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# Growth and Development of Premature Infants Fed Predominantly Human Milk, Predominantly Premature Infant Formula, or a Combination of Human Milk and Premature Formula

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**ABSTRACT**

**Background:** In a recent meta-analysis, human milk feeding of low birth-weight (LBW) infants was associated with a 5.2 point improvement in IQ tests. However, in the studies in this meta-analysis, feeding regimens were used (unfortified human milk, term formula) that no longer represent recommended practice.

**Objective:** To compare the growth, in-hospital feeding tolerance, morbidity, and development (cognitive, motor, visual, and language) of LBW infants fed different amounts of human milk until term chronologic age (CA) with those of LBW infants fed nutrient-enriched formulas from first enteral feeding.

**Methods:** The data in this study were collected in a previous randomized controlled trial assessing the benefit of supplementing nutrient-enriched formulas for LBW infants with arachidonic acid and docosahexaenoic acid. Infants (n = 463, birth weight, 750–1,800 g) were enrolled from nurseries located in Chile, the United Kingdom, and the United States. If human milk was fed before hospital discharge, it was fortified (3,050–3,300 kJ/L, 22–24 kcal/oz). As infants were weaned from human milk, they were fed nutrient-enriched formula with or without arachidonic and docosahexaenoic acids (3,300 kJ/L before term, 3,050 kJ/L thereafter) until 12 months CA. Formula fed infants were given nutrient-enriched formula with or without added arachidonic and docosahexaenoic acids (3,300 kJ/L to term, 3,050 kJ/L thereafter) until 12 months CA. For the purposes of this evaluation, infants were categorized into four mutually exclusive feeding groups: 1) predominantly human milk fed until term CA (PHM-T, n = 43); 2) ≥ 50% energy from human milk before hospital discharge (≥ 50% HM, n = 98); 3) < 50% of energy from human milk before hospital discharge (< 50% HM, n = 203); or 4) predominantly formula fed until term CA (PFF-T, n = 119).

**Results:** PFF-T infants weighed approximately 500 g more at term CA than did PHM-T infants. This absolute difference

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persisted until 6 months CA. PFF-T infants were also longer (1.0–1.5 cm) and had larger head circumferences (0.3–1.1 cm) than both PHM-T and ≥ 50% HM infants at term CA. There was a positive association between duration of human milk feeding and the Bayley Mental Index at 12 months CA ($P = 0.032$ full and $P = 0.073$ reduced, statistical models) after controlling for the confounding variables of home environment and maternal intelligence. Infants with chronic lung disease fed ≥ 50% HM until term CA (n = 22) had a mean Bayley Motor Index about 11 points higher at 12 months CA compared with infants PFF-T (n = 24, $P = 0.033$ full model).

**Conclusion:** Our data suggest that, despite a slower early growth rate, human milk fed LBW infants have development at least comparable to that of infants fed nutrient-enriched formula. Exploratory analysis suggests that some subgroups of human milk fed LBW infants may have enhanced development, although this needs to be confirmed in future studies. ***JPGN 37:437–446, 2003.*** **Key Words:** Low birth weight—Infant nutrition—Human milk—Formula feeding—Growth—Development.

In a recently published meta-analysis, Anderson et al. (1) conclude that breast feeding is associated with higher scores for cognitive development than is formula feeding, even after adjustment for confounding factors. Interestingly, this benefit was greatest for low birth weight (LBW) infants, among whom those fed human milk showed a 5.2 point advantage in IQ. The conclusions of Anderson et al. are consistent with the individual observations of Lucas et al. (2,3) and others (4,5). Lucas et al. reported that LBW infants fed unfortified human milk for 4 weeks after initiation of enteral feeding performed better on standardized tests of development at 18 months corrected age (CA) than did LBW infants fed a significant proportion of total energy via standard term formula. Lucas et al. also reported that LBW infants fed a specially designed nutrient-enriched preterm formula for 4 weeks postnatally had more advanced motor and mental development at 18 months CA than did infants fed term formula. They also observed higher IQ, most notably verbal IQ, in boys 7½ to 8 years of age who were fed nutrient-enriched formula compared with those fed term formula in infancy (6).

In contrast to these comparisons between unfortified human milk and term formula, Lucas et al. (2) found no difference in the developmental outcomes of LBW infants fed unfortified human milk for 4 weeks compared with those fed a specially designed nutrient-enriched preterm formula. These comparisons suggest that human milk feeding and nutrient enrichment may have independent, perhaps additive, effects on the development of infants born prematurely.

In contemplating how these observations might be applied to current clinical practice, the following points are worthy of consideration. First, the American Academy of Pediatrics (7) now recommends that, under most circumstances, fortified human milk is the feeding of choice for hospitalized LBW infants. Neither unfortified human milk nor term formulas are currently recommended during the initial in-hospital course because they do not meet the nutritional requirements of LBW infants, especially those of very LBW infants(<1,500 g) (7,8). Thus, the aforementioned studies compared feeding regimens that no longer represent ideal or recommended feeding practices for LBW infants. Few published data exist to date that directly examine the development of LBW infants fed fortified human milk compared with specially designed nutrient-enriched formulas during and after hospital discharge.

The purpose of this article is to compare the growth, in-hospital feeding tolerance, morbidity, and development at 14 months CA of LBW infants fed different amounts of human milk until term-corrected age (CA) and then fed nutrient-enriched formulas until 12 months CA when weaned with those of LBW infants fed nutrient-enriched formulas from first enteral feeding until 12 months CA.

## SUBJECTS AND METHODS

### Subjects

The data presented here represent a further analysis of LBW infants from a large prospective, randomized controlled trial designed to assess possible benefits of supplementing nutrient-enriched formulas for premature infants with oils containing arachidonic acid (AA) and docosahexaenoic acid (DHA) (9). Statistical comparisons of growth and development outcomes in the original study were made among study formula groups as randomized, but not according to the quantity of human milk consumed.

Four hundred seventy preterm infants (< 33 wks gestational age) with birth weights of 750 to 1,805 g were enrolled between October 1996 and January 1998 from Neonatal Intensive Care Units in the United States (n = 334), United Kingdom (n = 85), and Chile (n = 51). Of these infants, 463 consumed either human milk and/or formula before exiting the study and were included in this data analysis. The remaining seven infants exited the study before their first enteral feeding because of medical circumstances or parental withdrawal of consent. Singleton, twin, appropriate-for-gestational age, and small-for-gestational age infants were eligible to participate, providing they could be enrolled within 72 hours of first enteral feeding (including trophic feeds or water) initiated by the 28th day of life. Infants with congenital abnormalities that could affect growth and development or who had undergone major surgery before randomization were not eligible to participate. Other exclusion criteria included periventricular/intraventricular hemorrhage > Grade II, maternal incapacity (including maternal cocaine or alcohol abuse), liquid ventilation, asphyxia resulting in neurologic damage, or uncontrolled systemic infection at the time of enrollment. A human ethics review board at each participating institution approved the study procedures.

### Study design

After written informed consent was provided by at least one parent or guardian, infants were randomized to one of three study formula regimens (one control, two containing AA+DHA). The study was designed to reflect actual feeding practices at the participating nurseries. Thus, on Study Day 1, infants could be exclusively human milk fed, exclusively formula fed, or fed a combination of human milk and formula. Study Day 1 was defined as the day on which infants were randomized and began enteral feeding. There were no restrictions in the study protocol limiting or discouraging either the exclusivity or duration of human milk feeding. The protocol did specify that from birth until hospital discharge, human milk was to be fortified with a powdered or liquid fortifier to contain 3,050 to 3,300 kJ/L (22–24 kcal/oz) and to deliver a minimum of 2.8 g/kg/d of protein. No guidelines were provided with regard to fortification of human milk after discharge. The energy density of unfortified human milk was estimated to be 2,800 kJ/L (20 kcal/oz). Formula-fed infants were fed a specially designed in-hospital preterm formula (modified Similac Special Care® ready-to-feed [3,300 kJ/L] Ross Products Division, Columbus, Ohio, USA) with or without (control) AA- and DHA-enriched oils from the time of first enteral feeding until term CA as described previously (9). Corrected age (CA) is equal to the menstrual age plus chronological age of an infant. At term CA, formula-fed infants were transitioned to their assigned postdischarge nutrient-enriched formula (modified NeoSure® powder [3,050 kJ/L] Ross Products Division, Columbus, Ohio, USA) with or without the same sources of AA+DHA as in the assigned preterm formula to 12 months CA. In the AA+DHA-containing formulas, AA and DHA provided 0.42% and 0.26% of fatty acids, respectively, in the premature formula and 0.44% and 0.16%, respectively, in the enriched formula. As infants were weaned from human milk, they were transitioned onto their randomized study formula (3,300 kJ/L until term, 3,050 kJ/L until 12 months CA).

### Human milk feeding groups

Infants were classified into four mutually exclusive feeding groups based on their relative human-milk-to-formula intake from the first enteral feeding until their term CA birth date. Infants were categorized as follows: 1) predominantly human milk until term CA (PHM-T) if they consumed < 100 mL/kg birth weight of formula for the total duration of their initial hospital stay and > 80% of all feedings provided as human milk at term CA ; and 4) predominantly formula fed until term CA (PFF-T) if they consumed < 100 mL/kg birth weight of human milk for the total duration of their initial hospital stay and > 80% of all feedings provided as formula at term CA. Infants failing to meet the criteria for PHM-T or PFF-T were categorized as: 2) ≥ 50% of total energy as human milk (≥ 50% HM); and 3) < 50% total energy as human milk (< 50% HM). Because of the significant dilution of human milk, liquid fortifiers (e.g., Similac Natural Care, liquid formula concentrates, etc) were classified as infant formula for the purposes of categorizing infants into human milk feeding groups.

### Duration and exclusivity of human milk feeding

Human milk and formula intake data were obtained from flow sheets during initial hospitalization and from 3-day dietary records before the term, 2, 4, 6, 9, and 12 months CA study visits. In addition, breast-feeding mothers were asked at each post-term study visit if they were still breast-feeding. If they had discontinued breast-feeding, the date of discontinuation was recorded.

### Demographic data

Neonatal, perinatal, and family characteristics of enrolled infants were obtained from medical records or parental report as described previously (9). The HOME Inventory (10) and the vocabulary subtest of the WAIS-R (11) administered to the biologic mother (if living in the home) were obtained to assess the quality and quantity of cognitive, social, and emotional support available to each infant in the home environment and maternal intelligence, respectively.

### Growth, in-hospital feeding tolerance, and morbidity

Weight, length, and head circumference of infants were measured according to standardized procedures on Study Day 1 and at term, 2, 4, 6, 9, and 12 months CA as described in detail previously (9). Visit windows of ± 7 days were allowed up to 9 months CA and ± 10 days at 12 months CA. The percentages of infants who had enteral feedings withheld for at least 1 day, necrotizing enterocolitis (NEC), systemic infection, or chronic lung disease were determined from medical records, as were the number of days infants took to reach full enteral feeding (420 kJ/kg/d or 100 kcal/kg/d) (9). Chronic lung disease was defined as supplemental oxygen required beyond 1 month chronological age or 36 weeks postconception.

The number of serious adverse events (SAEs) was determined from study day 1 until each infant's 12-month CA birth date. This definition of SAE excluded events during initial hospitalization that might be expected in the natural course of the preterm infant (except death) (9).

### Visual, cognitive, motor, and language development

Visual acuity of each infant was assessed using the Teller Acuity Card Procedure (Vistech Inc, Dayton, OH) (12) at 2, 4, and 6 months CA. Each tester and his or her backup was trained and certified. The Bayley Scales of Infant Development II (13) were administered primarily by a single certified tester at each site at 12 months CA to assess cognitive (Mental Index) and motor development (Motor Index). The vocabulary checklist from the infant version of the MacArthur Communicative Development Inventories (14), a standardized parent-report instrument, was completed to provide information about each child's vocabulary comprehension at 9 and 14 months CA and vocabulary production at 14 months CA. Details of the training of developmental testers and quality control procedures to reduce variability among testers have been described previously (9).

### Statistical methods

All available data from enrolled infants who received either human milk or formula before exiting the study (463 of 470 infants) were used in these analyses. Once enrolled, no infants

were dropped from follow-up for any reason other than parental withdrawal of consent, infant death, or change in family residence precluding follow-up (intent-to-treat analysis). Categorical variables were analyzed using $\chi^2$ or Cochran-Mantel-Haenszel tests. Continuous variables were evaluated using analysis of covariance (ANCOVA). Data obtained at more than one time point were analyzed using repeated-measures analyses (SAS® PROC MIXED, Cary, NC) (15). In addition, analyses of continuous outcome variables considered site, randomization strata (gender and birth weight group [750–1,250 g or 1,251–1,800 g]), and the formula assignment to which the infant was originally randomized as preplanned covariates. For the growth analyses, the infant's size for gestational age (either appropriate-for-gestational age [AGA] or small-for-gestational age [SGA]) were included as additional preplanned covariates. For developmental outcomes, additional preplanned covariates included size for gestation, gestational age, HOME Inventory, the vocabulary subtest of the maternal WAIS-R, prenatal smoking, and in-home smoking at hospital discharge. Because of its previously reported influence on development, chronic lung disease (yes/no) was included as a covariate in developmental analyses (16–18). Weight at 2 months' corrected age was added to these analyses to serve as a proxy for growth after hospital discharge (only three infants remained in the hospital at this time). Because of the small numbers of infants, the Little Rock ($n = 24$) and New York sites ($n = 16$) were treated as a single site in the statistical analysis.

Because of the large number of preplanned covariates for development outcomes, a backward step-wise approach was used to produce a reduced statistical model. In this approach, covariates or factors, except the patient's feeding group, with a $P$ value $\geq 0.15$ were excluded sequentially until a final step was reached, with only feeding group and covariates with a $P$ value $< 0.15$ remaining. Unless there were differences between the full and reduced models with respect to the presence or absence of a feeding group effect on developmental outcomes, results for only the reduced models are presented. All statistical tests of hypotheses were two-tailed with $P = 0.05$ for main effects and $P = 0.10$ for interaction effects.

## RESULTS

### Duration and exclusivity of human milk feeding

Eighty-one percent of the 463 infants completed the study to 12 months CA. Ninety percent of all infants enrolled in the study remained on human milk and/or the assigned study formula feeding until term CA. At 12 months CA, 68% of infants remained on human milk or the assigned study formula. Forty-three (9%) infants were predominantly human milk fed until term CA (PHM-T, human milk feeding group 1). Ninety-eight (21%) infants were fed $\geq$ 50% of total energy during initial hospitalization from human milk ($\geq$ 50% HM, human milk feeding group 2). Two hundred three (44%) infants were fed $<$ 50% of total energy during initial hospitalization from human milk ($<$ 50% HM, human milk feeding group 3), and 119 (26%) infants were predominantly formula fed until term CA (PFF-T, human milk feeding group 4). Of the 232 mothers providing any human milk to their infants after hospital discharge, 26 (11%) supplemented human milk feedings with a fortifier (primarily a liquid) or other nonstudy formula.

The duration of human milk feeding was highly related to the exclusivity of human milk feeding to term CA (Fig. 1). Infants no longer on the assigned study feeding were generally transitioned to a standard term formula, unless they were transitioned very close to the 12-month CA birth date. In this case, they were switched to cow's milk. The time at which solids were introduced did not differ among human milk feeding groups. Solids were introduced at a median age (1st, 3rd quartile) of 4 months CA (2–5 months). Study formula assignments (one control, two containing AA + DHA) were equally distributed among the four human milk feeding groups.

### Demographic data

Human milk feeding groups differed statistically in a number of infant and family baseline characteristics (Tables 1 and 2). Birth weights for male infants were similar in the four human milk feeding groups, but among female infants, those in the $\geq$ 50% HM group had lower mean birth weights than did those in the PFF-T group (LS means ± SE, 1,188 ± 24 g vs. 1,314 ± 20 g). Infants in the $<$ 50% HM group had a slightly lower, but significant, gestational age at birth than did infants in the PFF-T group. The ethnicity of feeding groups was different. Predominantly human milk fed infants were mostly Caucasian (95%), whereas 54% to 65% of infants in the other groups were Caucasian, with the remainder being of African, Hispanic, or Latino.

The mothers of infants in the $<$ 50% HM group were 2.5 to 3.1 years younger than were mothers of infants in

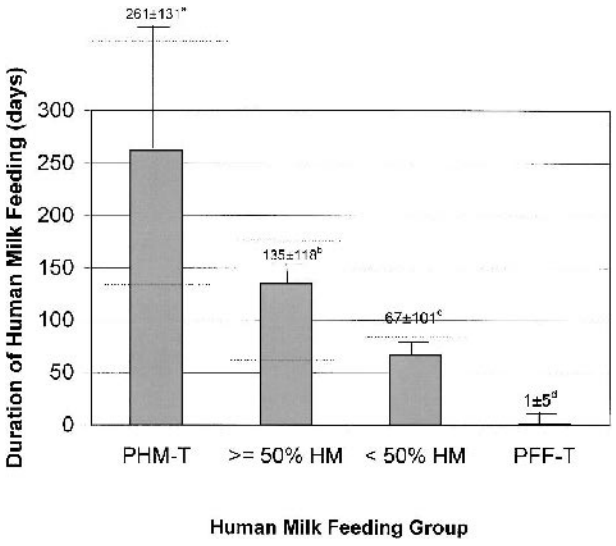


**FIG. 1.** Duration of human milk feeding (mean ± SD) by feeding group. Unlike superscript letters denote statistically significant differences. Horizontal hatched lines represent the first and the third quartile within each feeding group.

**TABLE 1.** *Neonatal and perinatal characteristics**

| Characteristics | PHM-T | ≥50% HM | <50% HM | PFF-T |
|---|---|---|---|---|
| Birth weight† (g) | 1,275 ± 312 (43) | 1,287 ± 279 (98) | 1,288 ± 287 (203) | 1,332 ± 279 (119) |
| Gestational age at birth (wks) | 29.7 ± 2.0[ab] (43) | 29.6 ± 1.9[ab] (98) | 29.5 ± 2.1[a] (203) | 29.9 ± 2.0[b] (119) |
| Size at birth, n (%) | | | | |
| Small for gestational age | 7 (16) | 11 (11) | 13 (6) | 13 (11) |
| Appropriate for gestational age | 36 (84) | 87 (89) | 190 (94) | 106 (89) |
| Gender, n (%) | | | | |
| Male | 20 (47) | 58 (59) | 114 (56) | 59 (50) |
| Female | 23 (53) | 40 (41) | 89 (44) | 60 (50) |
| Multiple birth status, n (%) | | | | |
| Singleton | 39 (91) | 81 (83) | 160 (79) | 87 (73) |
| Twin | 4 (9) | 17 (17) | 43 (21) | 32 (27) |
| Apgar score | 8.3 ± 1.2 (43) | 8.2 ± 1.0 (97) | 8.0 ± 1.4 (202) | 7.9 ± 1.5 (119) |
| Ethnicity‡, n (%) | | | | |
| Caucasian | 41 (95) | 64 (65) | 110 (54) | 71 (60) |
| African | 2 (5) | 10 (10) | 31 (15) | 28 (24) |
| Hispanic/Latino | 0 | 9 (9) | 44 (22) | 7 (6) |
| Other | 0 | 15 (15) | 18 (9) | 13 (11) |
| Postnatal age at study day 1 (d) | 5.5 ± 2.5 (43) | 5.1 ± 3.3 (98) | 5.0 ± 3.3 (203) | 5.0 ± 3.0 (119) |

* Values are mean ± SD (number of participants) unless otherwise noted. Unlike superscript letters within each row denote statistically significant differences.

† A statistically significant human milk feeding group*gender effect was found ($P = 0.042$). Birth weights for male infants were similar among the four feeding groups, but among female infants, those in the ≥50% HM group had a lower mean birth weight than did female infants in the PFF-T group (LS, means ± SE; 1,188 ± 24 g versus 1,314 ± 20 g).

‡ A statistically significant feeding group effect was found ($P = 0.015$).

the other feeding groups. At the United States sites, mothers of infants fed PHM-T or ≥ 50% HM had about 2 more years of education than did mothers of infants fed < 50% HM or PFF-T. Similarly, about 40% of mothers in the PHM-T or ≥ 50% HM groups from the United Kingdom had a university degree, compared with fewer than 10% in the < 50% HM or PFF-T groups. Maternal smoking during pregnancy and the proportion of infants ex-

**TABLE 2.** *Family characteristics**

| Characteristics | PHM-T | ≥50% HM | <50% HM | PFF-T |
|---|---|---|---|---|
| Maternal age (yrs) | 29.7 ± 5.1[b] (43) | 29.0 ± 6.5[b] (98) | 25.6 ± 6.3[a] (203) | 28.0 ± 6.4[b] (119) |
| Maternal education | | | | |
| US (yrs) | 15.1 ± 2.0[b] (34) | 14.0 ± 2.6[b] (72) | 12.7 ± 2.2[a] (126) | 12.4 ± 1.9[a] (96) |
| Chile (yrs) | N/A | 11.8 ± 1.5 (8) | 9.3 ± 2.4 (39) | 11.3 ± 1.0 (4) |
| UK, highest qualification obtained,† n (%) | | | | |
| None | 1 (11) | 4 (22) | 9 (26) | 6 (35) |
| <3 O-level‡ | 0 (0) | 2 (11) | 8 (23) | 3 (18) |
| >3 O-level§ | 2 (22) | 4 (22) | 16 (46) | 7 (41) |
| A levels | 2 (22) | 1 (6) | 1 (3) | 0 (0) |
| Degree+ | 4 (44) | 7 (39) | 1 (3) | 1 (6) |
| Maternal smoking during pregnancy,† n (%) | | | | |
| Yes | 2 (5) | 18 (19) | 57 (28) | 41 (34) |
| No | 41 (95) | 79 (81) | 146 (72) | 78 (66) |
| Postnatal smoking in the home,† n (%) | | | | |
| Yes | 4 (10) | 15 (17) | 70 (35) | 35 (30) |
| No | 38 (90) | 73 (83) | 132 (65) | 80 (70) |
| Prenatal care, n (%) | | | | |
| 1st trimester | 42 (98) | 85 (87) | 163 (81) | 98 (83) |
| 2nd trimester | 0 (0) | 11 (11) | 32 (16) | 13 (11) |
| 3rd trimester or none | 1 (2) | 2 (2) | 3 (1) | 7 (6) |
| HOME inventory score† | 39.4 ± 3.4[b] (40) | 36.9 ± 5.8[b] (81) | 35.0 ± 5.8[ab] (175) | 35.2 ± 5.6[a] (103) |
| Maternal WAIS-R raw vocabulary score‖ | 53.2 ± 8.9 (40) | 45.0 ± 13.5 (79) | 35.7 ± 12.7 (174) | 36.3 ± 15.6 (100) |

* Values are mean ± SD (number of participants) unless otherwise noted. Unlike superscript letters within each row denote statistically significant differences.

† A statistically significant human milk feeding group effect was found ($P < 0.01$).

‡ UK education equivalents: <3, certificate of education or general CSE below C grade.

§ UK education equivalents: >3, certificates of education or any O level or general certificates of education grade A–C.

‖ A statistically significant human milk feeding group*gender effect was found ($P = 0.032$).

posed to cigarette smoke in the home after hospital discharge were greater in the primarily formula-fed groups.

HOME Inventory scores were higher (better) in the families of infants in the PHM-T and ≥ 50% HM groups than those of infants in the PFF-T group but not the < 50% HM group. Scores on the verbal subtest of the WAIS-R were higher in mothers of infants in the PHM-T group than in those of the < 50% HM or PFF-T groups. These scores were also higher for mothers of male infants in the ≥ 50% HM-T group than for mothers of male infants predominantly fed formula, but these differences were not seen among female infants.

## Growth

There were consistent differences in the growth of infants depending on human milk feeding group (Table 3). Predominantly formula-fed infants weighed more (35–48 g) at study entry than did infants in the other feeding groups. By term CA, a dose-dependent relationship existed between infant weight and the proportion of energy consumed as infant formula. On average, infants fed predominantly formula weighed about 500 g or 18.5% more at term CA than did infants fed predominantly human milk. This absolute difference in weight persisted until 6 months CA, after which the < 50% HM group, but not the PFF-T group, continued to weigh more than the PHM-T group until 12 months CA. PFF-T infants also tended to be slightly longer and had larger head circumferences at study entry. By term CA, PFF-T infants had significantly greater mean length (1.0–1.5 cm) and head circumference (0.3–1.1 cm) than did infants fed either PHM-T or ≥ 50% HM. Statistically significant differences disappeared by 9 months CA for length and by 4 months CA for head circumference. No statistically significant interaction was found between the human milk feeding group or birth weight (750–1,250 g or 1,251–1,800 g) for weight, length, and head circumference measurements, suggesting that feeding type did not differentially influence the growth of smaller versus larger infants.

## In-hospital feeding tolerance and morbidity

Infants in the four feeding groups were similar in most measures of early feeding tolerance and in-hospital morbidity (Table 4). The slightly shorter interval for the PFF-T group to reach full enteral feeding may have resulted from differences in caloric density between preterm formula (3,500 kJ/L) and unfortified human milk (2,800 kJ/L). It was standard practice in the participating nurseries not to fortify human milk until full enteral feeding (100 kcal/kg/d) was established. The mean age of infants at study entry (5 days) did not differ among feeding groups, nor did the number of days between study day 1 and hospital discharge (about 40 days).

The percent of infants with at least one SAE or rehospitalization was lower in the groups that received more human milk ($P < 0.05$, Table 4). Thirteen infants died (8

**TABLE 3.** *Weight, length, and head circumference*†*

| Characteristic | PHM-T | ≥50% HM | <50% HM | PFF-T |
|---|---|---|---|---|
| Weight (g) | | | | |
| Study day 1 | 1,198 ± 326[a] (43) | 1,192 ± 270[a] (98) | 1,205 ± 278[a] (203) | 1,240 ± 278[b] (119) |
| Term-corrected age (CA) | 2,740 ± 374[a] (42) | 2,952 ± 524[b] (90) | 3,152 ± 491[c] (199) | 3,249 ± 496[d] (115) |
| 2 months CA | 4,389 ± 656[a] (41) | 4,793 ± 741[b] (85) | 4,920 ± 723[b] (191) | 4,898[b] ± 692 (112) |
| 4 months CA | 5,658 ± 845[a] (41) | 6,065 ± 878[b] (79) | 6,286 ± 861[b] (189) | 6,163 ± 871[b] (106) |
| 6 months CA | 6,755 ± 958[a] (40) | 7,101 ± 964[ab] (79) | 7,326 ± 955[b] (181) | 7,228 ± 957[b] (104) |
| 9 months CA | 7,948 ± 1,072[a] (41) | 8,083 ± 1,080[ab] (80) | 8,376 ± 1,048[b] (174) | 8,342 ± 991[ab] (103) |
| 12 months CA | 8,814 ± 1,151[a] (41) | 8,871 ± 1,021[ab] (79) | 9,161 ± 1,112[b] (172) | 9,157 ± 1,076[ab] (96) |
| Length (cm) | | | | |
| Study day 1 | 38.6 ± 3.1[ab] (41) | 38.4 ± 2.9[a] (94) | 38.9 ± 3.1[a] (190) | 39.3 ± 2.9[b] (109) |
| Term-corrected age (CA) | 46.9 ± 2.2[a] (42) | 47.4 ± 2.4[a] (88) | 48.2 ± 2.4[b] (197) | 48.5 ± 2.2[c] (112) |
| 2 months CA | 53.5 ± 2.6[a] (41) | 54.9 ± 2.3[b] (84) | 55.3 ± 2.6[b] (189) | 55.2 ± 2.3[b] (111) |
| 4 months CA | 59.3 ± 2.9[a] (41) | 60.6 ± 2.5[b] (79) | 61.0 ± 2.6[b] (188) | 60.7 ± 2.1[b] (106) |
| 6 months CA | 63.7 ± 3.0[a] (40) | 64.9 ± 2.4[ab] (79) | 65.5 ± 2.6[b] (180) | 64.9 ± 2.6[b] (103) |
| 9 months CA | 68.8 ± 2.9[a] (41) | 69.3 ± 2.6[a] (80) | 69.9 ± 2.9[a] (173) | 69.5 ± 2.5[a] (102) |
| 12 months CA | 73.1 ± 2.8[a] (41) | 73.1 ± 2.7[a] (79) | 73.8 ± 3.0[a] (172) | 73.0 ± 2.6[a] (96) |
| Head circumference (cm) | | | | |
| Study day 1 | 27.0 ± 2.2[ab] (40) | 27.1 ± 2.0[a] (95) | 27.3 ± 2.0[ab] (191) | 27.4 ± 1.8[b] (111) |
| Term-corrected age (CA) | 34.4 ± 1.1[a] (42) | 35.2 ± 1.5[ab] (89) | 35.4 ± 1.5[bc] (198) | 35.5 ± 1.5[c] (113) |
| 2 months CA | 38.4 ± 1.2[a] (41) | 39.4 ± 1.5[b] (84) | 39.2 ± 1.5[ab] (189) | 39.2 ± 1.5[b] (112) |
| 4 months CA | 41.3 ± 1.3[a] (41) | 41.9 ± 1.6[a] (79) | 41.8 ± 1.5[a] (189) | 41.7 ± 1.7[a] (106) |
| 6 months CA | 43.3 ± 1.5[a] (40) | 43.8 ± 1.7[a] (79) | 43.6 ± 1.5[a] (179) | 43.5 ± 1.6[a] (103) |
| 9 months CA | 45.1 ± 1.4[a] (41) | 45.3 ± 1.7[a] (80) | 45.3 ± 1.7[a] (174) | 45.3 ± 1.7[a] (103) |
| 12 months CA | 46.1 ± 1.4[a] (41) | 46.4 ± 1.7[a] (79) | 46.4 ± 1.7[a] (172) | 46.3 ± 1.7[a] (96) |

* Values are mean ± SD (number of participants) unless otherwise noted. Unlike superscript letters within each row (corrected age of child or visit) denote statistically significant differences ($P < 0.05$).

† A statistically significant feeding group*visit effect ($P < 0.0001$) was found for all anthropometric measures.

**TABLE 4.** *In-hospital feeding tolerance and clinical problems**

| Characteristics | PHM-T | ≥50% HM-T | <50% HM-T | PFF-T |
|---|---|---|---|---|
| Number of subjects | 43 | 98 | 203 | 119 |
| Feedings withheld for at least 1 days (% of infants) | 26 | 38 | 28 | 28 |
| Feedings withheld because of gastric residuals (% of infants) | 14 | 18 | 18 | 18 |
| Days to reach full enteral feeds (100 kcal/kg/d)† mean ± SD (1st, 3rd quartile) | 16 ± 19 (4, 21)[a] | 15 ± 16 (5, 18)[a] | 15 ± 15 (4, 21)[b] | 8 ± 8 (3, 10)[b] |
| Suspected cases of NEC (% of infants) | 21 | 21 | 22 | 30 |
| Confirmed cases of NEC (% of infants) | 0 | 5 | 1 | 7 |
| Suspected systemic infection (% of infants) | 33 | 33 | 39 | 33 |
| Confirmed cases of systemic infection (% of infants) | 7 | 11 | 16 | 14 |
| Chronic lung disease (% of infants) | 28 | 22 | 27 | 20 |
| Days from study day 1 to hospital discharge mean ± SD (1st, 3rd quartile) | 42 ± 23 (20, 54) | 37 ± 19 (25, 49) | 45 ± 25 (28, 58) | 37 ± 23 (21, 43) |
| Serious adverse events (SAEs),† n (%) | 14 (33) | 38 (39) | 93 (46) | 61 (51) |
| Hospital readmissions† n (%) | 14 (33) | 28 (29) | 85 (42) | 54 (45) |

* Unlike superscript letters within each row denote statistically significant differences.

† A statistically significant human milk feeding group effect was found (days to first enteral feeding $P < 0.0001$; SAEs and hospital readmissions, $P < 0.05$).

before discharge), of whom 0, 9, 2, and 2 died in the PHM-T, ≥ 50% HM, < 50% HM, and PFF-T groups, respectively.

### Visual, cognitive, motor, and language development

A statistically significant main effect of human milk feeding on visual acuity as assessed by the Teller Acuity Card Procedure was found ($P = 0.003$), although absolute differences were not large (Table 5). Infants in the feeding groups consuming any appreciable amount of human milk had higher Teller Acuity scores during the 2- to 6-month period than did infants in groups predominantly formula fed. Site ($P < 0.0001$), absence of maternal prenatal smoking ($P = 0.028$), greater weight at 2 months CA ($P < 0.001$), higher scores on the HOME Inventory ($P = 0.004$), and higher maternal scores on the vocabulary subtest of the WAIS-R ($P = 0.025$) were statistically significant factors in predicting Teller Acuity scores (reduced statistical model).

No differences in the Bayley Mental Index or Motor Index were found among feeding groups. However, a positive association between duration of human milk feeding and Bayley Mental Index was found in the full ($P = 0.032$), but not the reduced, statistical model ($P =$

**TABLE 5.** *Visual, cognitive, motor, and language development**

| Characteristics | PHM-T | ≥50% HM-T | <50% HM-T | PFF-T |
|---|---|---|---|---|
| Visual acuity, mean (cycles/degree) ± SD (octaves) | | | | |
| Teller Acuity Card Procedure† | | | | |
| 2 months CA | 1.8 ± 0.8 (40) | 1.8 ± 0.7 (84) | 2.0 ± 0.6 (179) | 1.7 ± 0.7 (110) |
| 4 months CA | 3.8 ± 0.6 (41) | 3.6 ± 0.6 (76) | 3.7 ± 0.5 (183) | 3.4 ± 0.6 (102) |
| 6 months CA | 7.4 ± 0.8 (40) | 7.2 ± 0.5 (75) | 7.0 ± 0.5 (174) | 6.8 ± 0.8 (101) |
| Bayley Scales of Infant Development II at 12 months CA‡ | | | | |
| Mental Index§ | 93.1 ± 14.5 (41) | 95.0 ± 13.4 (79) | 91.6 ± 10.5 (172) | 92.9 ± 13.4 (96) |
| Motor Index¶ | 86.8 ± 15.2 (41) | 84.6 ± 14.8 (79) | 86.5 ± 15.1 (172) | 88.1 ± 14.6 (95) |
| MacArthur Communicative Development Inventories | | | | |
| Vocabulary comprehension scores¥ | | | | |
| 9 months CA | 96.2 ± 17.6 (39) | 100.3 ± 21.5 (78) | 105.0 ± 20.5 (168) | 102.6 ± 18.4 (100) |
| 14 months CA | 97.0 ± 14.5 (38) | 101.3 ± 16.1 (68) | 100.8 ± 18.3 (145) | 100.7 ± 17.0 (79) |
| Vocabulary production score** | | | | |
| 14 months CA | 96.6 ± 18.9 (38) | 98.0 ± 18.5 (68) | 97.7 ± 17.6 (146) | 96.7 ± 18.0 (79) |

* Values are mean ± SD (number of participants).

† A statistically significant human milk feeding group effect was observed for behavioral acuity (PHM-T, ≥50% HM, <50% HM, >PFF-T, $P = 0.003$).

‡ Infants with a Bayley Mental or Motor score of <50 were excluded from the Mental Index statistical analyses. Likewise, infants with a Motor Score <50 were excluded from the Motor Index statistical analysis.

§ No statistically significant human milk feeding group effect was found; however, in the full ($P = 0.032$) but not reduced statistical model ($P = 0.0731$) duration of human milk feeding was positively associated with the Mental Index.

¶ A statistically significant human milk feeding group*chronic lung disease effect was found in the full ($P = 0.080$) but not reduced model ($P = 0.152$). Among children with chronic lung disease, ≥50% HM > PFF-T.

¥ A statistically significant human milk feeding group*visit effect was found in the full ($P = 0.033$) but not reduced statistical model ($P = 0.058$). At 9 months CA, PFF-T > 50 ≥50% HM.

** A statistically significant human milk feeding group*birth weight stratum effect was found in the full ($P = 0.019$) and reduced models ($P = 0.0632$). Among infants born >1,250 g, ≥50% HM > PFF-T.

0.073). Site ($P < 0.0001$), gender (female > male, $P = 0.001$), gestational age at birth (+ association, $P = 0.005$), and birth size (AGA > SGA, $P = 0.034$) were all statistically significant factors in the final reduced model.

A relationship was found between chronic lung disease and feeding group in the full model ($P = 0.08$) for the Bayley Motor Index but was not sustained in the reduced statistical model. Both the WAIS (– association, $P < 0.0001$) and HOME Inventory (+ association, $P = 0.004$) were statistically significant factors in the full statistical model. In the full model, there was an indication that the subset of infants with chronic lung disease in the ≥ 50% HM-T group (n = 22, LS mean ± SE, 87.9 ± 1.7) had greater Motor Index scores than did the same subset of infants in the PFF-T group (n = 24, 76.3 ± 3.5, $P = 0.033$). Infants in the < 50% HM-T (n = 54) group did not differ from infants in either the ≥ 50% HM-T or the PFF-T groups. Because of the large number of covariates included in the full model and the small number of PHM-T infants (n = 9) with chronic lung disease, we were unable to produce estimates for this group.

A statistically significant relationship between feeding group by age was observed for vocabulary comprehension ($P = 0.033$ full, $P = 0.058$ reduced). At 9 months CA, the vocabulary comprehension score of PFF-T infants (LS mean ± SE, 105.6 ± 1.8) was greater than that of PHM-T infants (97.7 ± 2.9, $P = 0.023$), although neither differed from infants in the mixed feeding groups. This difference was not sustained at 14 months CA. Site ($P < 0.0001$), lower maternal age ($P < 0.0001$), greater gestational age ($P < 0.001$), and higher scores on the HOME Inventory ($P < 0.001$) were statistically significant predictors of vocabulary comprehension in the reduced model.

A significant interaction between feeding and birth weight group was found for vocabulary production at 14 months CA using both full ($P = 0.019$) and reduced ($P = 0.063$) models. Infants born weighing more than 1,250 g in the ≥ 50% HM-T group (LS mean ± SE, 96.8 ± 3.5) had greater vocabulary production scores than did infants weighing more than 1,250 g in the PFF-T group (88.3 ± 3.7). Site ($P < 0.041$), chronic lung disease (No > Yes, $P = 0.008$), weight at 2 months CA (+ association, $P = 0.006$), and maternal scores on the HOME Inventory (+ association, $P < 0.0001$) and vocabulary subtest of the WAIS-R (– association, $P = 0.006$) were significant factors in the reduced statistical model.

## DISCUSSION

This study suggests that the growth of LBW infants is inversely related to the percentage of total energy consumed as human milk until term CA. These results, particularly the post-discharge growth comparisons between human milk-fed and formula-fed preterm infants, are consistent with previous reports in the literature (19–21).

Our data suggest that, despite slower early growth, human milk-fed LBW infants have development at least comparable to that of infants fed nutrient-enriched formula from the time of first enteral feeding to 12 months CA. Our exploratory analyses, which require confirmation in future studies, suggest that some subgroups of human milk-fed LBW infants may have improved scores on developmental tests. Specifically, infants in the feeding groups that consumed any appreciable amount of human milk had higher Teller visual acuity scores than did predominantly formula-fed infants, although the quantitative difference was not clinically obvious. This is of particular interest because two-thirds of formula-fed infants in the current study consumed nutrient-enriched feeding containing AA+DHA, supplements previously shown to improve the visual acuity of LBW formula-fed infants (9).

No differences in the Bayley Mental Index or Motor Index were found among feeding groups. However, a positive relationship between duration of human milk feeding and the Bayley Mental Index was observed, even after controlling for maternal and family characteristics known to influence development. In addition, infants with chronic lung disease who were fed ≥ 50% HM had a mean Bayley Motor Index score about 11 points higher than that of corresponding infants in the PFF-T group. It is important to note that mean Bayley Mental (92–95) and Motor (85–88) Index scores of LBW infants in this study, regardless of feeding group, were below those of term infants, suggesting that additional strategies, including nutritional ones, should be considered to improve the development of LBW infants.

The relationship between human milk intake and measures of language development was mixed. It is conceivable that growth differences among feeding groups may be confounding the relationship between human milk feeding and development. A positive association between infant weight at 2 months CA and Teller visual acuity scores was likewise observed ($P = 0.001$). The observed growth and development relationship is consistent with that reported by Mattia and deRegnier (22), in which slower growth during the first month of life was associated with poorer receptive and expressive language development at 2 and 3 years of age. Hack et al. also found that very LBW (VLBW) infants (n = 249) whose head circumference had not reached a normal percentile by 8 months CA had poorer cognitive, educational, and psychosocial development at 8 years of age (23). Several studies, although not all, suggest that nutritional interventions that support growth and, in particular, brain growth will lead to an improved outcome (6,24–27). For example, Lucas et al. followed the test results of cognitive function of premature infants fed a term or an enriched preterm formula for about 4 weeks after birth (6,24). Those fed nutrient-enriched formula demonstrated not only better growth but also improved motor

and mental development at 18 months CA (Bayley) and improved IQ, notably verbal IQ in boys, at 7½ to 8 years when compared with those who were fed term formula.

In addition to possible developmental advantages, human milk feeding was associated with fewer serious adverse events, specifically a reduction in the number of hospitalizations after initial discharge. Several studies, although not all, have shown an inverse relationship between breast-feeding and incidence of infection in term infants (28–37). There are a number of compounds in human milk that might account for these observations, including immunoglobulin A, lactoferrin, lysozyme, oligosaccharides, growth factors, and cellular components. Nonetheless, differences across feeding groups in maternal education, maternal intelligence, in utero/postnatal smoke exposure, and quality of the home environment may also have influenced morbidity, independent of the anti-infective and other unique components of human milk (38).

The strengths of this study are the large sample size, the detailed accounting of milk feedings, and the inclusion of a comprehensive set of growth, tolerance, morbidity, and developmental tests. Unlike in most comparisons of human milk-fed and formula-fed LBW infants, in this study we attempted to control for genetic and environmental differences between human milk-feeding and formula-feeding families. In addition, infants in this study were fed according to current recommendations (7,8). We acknowledge that the self-selection of families to human milk-feeding groups, as opposed to random assignment, allows for the possibility that study findings could be attributable to unknown, and thus uncontrolled, genetic and environmental differences among feeding groups (e.g., quality of medical care). In addition, as a consequence of the exploratory nature of this retrospective study, a large number of comparisons were made without statistical adjustment for multiple comparisons; thus, it is possible that some of our observations could have occurred by chance. Finally, the relatively small PHM-T group compared with the other feeding groups and the variability in feeding after term CA diminishes the power of these analyses.

In summary, LBW infants fed predominantly human milk from first enteral feeding until term CA (fortified in-hospital) and weaned to nutrient-enriched formula until 12 months CA are physically smaller for some time after hospital discharge compared with LBW infants fed a nutrient-enriched formula. Nonetheless, their development is at least comparable. In addition, human milk-fed LBW infants appear to have reduced postdischarge morbidity, and in some subgroups perhaps even enhanced development compared with infants fed nutrient-enriched formula from the time of first enteral feeding to 12 months CA. Given the exploratory nature of this study, future studies are needed to confirm these latter observations.

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