

# Enhanced Protein Diet for Preterm Infants: A Prospective, Randomized, Double-blind, Controlled Trial

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## ABSTRACT

**Objective:** To evaluate dietary protein's effect on fat accretion and weight gain in hospitalized preterm infants.

**Methods:** Prospective, randomized, double-blind, controlled trial of 36 infants born at <32 weeks, hospitalized in a tertiary neonatal intensive care unit. After achieving full enteral volume, infants were randomized to either an enhanced protein diet (EPD) (protein-energy ratio [PER] 4 g/100 calories) or a standard protein diet (SPD) (PER 3 g/100 calories). Macronutrients were calculated using published values for formula, donor milk bank analysis, or weekly analysis of a 24-hour pooled maternal milk sample. Human milk fortifier and/or liquid protein were used to achieve the target PER until discharge or a maximum of 4 weeks. Body composition was measured weekly using air displacement plethysmography. The principal outcomes, rates of weight gain and fat accretion, were compared between groups in linear mixed models.

**Results:** Thirty-three infants received approximately 17 days of the study diet. Relative weight gain was  $21.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (95% confidence interval [CI] 19.5–23.8) for the EPD group ( $n = 16$ ) versus  $19.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (95% CI 17.0–21.2) for the SPD group ( $n = 17$ ),  $P = 0.095$ . Baseline percent fat mass (FM) in the EPD group was 5.15% (95% CI 3.58%–6.72%) compared with 7.29% (95% CI 5.73%–8.84%) in the SPD group,  $P = 0.0517$ . Percent FM increased 0.398%/day (95% CI 0.308–0.488) for the EPD group versus 0.284%/day (95% CI 0.190–0.379) for the SPD group ( $P = 0.0878$ ).

**Conclusions:** Preterm infants with a lower baseline FM percentage who received an EPD demonstrated a more pronounced catch-up percentage of fat accretion.

**Key Words:** body composition, inpatient, nutrition

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## What Is Known

- Postnatal growth restriction among preterm infants is common.
- Increased protein intake leads to increased weight gain in premature infants after discharge from the hospital.

## What Is New

- Increased protein intake may lead to an increase in fat mass during hospitalization in preterm infants.
- There may be a negative correlation between protein intake and rate of increase in head circumference.

Historically, the American Academy of Pediatrics defined adequate growth in preterm infants as replicating that of an age-equivalent fetus (1). With this definition, many preterm infants are growth-restricted at term-equivalent age, especially very low birth weight who are discharged weighing <10th percentile (2–4). Restricted postnatal growth negatively affects neurodevelopment at age 2 years (3,5). However, preterm infants are not fetuses and do not often achieve the same growth because of differing environments and nutrition; new research suggests novel methods for monitoring postnatal growth (4,6,7).

Customary nutritional strategies for preterm infants may result in accelerated growth, which is concerning because of a possible relationship between accelerated growth and increased fat accretion (8,9). Furthermore, the lifelong effects of higher body fat accretion are troubling because of presumed associations between weight gain of premature infants and later development of insulin resistance, type 2 diabetes, and metabolic syndrome (6,8).

Newer nutritional strategies emphasize increased protein intake: early initiation of amino acids (AA) in parenteral nutrition, high-protein preterm formulas, and supplementing human milk (HM) with liquid protein (3,4,7,10). Although clinicians expect these strategies to enhance fat-free mass (FFM) weight gain, few data are available, which demonstrate how these strategies affect preterm infant body composition.

This study compared weight gain and fat accretion in 2 infant groups, those receiving either a standard protein diet (SPD) (protein-energy ratio [PER] of 3 g/100 kcal) or an enhanced protein diet (EPD) (PER of 4 g/100 kcal).

## METHODS

This prospective, randomized, double-blind controlled trial that was performed in the neonatal intensive care unit (NICU) at the University of Oklahoma Children's Hospital, was registered with ClinicalTrials.gov (NCT02353013) and approved by the University

of Oklahoma Health Sciences Center's Institutional Review Board (#4885).

Eligible infants were born <32 weeks gestational age (GA) with a current weight of  $\geq 1000$  g and enteral intake of  $\geq 100$  ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup> at screening. Only parents fluent in English were approached as the informed consent form was only available in English. Infants with a higher baseline risk for abnormal growth (eg, severe congenital anomalies, inborn errors of metabolism, history of necrotizing enterocolitis Bell stage III, born small or large for GA) were excluded. Due to validation requirements of the air displacement plethysmography device, infants could not have cerebrospinal fluid shunts, permanent feeding tubes, continuous intravenous medications, or supplemental oxygen unable to be temporarily halted for  $\geq 10$  minutes.

Randomization was stratified based on birthweight (<1000 and  $\geq 1000$  g) in blocks of 4. After obtaining informed consent, researchers opened a sealed, opaque, computer-generated, sequentially numbered envelope for randomization assignment. Infants in the SPD (control) group received a target PER of 3 g/100 kcal. Those randomized to the EPD (intervention) group received a target PER of 4 g/100 kcal.

Breastfeeding mothers were asked to collect a 24-hour pooled sample weekly. Thirty milliliters from the pooled sample were analyzed at the Oklahoma Mothers' Milk Bank for macronutrients and caloric content. The Milk Bank also provided analyzed donor human milk (DHM) for mothers with inadequate volume who preferred HM to formula feeds. In formula-fed infants, published values from the manufacturers were used for weekly analysis. On the basis of the protein content of DHM and maternal milk, the infants' diets were modified to meet their groups' PER targets as follows:

1. Maternal milk and DHM were fortified at approximately 120 ml kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup> using Similac Human Milk Fortifier Liquid Concentrate (Abbott Laboratories, Abbott Park, IL), starting with 2 5 mL packets per 100 mL of milk the first day and advancing to 4 5 mL packets per 100 mL of milk in subsequent days. Similac Liquid Protein (Abbott Laboratories) was added for infants requiring additional protein.
2. Formula-fed infants requiring additional protein had Similac Liquid Protein added to the milk.

The Pea Pod Infant Body Composition System (Life Measurement, Inc., Concord, CA) has been shown to be accurate and reliable for measuring body composition in preterm infants using the principle of air displacement plethysmography (11). A detailed description of the physical design, operating principles, and measurement procedures for the Pea Pod are described elsewhere (12). Head circumference was measured using a disposable nonstretch paper tape measure. Length was measured using a hard plastic stadiometer. The Pea Pod was calibrated according to manufacturer's instructions before each use. The integrated electronic scale measured body weight. Infants were placed inside the machine for approximately 5 minutes. Using air displacement techniques, the Pea Pod calculates absolute fat mass (FM), percent of body mass attributed to fat (%FM), absolute fat-free mass (FFM), and percent of body mass attributed to FFM (%FFM).

Baseline anthropometrics and body composition were measured up to 24 hours before initiation of fortification and weekly thereafter, throughout the study period. Subjects were enrolled for 4 weeks or until discharge, whichever occurred first, resulting in up to 5 measurements.

Daily enteral intake volume was obtained from the electronic medical record. All data collected were stored in a HIPAA-secure database (REDCap). Only the team members who were mixing the

milk and the statistician were aware of group assignment. Team members performing body composition measurements and clinicians caring for the infants were blinded.

Using pilot data from our previous work (13), this study was powered to detect a between-group difference of 12% in weight gain attributable to fat. Assuming a 20% drop-out rate, 36 infants were needed to afford a power of 0.8 to detect this difference.

Relative weight was defined as weight (g) per kg of weight at study entry. By this definition, relative weight at study entry was 1000 g/kg. The percentage of weight gain attributable to fat at each measurement was defined as the difference in FM (g) between the day of measurement (FM<sub>i</sub>) and baseline (FM<sub>0</sub>) divided by the difference in body weight (g) between the day of measurement (BW<sub>i</sub>) and baseline (BW<sub>0</sub>): (FM<sub>i</sub> - FM<sub>0</sub>)/(BW<sub>i</sub> - BW<sub>0</sub>).

Categorical variables were compared between groups using Fisher exact tests. Continuous variables were compared using *t*-tests. We estimated change over time for each outcome variable in separate linear mixed models that accounted for repeated measurements on each subject. Each model, in addition to estimating the rate of change over time in the outcome variable, compared the 2 groups on the variable's rate of change. The linear models also produced infant-specific predictions of rates of change, which we used to explore the influence of baseline %FM. Statistical significance was defined as an alpha of <0.05. All analyses were performed in accordance with the intention-to-treat principle.

When we discovered after random assignment that male infants predominated in the SPD group whereas female infants predominated in the EPD group, we further explored the study groups' comparability with respect to %FM. Finally, each model was modified to explore the usefulness of adjusting its comparisons for the percentage of volume that infants obtained from HM (<75% vs  $\geq 75\%$ ), and for between-group differences in sex composition.

## RESULTS

Thirty-six infants were randomized from July 2015 to March 2017 (Fig. 1). Two infants were voluntarily withdrawn from the EPD group and 1 from the SPD group because of subgaleal shunt placement. The remaining 33 infants, 16 in the EPD group and 17 in the SPD group (including 1 who did not receive the allocated intervention) were analyzed. Table 1 shows demographic and anthropomorphic information, with nutritional data for both groups, averaged for each subject over the course of the study. Infants in the groups differed, as expected, on protein intake but not on other nutritional components.

The rate of increase in relative weight over the course of the study, seen in Figure 2A, was 21.6 g  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup> (95% confidence interval [CI] 19.5–23.8) for the EPD group versus 19.1 g  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup> (95% CI 17.0–21.2) for the SPD group (*P* = 0.095).

The rate of increase in %FM over the study course (Fig. 2B) was 0.398%/day (95% CI 0.308–0.488) for the EPD group versus 0.284%/day (95% CI 0.190–0.379) for the SPD group (*P* = 0.0878). These estimates were unaffected by adjustment for group differences in sex and HM consumption (Table 1).

Figure 2B illustrates that, at study entry (day 0), the estimated mean %FM was 2.14% higher (95% CI -0.02% to 4.29%; *P* = 0.0517) for infants in the SPD group versus infants in the EPD group. This baseline difference in %FM was seen in both boys and girls (Table 1). Estimated GA was similar between the groups at birth and study entry.

A statistical model that adjusted for %FM at study entry confirmed that infants with lower %FM gained FM more quickly (*P* < 0.0001). The model suggested further that, after adjusting for between-group differences in %FM at study entry, the rate of increase in %FM may not differ significantly (adjusted *P* = 0.3586) between infants receiving the 2 diets.

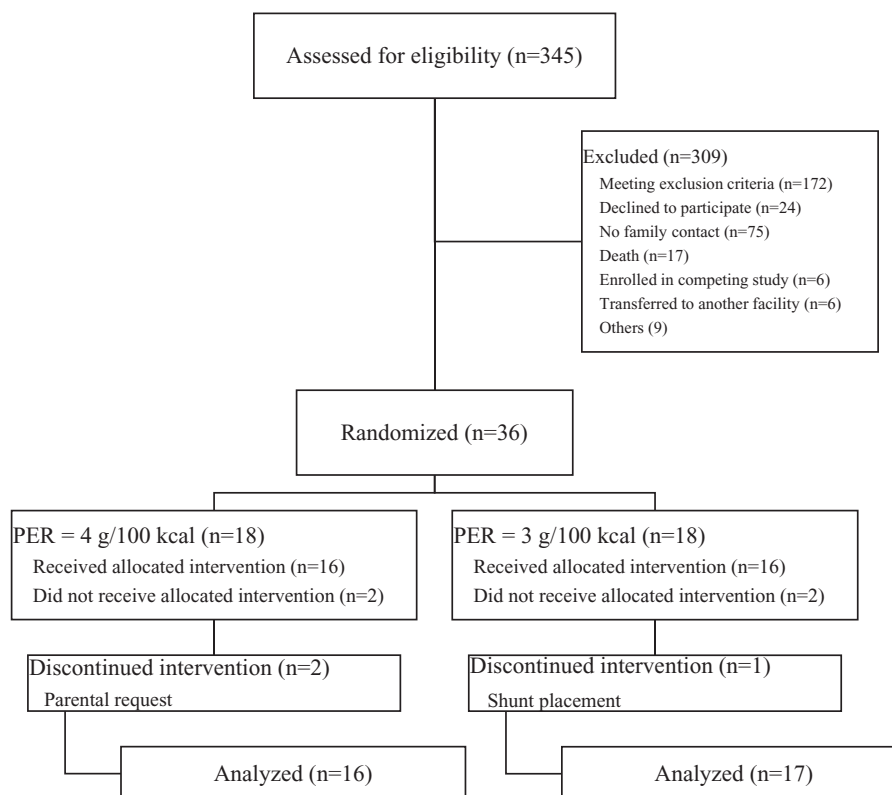


FIGURE 1. Flow diagram of recruitment.

TABLE 1. Infant characteristics and nutritional information

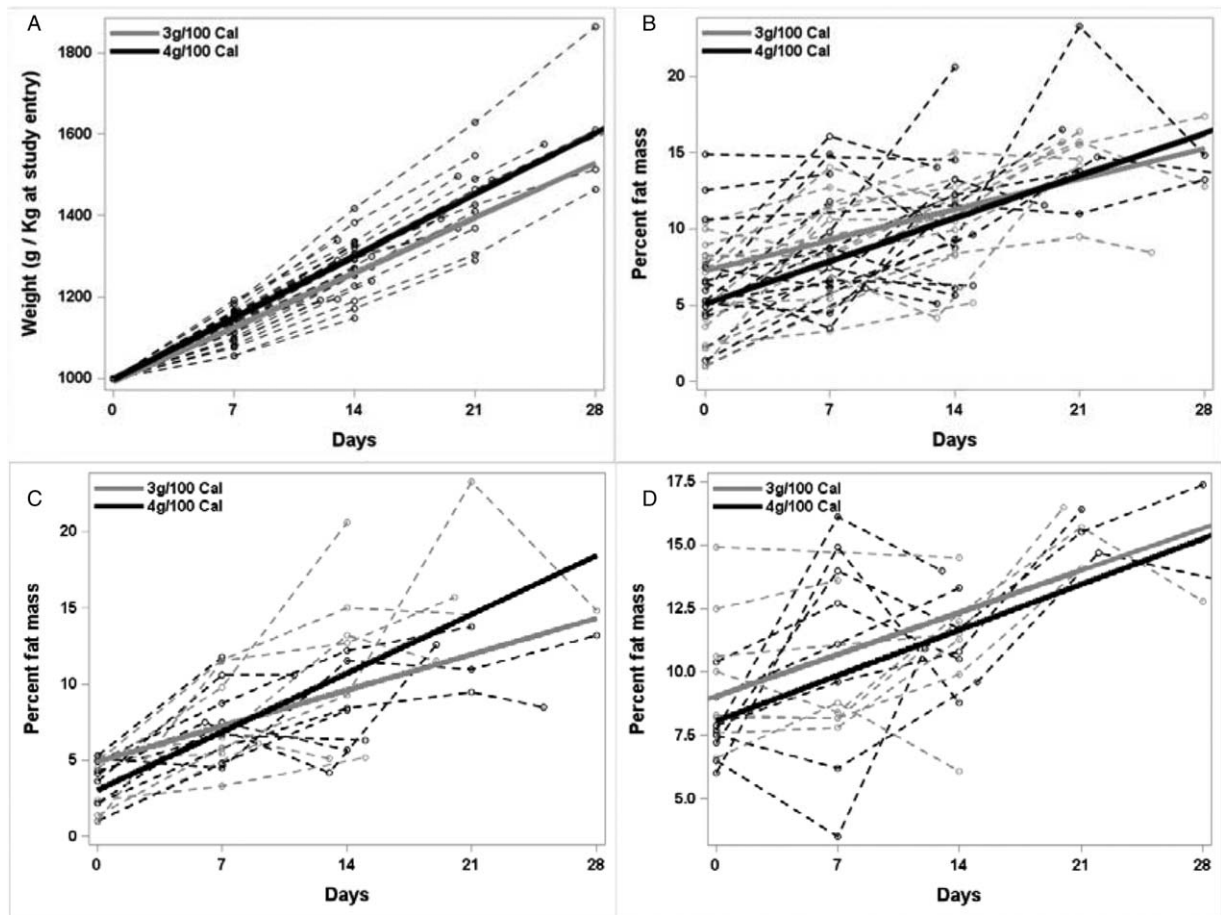
	SPD, 3 g/100 Cal (n = 17)	EPD, 4 g/100 Cal (n = 16)	P value
At birth			
Male (n, pct)	12 (70.6)	6 (37.5)	0.0844
Multiple gestation (n, pct)	8 (47.1)	6 (37.5)	0.7282
Maternal hypertension (n, pct)	9 (52.9)	6 (37.5)	0.4905
Birth weight, g; mean (SD)	1416.9 (263.5)	1374.7 (282.8)	0.6598
EGA, weeks; mean (SD)	30.0 (0.8)	29.5 (1.6)	0.2451
At study entry			
EGA, weeks; mean (SD)	32.6 (0.7)	32.6 (0.8)	0.8754
Weight, g; mean (SD)	1587.5 (246.1)	1588.0 (192.9)	0.9947
Length, cm; mean (SD)	41.2 (2.7)	41.6 (1.8)	0.6000
Head circumference, cm; mean (SD)	28.8 (1.4)	28.9 (1.0)	0.7990
Percent fat mass (95% CI)*	7.29 (5.73%–8.84%)*	5.15 (3.58%–6.72%)*	0.0517*
Among male infants <sup>†</sup>	7.13 <sup>†</sup>	4.23 <sup>†</sup>	0.0785 <sup>†</sup>
Among female infants <sup>‡</sup>	7.98 <sup>‡</sup>	4.84 <sup>‡</sup>	0.1162 <sup>‡</sup>
Nutritional information			
Caloric intake (kcal · kg <sup>-1</sup> · day <sup>-1</sup> ), mean (SD)	115.0 (6.35)	116.7 (5.8)	0.4496
Protein (g/kg/day), mean (SD)	3.5 (0.3)	4.7 (0.3)	<0.0001
Fat, g · kg <sup>-1</sup> · day <sup>-1</sup> ; mean (SD)	5.7 (0.6)	5.7 (0.5)	0.9859
Carbohydrate, g · kg <sup>-1</sup> · day <sup>-1</sup> ; mean (SD)	12.3 (1.1)	11.5 (1.5)	0.0847
Percentage of volume from human milk <sup>‡</sup>			
Less than 75% (n, pct)	6 (35.29)	7 (43.75)	0.7283 <sup>‡</sup>
At least 75% (n, pct)	11 (64.71)	9 (56.25)	

All information is averaged over the course of the study. EPD = enhanced protein diet; EGA = estimated gestational age; SPD = standard protein diet.

\*Estimates (and 95% confidence intervals) are from linear mixed model (see Fig. 2B).

<sup>†</sup>Values for male infants and female infants are observed baseline means (and SD) and are compared using nonparametric exact permutation tests (SAS PROC NPAR1WAY).

<sup>‡</sup>Human milk = mother's own milk + pasteurized donor human milk (Fisher exact test).



**FIGURE 2.** (A) Rate of increase in relative weight; (B) rate of increase in percent fat mass; (C) rate of increase in percent fat mass in those whose baseline percent fat mass was at or below the median; (D) rate of increase in percent fat mass in those whose baseline percent fat mass was above the median.

The lower the %FM at study entry, the more rapid the rate of increase in %FM that the linear model predicted for each infant. This negative correlation was larger in the EPD group ( $r = -0.61$ ;  $P = 0.0123$ ) than in the SPD group ( $r = -0.34$ ;  $P = 0.1816$ ). Differences between groups in the rate of change over time in %FM are shown in Figure 2C for subjects whose %FM at study entry was at or below the median value of 5.3% ( $P = 0.0270$ ). Figure 2D shows these differences for subjects whose %FM at study entry was above the median ( $P = 0.8062$ ). (Supplemental Figure, Supplemental Digital Content, <http://links.lww.com/MPG/B639>).

Between-group differences in %FM at study entry were not attributable to group differences in multiple births or maternal hypertension. Percent FM at study entry was 6.08% for singletons and 5.98% for multiples ( $P = 0.9346$ ). Mean %FM at study entry was nonsignificantly higher in infants of hypertensive mothers (6.6%) than nonhypertensive mothers (5.6%,  $P = 0.3807$ ).

The initial statistical analysis found no evidence that the percentage of weight gain attributable to fat changed over time in either group. Percentage of weight attributable to fat remained consistent over the course of the study at 32.6% (95% CI 26.1–39.1) for the EPD group versus 26.3% (95% CI 19.7–32.8) for the SPD group and did not differ between groups ( $P = 0.1722$ ).

Across the course of the study, the mean rate of increase in length (Fig. 3A) was 0.18 cm/day (95% CI 0.14–0.22) for the EPD group versus 0.20 cm/day (95% CI 0.16–0.23) for the SPD group ( $P = 0.4784$ ). The mean rate of increase in head circumference

(Fig. 3B) was 0.14 cm/day (95% CI 0.12–0.16) for the EPD group versus 0.17 cm/day (95% CI 0.15–0.19) for the SPD group ( $P = 0.0285$ ). This is a difference of 0.03 cm/day or 0.21 cm/week. Neither the analysis of length nor head circumference was affected by excluding the outlier shown in Figure 3.

### DISCUSSION

This study provides support for the hypothesis that increased protein intake leads to increased relative weight gain in preterm infants. However, infants who received an EPD increased their %FM more quickly than those who received a standard amount of protein. The more rapid relative weight gain observed in infants who received the EPD was partially because of the more rapid increases in %FM. The percentage of weight gain attributable to fat was consistent across the study duration, and did not differ significantly between groups.

Although FM as a percentage of body mass increased faster in the EPD group, it is unclear whether the diet itself was responsible for this difference. Infants who received the EPD had a lower %FM at study entry than those who received the SPD. The difference in FM at study entry was not because of being part of a group of multiples. Demarini et al (14) also found no significant differences in bone, fat, and lean mass (LM) between appropriate for GA singletons and multiples.

Despite randomization, our study included more boys in the SPD group and more girls in the EPD group. Even though male and

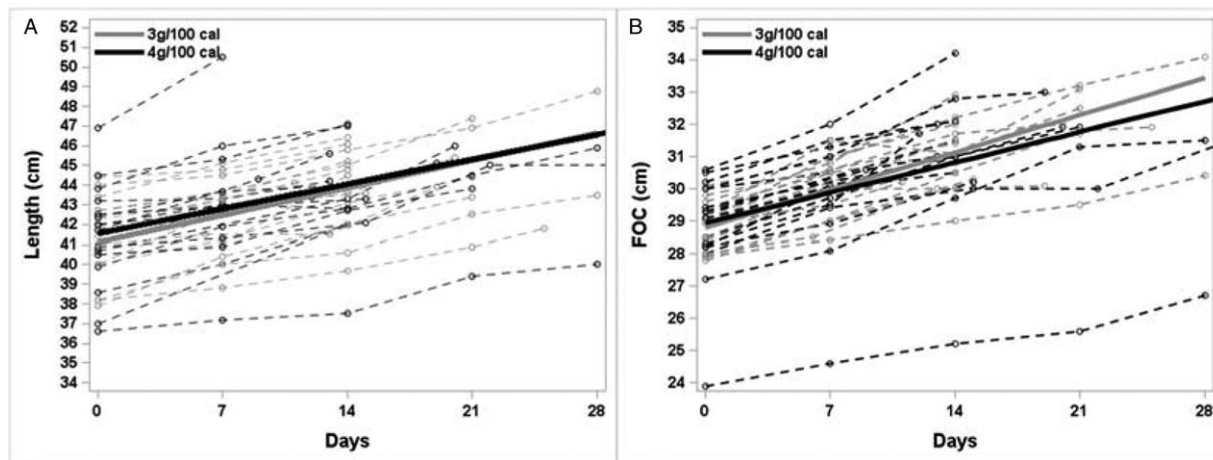


FIGURE 3. (A) Rate of increase in length and (B) rate of increase in head circumference.

female infants are known to differ in body composition, Table 1 illustrates that overall group differences in baseline FM were not because of differences in sex between groups. Hawkes et al (15) studied a large cohort of term infants to determine normal reference values of percent body fat. They found that term female infants had a higher percentage of fat than male infants and this difference increased with increasing GA. Male infants were also heavier, meaning the increased weight was because of FFM.

This study found that infants who received an EPD increased their %FM more quickly than those who received a SPD. Although the infants who received the EPD had lower baseline %FM, the finding nevertheless contrasts with those of previously published studies, which found that increased protein intake after discharge from the NICU resulted in increased weight gain because of LM. Roggero et al (16) showed that a protein intake of  $\geq 3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  led to significantly more gain in LM (measured via Pea Pod) than a protein intake of  $< 3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  in 48 Italian infants. Amez et al (3) also showed that 102 infants in the Netherlands fed a postdischarge formula with a higher PER gained more LM (measured via dual-energy X-ray absorptiometry) from discharge to 6 months corrected age than infants fed a lower PER term formula. Both studies were done after NICU discharge and they fed infants a postdischarge formula with no HM consumption.

In 2011, Costa-Orvay et al (4) used total body electrical impedance to analyze body composition of 38 premature Spanish infants during their NICU stay and found an inverse relationship between protein intake and FM. They assumed HM content based on published values but did not directly measure its composition. Furthermore, infants in their study were mostly fed formula (brand not available in the United States) whereas 61% of our infants received  $\geq 75\%$  of volume as HM. A more recent feasibility study of 27 infants by McLeod et al (17) from Australia also showed increased FM (measured via Pea Pod) associated with fat and energy intakes but not associated with protein intake. Most of their subjects received HM after the composition of the milk was obtained from biochemical analysis.

Whatever the reason for the between-group difference in baseline %FM, this may have contributed to the faster %FM increase among infants receiving EPD. Those infants may have had more “room to grow” than those in the SPD group. Diet itself may not have been responsible for the difference.

This study also differed from previous studies by permitting diversity in the source of milk infants consumed, including maternal milk, DHM, and/or formula. Differences in body composition may

relate to how infants digest and absorb AA from formula and HM as the AA in HM differ from those found in cow milk (18). To produce infant formula whose protein profile resembles HM, whey is added to cow milk to achieve a whey:casein ratio of 60:40 (18). Formulas that are whey-dominant create free plasma AA concentrations more like HM than formulas that are casein-dominant (18). Human milk also contains bioactive proteins like lactoferrin, lysozyme, secretory immunoglobulin A, bile salt-stimulated lipase, and others that enhance nutrient absorption and stimulate growth. These bioactive proteins are missing from formulas and their bioactivity is altered during the pasteurization of DHM (18).

Studies have shown that body composition differs between formula-fed versus breastfed infants. Bell et al (19) found that term infants who were formula-fed had considerably greater LM as early as 3 months of age whenever compared with breastfed infants. A systematic review of 15 studies conducted by Gale et al (20) encompassing over 1100 term infants also found differing body composition based on feeding method. They revealed that during the first year, formula-fed infants had higher FFM and lower FM than breastfed infants; however, at 12 months, FM was actually higher in formula-fed infants than in those who received HM. Similarly, Mulol and Coutsoudis (21) found that exclusive breastfeeding for the first 6 months in 100 term infants yielded higher %FFM at 12 months than did formula feeding. Finally, a review conducted by Huang et al (22) that included 642 preterm infants showed that the higher FM seen in formula-fed infants at 32 and 36 weeks corrected GA was no longer evident at 3 months corrected age. Furthermore, formula-fed infants had higher FFM from 36 weeks corrected GA to 12 months corrected age. There is no clear consensus on how body composition evolves over the first year of life in infants who consume different diets.

Increased protein intake did not significantly impact the rate of change in length. Infants who received the EPD demonstrated a slower increase in head circumference, a difference that could be clinically significant and was also observed by Uthaya et al (23).

This study was limited by several factors. Enrolling premature infants proved difficult because of constraints (respiratory support, shunt placement, etc.) associated with the Pea Pod. Moreover, infrequent parental visitation limited opportunities for obtaining consent. We had no information on maternal prepregnancy body mass index (BMI), so could not adjust for it, even though maternal BMI is known to affect neonatal body composition. Infants born to mothers with a normal prepregnancy BMI have less FM and %FM

than those born to mothers with a BMI that classifies them as overweight/obese (24). Furthermore, infants born to obese mothers also show growth deceleration in early infancy even without gestational diabetes and independent of size at birth (25). Finally, despite not being able to measure the composition of every HM feeding (because of the quantity of sample needed for analysis), we used the average for a 24-hour pooled specimen as the weekly target for fortification.

Even with its limitations, this randomized, controlled trial is one of the first conducted in this area of research. Although this study confirms that an increased PER does increase overall weight gain, this weight gain may be because of fat accretion. However, the trial is inconclusive on whether observed differences in fat accretion are due only to diet or whether they also relate to a “catch-up effect” among those with relatively low %FM at study entry. The analysis suggests that such an effect exists; baseline %FM was associated with fat accretion over the course of the study. However, the effect’s magnitude, compared with that of diet, is hard to discern because of the large amount of variability in the rates of fat accretion, especially in those with the lowest baseline %FM. Therefore, we conclude that preterm infants with a lower baseline FM percentage who received 2 to 3 weeks of an EPD demonstrated a more pronounced catch-up percentage of fat accretion. Further research into weight gain because of fat with differing PERs using only HM should be conducted to help understand this relationship.

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