0.01 HMF-C, \( P = .34 \); protein intake (g/kg per day) from total enteral and parenteral intake: 4.0 ± 0.04 HMF-T, 3.8 ± 0.04 HMF-C, \( P < .001 \)). Results from the subgroup analyses did not parallel those seen in the overall study population in 2 instances: in the subgroup analyses, there was no trend for the HMF-T group to have a higher energy intake from the total enteral and parenteral nutrition, and protein intake from fortified human milk was significantly greater for those who consumed human milk fortified with HMF-T than for those who received human milk fortified with HMF-C (Table 3).

Growth

In regard to mean weight gain during the study period, there were no statistically significant differences between study fortifier groups (Table 3). Achieved weight, achieved length, and achieved head circumference on study days 7, 14, 21, and 28 were similar between study fortifier groups (Fig 1).
greater for the HMF-T group than for the HMF-C group.

Laboratory Studies

Blood samples were drawn on study days 0, 14, and 28 for hematology and serum chemistry studies, including hematocrit, albumin, transthyretin, alkaline phosphatase, blood urea nitrogen, triglycerides, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, zinc, copper, ferritin, and vitamin D. There were no statistically significant differences between the groups at any time point for any laboratory study, with 1 exception: on study day 14, infants in the HMF-C group had a higher bicarbonate value than did infants in the HMF-T group ($P = .049$; HMF-C median: 26.53; HMF-T median: 26.01).

Transfusions and Iron Status

The number and percentage of infants in each study group who received a blood transfusion before study day 0, from study day 0 through study day 14, or from study day 15 through study day 28 are shown in Table 4. From study day 15 through study day 28, fewer HMF-T infants required a transfusion than did HMF-C infants ($P = .014$).

There were no significant differences between the study fortifier groups in regard to the receipt of medically indicated oral vitamin D, iron, sodium, or potassium supplements on or before study day 14.

<table>
<thead>
<tr>
<th>TABLE 4. Blood Transfusion and Morbidity Results</th>
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<td>Receiving blood transfusions</td>
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<tr>
<td>Before study day 0</td>
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<tr>
<td>From study days 0 through 14</td>
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<td>From study days 15 through 28†</td>
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<tr>
<td>With morbidity*</td>
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<tr>
<td>Suspected sepsis</td>
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<tr>
<td>Confirmed sepsis</td>
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<tr>
<td>Suspected NEC‡</td>
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<tr>
<td>HMF-T, $n$ (%)</td>
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<tr>
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<td>HMF-C, $n$ (%)</td>
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<td>4 (5)</td>
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</table>

* No statistically significant differences were detected between fortifier groups.
† Statistically significant, $P = .014$.
‡ Bell’s stage 2 or more.
(data not shown). The iron status of the study participants as reflected by median hematocrit and ferritin values on study days 0, 14, and 28 are shown in Table 5. There were no statistical differences between the study groups at any time point; however, it is significant to note that both study groups experienced a worsening in their iron status during the study period as reflected by these 2 laboratory studies.

Acceptance and Feeding Tolerance

The study fortifiers were equally well tolerated. Only 5 infants (2 HMF-T, 3 HMF-C) left the study as a result of feeding intolerance. There were no statistically significant differences between the fortifier groups in regard to the mean daily amount of residuals, expressed as a percentage of enteral intake (1.4 ± 0.2% for HMF-T and 1.4 ± 0.3% for HMF-C); the percentage of days that abdominal distention was present (3.2 ± 1.4% for HMF-T and 4.9 ± 1.5% for HMF-C); the percentage of days that guaiac-positive stools were present (1.4 ± 1.4% for HMF-T and 2.4 ± 1.5% for HMF-C); or the percentage of days that feedings were withheld as a result of intolerance (2.6 ± 1.5% for HMF-T and 1.6% for HMF-C). The number of participants with suspected or confirmed sepsis or with suspected or confirmed NEC did not result in greater growth for the HMF-T infants because protein intake levels in both fortifier groups exceeded 3 g/kg per day, the value determined by Polberger et al8 to be the upper limit of protein intake that affects growth. However, even incrementally greater intakes of protein during initial hospitalization in these VLBW preterm infants may be advantageous. In his review of the nutritional requirements in preterm infants with special reference to “catch-up” growth, Heird10 proposed that there is a finite period, likely the first 1 to 2 months postterm, during which the catch-up response to higher nutrient intake is most likely to occur. He suggested that feeding even higher protein and energy intakes than are provided by current formulas or HMFs during hospitalization and through 40 to 48 weeks’ postmenstrual age is the most effective strategy for taking advantage of this sensitive period of catch-up growth.

Respiratory Outcomes, Morbidity, and Adverse Events

The percentage of days that participants had apnea or bradycardia or required supplemental oxygen or mechanical ventilation did not differ significantly between the study fortifier groups (data not shown). The number of participants with suspected or confirmed sepsis or with suspected or confirmed NEC did not differ significantly between the HMF-T (iron-fortified) and HMF-C (non iron-fortified) study groups (Table 4). There were no differences between the fortifier groups in the incidence of monitored adverse events.

Table 5. Hematocrit and Serum Ferritin Values on Study Days 0, 14, and 28

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Group</th>
<th>Median</th>
<th>Interquartile Range</th>
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<tbody>
<tr>
<td>0</td>
<td>HMF-T</td>
<td>36.1</td>
<td>32.9–40.1</td>
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<tr>
<td></td>
<td>HMF-C</td>
<td>36.9</td>
<td>31.0–42.0</td>
</tr>
<tr>
<td>14</td>
<td>HMF-T</td>
<td>30.0</td>
<td>26.2–34.0</td>
</tr>
<tr>
<td></td>
<td>HMF-C</td>
<td>29.4</td>
<td>25.1–34.0</td>
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<tr>
<td>28</td>
<td>HMF-T</td>
<td>27.0</td>
<td>24.0–29.6</td>
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<tr>
<td></td>
<td>HMF-C</td>
<td>26.0</td>
<td>24.0–31.0</td>
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</table>

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<tr>
<th>Ferritin, ng/mL</th>
<th>Study Day</th>
<th>Study Group</th>
<th>Median</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td></td>
<td>HMF-C</td>
<td>272.5</td>
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</tr>
<tr>
<td>14</td>
<td>HMF-T</td>
<td>100.0</td>
<td>54–200</td>
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<td></td>
<td>HMF-C</td>
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<tr>
<td>28</td>
<td>HMF-T</td>
<td>77.0</td>
<td>37–155</td>
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<tr>
<td></td>
<td>HMF-C</td>
<td>92.0</td>
<td>33–110</td>
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</table>

* No statistically significant differences were detected between fortifier groups.

**DISCUSSION**

**Growth**

Although survival rates for preterm infants who weigh between 501 g and 1500 g at birth have increased from 74% in 1988 to 80% in 1991 and to 84% by 1996, poor postnatal growth remains a major concern.1 Several investigators5–8 have recently expressed concerns that premature infants, especially those who weigh <1000 g, need increased caloric intakes, especially that provided by protein. Growth failure among many of the smaller infants in these studies was attributable to failure to ingest recommended dietary intakes parenterally5 and/or enterally6–8 for protein and calories.

In our current study, both fortifier groups demonstrated rates of weight gain near the expected average of 15 g/kg per day and rates of growth in length and head circumference near the expected average of 1.0 cm per week.9 Infants in both fortifier groups demonstrated acceptable mean achieved weights, lengths, and head circumferences across the study period. Total enteral and parenteral energy intakes in both groups approximated the 504 kJ/kg per day considered by Polberger et al8 to be required for optimum growth. Infants who received HMF-T had significantly greater mean total protein intake than those who received HMF-C. This increased protein intake may reflect the greater amount of protein in 4 packets of the HMF-T fortifier (1.1 g), compared with that in 4 packets of the HMF-C fortifier (1.0 g); however, it does not seem to have resulted in a difference in growth between the 2 study fortifier groups. We speculate that this greater protein intake did not result in greater growth for the HMF-T infants because protein intake levels in both fortifier groups exceeded 3 g/kg per day, the value determined by Polberger et al8 to be the upper limit of protein intake that affects growth. However, even incrementally greater intakes of protein during initial hospitalization in these VLBW preterm infants may be advantageous. In his review of the nutritional requirements in preterm infants with special reference to “catch-up” growth, Heird10 proposed that there is a finite period, likely the first 1 to 2 months postterm, during which the catch-up response to higher nutrient intake is most likely to occur. He suggested that feeding even higher protein and energy intakes than are provided by current formulas or HMFs during hospitalization and through 40 to 48 weeks’ postmenstrual age is the most effective strategy for taking advantage of this sensitive period of catch-up growth.

**Safety**

Both fortifiers were well tolerated; the number of infants who left the study for a reason related to the study fortifier was very low (1% for HMF-T infants and 2% for HMF-C infants). We had speculated that the lower osmolality of the HMF-T fortifier would result in its being better tolerated. Using indirect measures of feeding tolerance, infants who ingested HMF-T tended to have less abdominal distention, a lower percentage of guaiac-positive stools, and fewer
days when feedings were withheld as a result of intolerance. However, these differences did not achieve statistical significance as this study was not designed to assess these measures as primary study outcomes. Overall rates for discontinuation from the study were comparable between the fortifier groups (41 [43%] for the HMF-T group and 46 [54%] for the HMF-C group). The majority of the 87 infants who left early from the study did so for reasons not related to the fortifiers, such as discharge from the hospital before study day 28 or unavailability of human milk. These reasons for exiting the study are similar to those reported in an earlier HMF feeding study in the VLBW infant population.10

In this study, the rates of confirmed and suspected NEC and sepsis in both fortifier groups were lower than is reported for this age VLBW population.11,12 This is especially interesting as it refutes the premise that a higher iron content in the infant diet increases the risk for infection. Others13 have questioned whether the inclusion of iron in fortifiers will increase the incidence of feeding intolerance, sepsis, or NEC, but we found no such evidence to substantiate these concerns in this large clinical trial. In fact, the incidence of confirmed sepsis and NEC for both of our study groups were lower than that reported for VLBW infants11,12,14 and similar to that reported for breastfed infants.15–17 There was no difference between fortifier groups in regard to the occurrence of respiratory difficulties or any other monitored adverse event. No differences were observed between groups on study days 0, 14, 28 for the results of the laboratory studies except for the statistical difference in the bicarbonate value on study day 14, which was not considered to be clinically significant.

Efficacy
Infants in both groups experienced a decline in their iron status during the study period, as reflected by serum hematocrit and ferritin concentrations. However, from study day 15 through study day 28, significantly fewer HMF-T infants than HMF-C infants received a blood transfusion ($P = .014; 12 [14\%]$ HMF-T, 20 [32\%] HMF-C). This finding is consistent with the conclusion that the higher level of iron supplementation in the HMF-T fortifier reduces the need for blood transfusions. Neonatologists have come to realize that hematocrit values are a poor predictor of tissue oxygenation18,19 and have recently reduced the number of transfusions administered to VLBW infants by limiting transfusions to infants whose clinical condition warrant them, irrespective of a predefined hematocrit value.20,21 Investigators in this study, who were blinded to the fortifier being fed, were permitted to manage anemia of prematurity as they determined was best for each participant. We speculate that the differences between fortifier groups in the numbers of transfusions administered, despite the similarity in hematocrit values, may reflect differences in perceived clinical instability. It is reasonable to expect that any effect of the higher iron levels in the HMF-T fortifier on iron sufficiency in these VLBW infants would not be detected until 2 weeks after iron supplementation had begun as a result of red blood cell turnover time. For this reason, it is not surprising that there was no difference between the study groups from study day 0 through study day 14 in regard to the number and the percentage of infants who received a blood transfusion. That fewer HMF-T infants required a blood transfusion from study days 15 through 28 may well be attributed to the higher level of iron in the test fortifier (1.44 mg compared with 0.35 mg in 4 packets of powdered fortifier). Although this higher level of iron supplementation did not prevent anemia per se, it did reduce the frequency of one of the most serious adverse outcomes of anemia: the need for a blood transfusion.

The results of the current study parallel those of Franz et al.,22 who studied the effect of early enteral iron supplementation on serum ferritin levels and the prevention of iron deficiency at 2 months of age in infants with birth weights <1301 g. In this previous study, infants who did not receive enteral iron supplementation until 61 days of life were more often iron deficient (26 of 65 vs 10 of 68) and received more blood transfusions after day 14 of life compared with infants who were given 2 mg/kg per day of ferrous sulfate, despite similarities in their ferritin levels.22

CONCLUSIONS
When added to human milk and fed to VLBW infants from the start of enteral feedings, reformulated Enfamil Human Milk Fortifier is safe, facilitates good growth and development, and is well tolerated. In addition, the use of this iron-fortified product may reduce the need for blood transfusions in these very small infants.

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IRON-FORTIFIED HUMAN MILK FORTIFIER
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