

Formula Supplementation With Long-chain Polyunsaturated Fatty Acids: Are There Developmental Benefits?

David T. Scott, PhD*; Jeri S. Janowsky, PhD§; Robin E. Carroll, MS, RD||; James A. Taylor, MD‡; Nancy Auestad, PhD¶; and Michael B. Montalto, PhD¶

ABSTRACT. *Objective.* To evaluate the developmental outcomes of children who participated in an augmented randomized clinical trial of supplementing a standard infant formula with long-chain polyunsaturated fatty acids.

Design. Randomized clinical trial, augmented with a nonrandomized human milk comparison group. There were three randomized formula groups: standard formula, standard formula containing docosahexaenoic acid (DHA), and standard formula containing DHA and arachidonic acid.

Setting. Three clinical sites serving diverse populations: Kansas City, MO; Portland, OR; and Seattle, WA.

Participants. A total of 274 healthy full-term infants were enrolled in the infant-feeding protocol; of these, 197 (72%) participated in assessments of developmental outcome.

Formula Supplements. In the randomized trial, one group received a standard formula, another group received a formula that had been supplemented with DHA from fish oil, and a third group received a formula supplemented with both DHA and arachidonic acid from an egg phospholipid.

Outcome Measures. Mental and Motor Scales of the Bayley Scales of Infant Development at 12 months of age; vocabulary and gesture communication scores from the MacArthur Communicative Development Inventories at 14 months of age.

Results. There were no statistically significant differences for either the Bayley Mental Scale or the Bayley Motor Scale, neither when the analysis was restricted to the three randomized formula groups nor when the analysis included all four groups. However, the DHA formula group had significantly lower scores on two of the MacArthur scales: the DHA group scored lower than the nonrandomized human milk comparison group on the Vocabulary Comprehension Scale, and the DHA group scored lower than the randomized control formula group on the Vocabulary Production Scale. Moreover, additional analyses both in the formula groups and in the human milk comparison group found significant nega-

tive correlations between DHA levels and vocabulary outcomes.

Conclusion. We believe that additional research should be undertaken before the introduction of these supplements into standard infant formulas. *Pediatrics* 1998;102(5). URL: <http://www.pediatrics.org/cgi/content/full/102/5/e59>; fatty acids, infant formula, infant development, vocabulary.

ABBREVIATIONS. LCPFA, long-chain polyunsaturated fatty acids; DHA, docosahexaenoic acid; AA, arachidonic acid.

Infant brain growth requires the formation of large amounts of neural membrane. Synaptic membranes are especially rich in two long-chain polyunsaturated fatty acids (LCPFA)—docosahexaenoic acid (DHA) and arachidonic acid (AA). However, the origin of these fatty acids for brain accretion is not known. If synthesis is limited by a shortage of precursor fatty acids and/or by inadequate enzymatic capacity, then infants would be dependent on dietary sources of DHA and AA such as human breast milk. Therefore, it has been suggested that the absence of these fatty acids in current US formulas may put formula-fed infants at some neurodevelopmental disadvantage. Potential sources of LCPFA for formula supplementation include fish oils, egg lipids, and single-cell oils obtained from fermentation of algae and fungi.

In animal studies, dietary shortages of both DHA and its precursor α -linolenic acid have resulted in 1) reduced levels of DHA in brain^{1,2} and 2) adverse effects on early brain development (eg, visual deficits in a primate model¹ and altered learning behaviors in a rat model^{2,3}). Observational studies in self-selected human samples of breast-fed and formula-fed infants report IQ advantages favoring the breast-fed group,^{4,5} but these putative advantages sometimes disappeared after controlling statistically for familial factors such as maternal IQ and home environment,⁶ precluding easy inferences about causality. Meta-analysis of studies with human infants are difficult because of differences in the populations studied, methods used, and outcomes evaluated, as well as differences in the composition of the formulas studied (including levels of linolenic acid).⁷

We undertook a three-site, prospective, randomized clinical trial to pursue more directly whether neurodevelopmental benefits accrue to formula-fed infants if their formula contained either 1) DHA at

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TABLE 1. Bayley Scales of Infant Development at 12 Months of Age*

	Human Milk	Formula Groups		
		Control	AA + DHA	DHA
(n)	63	45	46	43
Mental Development Index	108 ± 15	105 ± 14	105 ± 12	104 ± 15
Psychomotor Development Index	100 ± 18	105 ± 15	98 ± 14	101 ± 14

* All scores are unadjusted means ± SD.

0.20% total fatty acids (without AA) or 2) DHA at 0.12% and AA at 0.43%. A breast-fed cohort was studied concurrently. Here we report the cognitive outcomes at 12 and 14 months of age.

METHODS

Details of the study were described previously.⁸ Briefly, 274 healthy full-term infants were enrolled after obtaining informed consent from their parents during the first week after delivery. Exclusion criteria included prematurity, intrauterine growth retardation, congenital anomalies, 5-minute Apgar scores <7, and other significant perinatal medical complications. Families who planned to formula-feed were randomized into one of three formula groups: a control formula with no added LCPFA (control formula group); a second formula with 0.2 wt% DHA from fish oil (DHA group); or a third formula with 0.12% DHA and 0.43% AA from egg phospholipid (AA + DHA group). Families who planned to breast-feed (human milk group) were not randomized; for these infants, breast milk was fed exclusively for the first 3 months, after which supplementation with Similac With Iron was permitted. Beginning at 4 months of age, solid food supplementation was permitted in all four groups.

At 12 months of age, the Mental and Motor Scales of the Bayley Scales of Infant Development⁹ were used to assess development. Examiners were unaware of the infants' group assignment or medical history. A language assessment was conducted at 14 months using the MacArthur Communicative Development Inventories, a parent-report instrument that evaluates early word production, language comprehension, and gestural communication.¹⁰

Analyses of variance and covariance were used to test for statistical differences, with a random block for site. Tukey's multiple comparison procedure or Bonferroni adjustments were used to test for pair-wise differences. Discrete variables were analyzed by χ^2 and Cochran-Mantel-Haenszel statistics. The significance level was $\alpha = 0.05$. The analyses of the cognitive outcome measures controlled statistically for maternal education, used here as a proxy for socioeconomic status.

RESULTS

Bayley scores were obtained for 197 infants at 12 months of age, and MacArthur scores were obtained for 173 infants at 14 months. There were no significant differences on demographic variables (infant gender, infant age at enrollment, maternal educa-

tion) between those who were and were not tested, except for ethnicity. Overall, infants were predominantly Caucasian. The ethnicity categories of Hispanic, African American, and Other collectively accounted for 12% of infants who completed the testing, but 30% of those who did not ($P < .05$).

Analysis of the 12-month Bayley scores revealed no significant differences, neither across all four groups nor across only the three randomized formula groups, for either the Bayley Mental Index or the Bayley Motor Index (Table 1). Because the MacArthur scale does not generate a composite score, we examined the scores for each of its constituent subscales. Two statistically significant differences were found with the MacArthur scale at age 14 months (Table 2). Vocabulary Comprehension was significantly lower in the DHA group than in the human milk group ($P = .017$). Vocabulary Production in the DHA group was marginally lower than that in the control formula group ($P = .052$). The DHA + AA and control formula groups did not differ from the human milk group. An additional comparison limited to the three randomized formula groups again found Vocabulary Production scores lower in the DHA group than in the control formula group ($P = .027$). No differences on the other subscales of the language assessment were found.

DISCUSSION

This study was undertaken to determine whether the addition of DHA (with or without AA) to infant formulae might facilitate early brain and cognitive development in formula-fed infants. We found no evidence that infants in the unsupplemented control formula group performed less well than breastfed infants or that supplementation conferred any developmental benefits. To the contrary, infants in the DHA (0.20%) group scored lower than those in the human milk and control formula groups on the lan-

TABLE 2. MacArthur Communicative Development Inventories at 14 Months of Age*

	Human Milk	Formula Groups		
		Control	AA + DHA	DHA
(n)	60	42	38	33
Phrases understood	104 ± 17	100 ± 16	99 ± 16	96 ± 12
Vocabulary comprehension	101 ± 13 ^a	100 ± 17	98 ± 14	92 ± 15 ^b
Vocabulary production	97 ± 17	101 ± 13 ^{c,e}	99 ± 17	91 ± 18 ^{d,f}
Early gestures	105 ± 12	105 ± 18	105 ± 19	102 ± 14
Late gestures	102 ± 13	101 ± 15	100 ± 16	97 ± 14

* All scores are unadjusted mean standardized scores ± SD.

After statistically controlling for maternal education and site, the following significant differences were found: comparisons across all four groups, ^{a,b} $P = .017$, ^{c,d} $P = .052$; across the three formula groups only, ^{e,f} $P = .027$. These differences in standardized scores correspond to vocabulary differences of approximately 140 words versus 90 words for vocabulary comprehension, and approximately 20 words versus 15 words for vocabulary production, comparing the human milk or control formula groups with the DHA group, respectively.

guage assessment at 14 months of age (on the Vocabulary Comprehension and Vocabulary Production subscales, respectively).

We considered a number of possible interpretations including an effect of fish oil per se, the absence of AA in the DHA group formula, the amounts of DHA provided (ie, 0, 0.12, 0.20 wt%), and the possibility of a chance finding. We reported previously that the plasma and red cell DHA levels in the formula groups reflected the relative amounts in the formulas; infants fed the DHA (0.20%) formula had the highest blood levels, even higher than those for breastfed infants.⁸

Previous studies have correlated LCPFA levels or ratios in blood at 4 months of age with growth¹¹ or with visual development.¹² In the present study, post hoc correlation analyses within the human milk group showed a statistically significant *negative* correlation between 4-month red cell DHA (wt% total fatty acids) and Vocabulary Production ($r = -0.30$; $P < .05$) and Vocabulary Comprehension ($r = -0.39$; $P < .01$). Among the formula groups, similar small (but statistically significant) relationships were found between red cell and plasma phospholipid DHA and Vocabulary Production ($r = -0.21$ to -0.28) and between plasma phospholipid DHA and Vocabulary Comprehension ($r = -0.19$; $P < .05$). No consistent correlations were found between 4-month AA levels and the vocabulary results at 14 months.

The group differences in vocabulary scores, together with the negative relationships between blood levels of DHA at 4 months and vocabulary scores at 14 months in both the breast-fed and the formula groups, make us reluctant to dismiss these differences as chance findings. Further, the negative correlations across groups between diet and vocabulary scores make it difficult to interpret these findings simply as an effect of 1) fish oil per se or 2) the absence of AA.

Whether these negative effects are specific to language and whether they will persist is not known. In

any case, we believe that it would be prudent to undertake additional study before adopting routine use of LCPFA supplements in commercial infant formulas.

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