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Growth and Development in Term Infants Fed Long-Chain Polyunsaturated Fatty Acids: A Double-Masked, Randomized, Parallel, Prospective, Multivariate Study

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ABSTRACT. *Objective.* **To evaluate the effects of dietary intake of the long-chain polyunsaturated fatty acids, arachidonic acid (AA), and docosahexaenoic acid (DHA) on multiple indices of infant growth and development.**

Design. **A double-masked, randomized, parallel trial was conducted with term infants fed formulas with or without AA+DHA for 1 year ($N = 239$). Reference groups of breastfed infants ($N = 165$) weaned to formulas with and without AA+DHA were also studied. Infants in the formula groups were randomized at ≤9 days of age to a control formula with no AA or DHA ($n = 77$) or 1 of 2 otherwise identical formulas containing AA+DHA (AA, 0.46% and DHA, 0.14% of total fatty acids) from either egg-derived triglyceride (egg-DTG [$n=80$]) or fish oil and fungal oil (fish/fungal [$n = 82$]) at levels similar to the average in breast milk samples as measured in the reference group. All formulas contained 50% of energy from fat with the essential dietary fatty acids, linoleic acid (20% fatty acids) and α-linolenic acid (2% fatty acids). The main study outcomes were AA and DHA levels in plasma and red blood cells, and multiple measures of infant development at multiple ages from birth to 14 months: growth, visual acuity, information processing, general development, language, and temperament.**

Results. **AA and DHA levels in plasma and red cells were higher in AA+DHA-supplemented groups than in the control formula group and comparable to those in reference groups. No developmental test results distinguished these groups. Expected differences in family demographics associated with breastfeeding were found, but no advantages to breastfeeding on any of the developmental outcome demonstrated.**

Conclusions. **These findings do not support adding AA+DHA to formulas containing 10% energy as linoleic acid and 1% energy as α-linolenic acid to enhance growth, visual acuity, information processing, general development, language, or temperament in healthy, term infants during the first 14 months after birth.** ***Pediatrics*** **2001;108:372–381;** ***infant development, breast feeding, infant formula, long-chain polyunsaturated fatty acids, docosahexaenoic acid.***

ABBREVIATIONS. AA, arachidonic acid; DHA, docosahexaenoic acid; egg-DTG, egg-derived triglycerides; SD, standard deviation.

Are there demonstrable benefits for infant development from feeding infant formulas containing the long-chain polyunsaturated fatty acids arachidonic acid (AA) and docosahexaenoic acid (DHA)? Some studies comparing children who were breastfed (BF) with children who were fed infant formula have reported an association between breastfeeding and intellectual development.[1–4] In these studies, however, children were not randomized to breast- or formula-feeding, and differences between these cohorts[5–7] other than diet may explain the findings. For example, parents of BF infants often have a higher socioeconomic status and more years of education,[6] and lifestyle choices known to affect cognitive development, such as cigarette smoking, may differ.[7] Several studies have evaluated whether supplementing formulas for term[8–17] or preterm[18–21] infants with DHA or both AA and DHA increases the circulating levels of these fatty acids and enhances visual and cognitive development. Although infants fed human milk or formulas supplemented with DHA or AA and DHA consistently have higher plasma and red blood cell levels of DHA or AA and DHA than infants fed unsupplemented formulas, findings of differences on visual and cognitive tests have been inconsistent in the studies with term infants. Associations between higher levels of DHA in plasma or red blood cells and enhanced visual and cognitive development, thus, have not been established. Unfortunately, these comparisons have likewise been confounded by uncontrolled variation in

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sample size, differences in formula composition (eg, amounts and ratios of the essential dietary fatty acids [linoleic acid, α-linolenic acid] or other nutrients [iron]), the source of DHA- and AA-enriched fats or oils studied, the amounts and ratios of DHA and AA, the tests and testing procedures used to evaluate child visual and developmental status, and the age(s) at which children have been tested.[22]

Infants can form AA and DHA from their essential dietary fatty acid precursors, linoleic acid and α-linolenic acid,[23–25] which are present in formulas but in varying amounts. Therefore, it is plausible that AA- and DHA-supplementation may not be necessary in the infant diet. Evidence has been published[11,12,26–28] suggesting that formulas containing a minimum of 1.75% fatty acids as α-linolenic acid and a ratio of linoleic to α-linolenic acids of 5:1 to 15:1 may adequately support visual and cognitive development, despite lower circulating levels of AA and DHA.

We conducted a comprehensive double-masked, randomized, parallel, prospective, and adequately powered multivariate study of infants fed a standard unsupplemented formula or 1 of 2 formulas supplemented with AA and DHA from different sources to help bring clarity to the controversial question about benefits to infant development from dietary supplementation. In comparison with published studies[9–12] available during the design phase of the trial, the sample size was larger, multiple domains of neurodevelopment were evaluated at multiple timepoints, infant temperament was assessed, and two sources of AA and DHA were studied concurrently. In addition to comparisons among infants fed formula with or without AA+DHA throughout the first year, the present study also evaluated infants who were BF for the first 3 months after which formula with or without AA+DHA may have been fed as a supplement to breast milk or as a weaning formula. Comparisons between formula-fed and BF infants are also provided.

METHODS

Participants

This 12-month, double-masked, parallel, prospective feeding study enlisted 2 cohorts of term infants, BF and formula-fed. Infants were recruited from hospitals and pediatric practices at 4 sites in the United States: Kansas City, Missouri; Little Rock, Arkansas; Pittsburgh, Pennsylvania; and Tucson, Arizona. The study was approved by institutional review boards at the respective sites. Infant inclusion criteria included: good health, term status (gestational age 37–42 weeks), either ≤9 days of age (formula groups) or ≤11 days of age and currently BF (BF groups), birth weight ≥2500 g, 5-minute Apgar score ≥7, ability to tolerate a milk-based formula or breast milk, parent or guardian agreement to feed the assigned study formula ad libitum according to the study design, and voluntary written informed consent. Infants were ineligible if they had evidence of significant cardiac, respiratory, ophthalmologic, gastrointestinal, hematologic, or metabolic disease; milk-protein allergy; or a maternal medical history known to have proven adverse effects on the fetus (eg, gestational diabetes if the infant's birth weight was ≥4150 g), tuberculosis, human immunodeficiency virus infection, perinatal infections, or substance abuse. Infants who were small-for-gestational-age (<10th percentile) and large-for-gestational-age (>90th percentile) were not excluded. The feeding period was to 12 months of age, and data were collected through 14 months of age.

Formulas

At enrollment, formula-fed infants were randomized to a control formula or 1 of 2 formulas supplemented with DHA and AA: 1) fish oil (Mochida International Co, Ltd, Tokyo, Japan) and fungal oil (Suntory Ltd, Osaka, Japan; fish/fungal) or 2) egg-derived triglyceride (egg-DTG, Eastman Chemical Co, Kingsport, TN). All formulas were liquid ready-to-feed formulas with (per L): 14.3 to 15.0 g protein; 72.4 to 74.8 g carbohydrate; 35.9 to 37.2 g fat; and 670 to 694 calories. The protein was from nonfat milk and whey protein concentrate, and the oil blend consisted of high-oleic safflower, coconut, and soy oils with or without the AA- and DHA-enriched oils. The study formulas were indistinguishable in appearance and odor and were coded to mask their identity. All formulas contained the essential dietary fatty acids, α-linolenic acid (2% fatty acids) and linoleic acid (20% fatty acids; Table 1), and met or exceeded nutrient levels established by the American Academy of Pediatrics Committee on Nutrition[29] and regulated by the Infant Formula Act of 1980 as amended in 1986.

The levels of DHA and AA in the supplemented formulas were chosen based on previous studies[10,11,30] and are similar to recently published levels in human milk in US women.[31,32] Infants fed

TABLE 1. Fatty Acid Composition* of the Control and AA+DHA-Supplemented Formulas and Breast Milk From Women Who Were Exclusively Breastfeeding at 4 Months' Postpartum and Whose Infants Were in the Breastfeeding Cohort

Fatty Acid	Formula Groups†			Breast Milk‡
	Control	AA+DHA (Egg-DTG)	AA+DHA (Fish/Fungal)	
Saturated				
12:0 (lauric acid)	10.5	10.2	12.9	4.5 ± 2.1§
14:0 (myristic acid)	5.8	4.1	5.2	6.1 ± 2.1
16:0 (palmitic acid)	8.4	9.3	8.2	20.4 ± 2.2
18:0 (stearic acid)	3.8	4.6	3.8	7.5 ± 1.2
Monounsaturated				
18:1 (oleic acid)	40.5	41.0	40.0	36.8 ± 3.0
Polyunsaturated				
18:2n-6 (linoleic acid)	22.2	22.4	21.0	16.6 ± 3.1
18:3n-3 (α-linolenic acid)	2.6	2.5	2.4	1.3 ± 0.4
20:4n-6 (AA)	ND	0.45	0.46	0.51 ± 0.13
20:5n-3 (EPA)	ND	ND	≤0.04	0.05 ± 0.03
22:6n-3 (DHA)	ND	0.14	0.13	0.12 ± 0.07

* g/100 g total fatty acids. ND indicates not detectable; EPA, eicosapentaenoic acid. Fatty acid levels were determined at the † Clinical Chemistry Department, Ross Products Division, Abbott Labs and ‡ University of British Columbia, Vancouver (analyses were carried out at the laboratory of Dr S. M. Innis). Fatty acids with ≤10 carbons and others present at <0.5% total fatty acids are not shown.
§ Values are mean ± SD, $n = 43$.

formulas with 0.10 to 0.15 g/100 g (%) fatty acids as DHA and about 0.4% as AA had plasma and red blood cell levels of DHA and AA most closely matching those of BF infants in the United States.[10,11,30] In the present study, both supplemented formulas contained DHA and AA at 0.13% and 0.45% fatty acids, respectively (Table 1). Eicosapentaenoic acid (20:5n-3) was not detectable in the egg-DTG formula and was ≤0.04% in the formula with fish oil (fish/fungal). Nine percent of the fat blend in the egg-DTG formula was egg-DTG. In the fish/fungal formula, 0.7% and 1.7% of the fat blend was fish and fungal oils, respectively. Coconut oil levels were reduced accordingly in both formulas.

Design

Infants in the 3 formula groups were randomized within 9 days after birth. Separate randomization schedules for each site were stratified by gender and were computer-generated using a random permuted blocks algorithm. The study formulas were fed ad libitum as the sole source of nutrition for 4 months and as the exclusive milk beverage to 12 months. Infants in the 2 BF groups were randomized to the control (BF/control) or the AA+DHA (egg-DTG; BF/AA+DHA) formulas within 11 days after birth and exclusively BF for at least 3 months. Although not encouraged, a small percentage of BF infants occasionally were fed small amounts of supplemental formula, but this was limited to <16 oz (480 mL) per week. The assigned study formulas were not provided nor fed until after 3 months of exclusive breastfeeding, and only if the parent(s) chose to provide supplemental formula or to wean to formula feeding. All infants were allowed water ad libitum, solid foods after 4 months of age, and alternate formulas for up to 5 days if recommended by a primary care physician or the investigator.

Study visits after enrollment took place at 1, 2, 4, 6, 9, and 12 months with a mail-in questionnaire at 14 months. A window of ± 5 days was permitted for the first 5 visits; the 12- and 14-month visits had a window of ± 7 days. Infant and family demographic information were obtained at the enrollment visit. Formula disposition records, parental records of formula intake at designated intervals throughout the study, and parent interviews at each study visit were used to encourage and monitor compliance with feeding the assigned study formula or human milk.

Red Blood Cell Fatty Acid Analysis

The fatty acid composition in plasma and the phosphatidylcholine and phosphatidylethanolamine membrane fractions of red blood cells were determined from a subset of infants (n = 23–41 per feeding group) at the 4- and 12-month visits. Blood (4 mL) was drawn by venipuncture by a physician or registered phlebotomist from infants whose parents agreed to the procedure. Red cells were stored at −20°C, shipped on dry ice every 2 to 3 months to a central laboratory (Dr S. M. Innis, University of British Columbia, Vancouver, Canada), verified frozen on arrival, and stored at −70°C until analyzed for fatty acid composition.[26,30]

Breast Milk Fatty Acids

A sample of breast milk was provided by a subset of mothers who were still exclusively breastfeeding at the 4-month visit (n = 43). After the infant had nursed for about 5 minutes, the mother removed the infant from the breast and expressed a midfeeding sample into a clean infant bottle, transferred ~3 mL to a vial, placed it in a sealable plastic vial, and stored in the home freezer until the study visit. The procedures for collection and storage of milk samples were consistent with recommendations by Jensen et al[33] and those reported by others.[31] The human milk samples were stored at −20° or −70°C at the study site, shipped on dry ice to a central laboratory (Dr S. M. Innis, University of British Columbia, Vancouver, Canada), verified to be frozen on arrival, and stored at −70°C before being analyzed for fatty acid composition as described above for red blood cell fatty acids. The methodologies for determining the fatty acid levels in breast milk samples and the infant formulas were similar.

Standardization of Developmental Procedures

Testing and scoring for all developmental measures and clinical procedures were standardized across all sites, and adherence to testing and scoring procedures was monitored throughout the study to assure reliability. Administrators and coders for the developmental testing were trained in proper procedures, had extensive experience in child development, and met certification requirements. All testers were masked to infant feeding groups.

Testers who administered the acuity card procedure were trained and certified (Dr V. Dobson, Tucson, Arizona; Dr L. Mayer, Boston, Massachusetts) before testing infants. Drs Dobson and Mayer conducted site visits during the study to monitor administration and scoring procedures. One hundred eighty-five infants, who represented approximately 1 of every 4 infants in the study plus additional nonstudy infants, were tested by 2 trained testers at each site to determine reliability. Agreement between the first and second tester was within 1 octave for ≥95% of tests and within 0.5 octave for ≥70% of the tests (Kendall's $\tau = 0.79$; $P < .0001$).

Procedures for administration of the Bayley Scales of Infant Development and the Fagan Test were coordinated centrally (Dr R. Arendt, Cleveland, Ohio). A workshop was held to standardize testing procedures (Drs L. Singer, R. Arendt, C. Segal, Cleveland, Ohio), and a videotape of the testing procedures was provided to all testers. Testers who administered the Fagan Test were trained and certified (Drs L. Singer, E. Shaver, Cleveland, Ohio) before testing infants. Approximately 1 out of every 10 Bayley test sessions at the 6- and 12-month time points were videotaped, and the videotapes were scored centrally (Dr R. Arendt, Cleveland, Ohio). The average percent agreement among testers for the Bayley mental index was 77% and 91% at the 6- and 12-months, respectively, and for the Bayley motor index was 87% and 91%, respectively.

Growth

Weight, length, and head circumference were measured at enrollment and 1, 2, 4, 6, 9, and 12 months using standardized procedures (*Guide to Growth Assessment of Infants in Clinical Studies* [34]).

Visual Acuity

Visual acuity was assessed using the Teller Acuity Card Procedure (Vistech Inc, Dayton, OH[35]) at 2, 4, 6, and 12 months. Infants were shown a series of 25.5 × 51-cm cards with black and white stripes varying in spatial frequency (stripe width) by half-octave steps. One octave is a halving or doubling of spatial frequency. The finest grating (stripe width) to which the infant showed a consistent fixation response is the visual acuity threshold in cycles/degree with the variance (SD) in octaves.

Information Processing

The Fagan Test of Infant Intelligence (Infantest Corporation, Cleveland, OH[36]) was administered at 6 and 9 months. During a familiarization period, a face stimulus was shown until the infant accumulated a predetermined amount of looking time; during the subsequent test period, the familiar face stimulus was shown concurrently with a novel face stimulus. The amount of looking time spent on each stimulus was recorded (IBM Thinkpad), and "novelty preference" (percentage of total looking time spent looking at the novel stimulus during the test phase averaged across 10 tests) was computed. In addition, mean duration of looking time, construed as a measure of efficiency of information processing, was computed for both the familiarization and test periods by dividing the total looking time by the number of looks averaged across 10 tests.[37,38]

General Developmental Level

The Bayley Scales of Infant Development (Psychological Corporation, 2nd ed, San Antonio, TX[39]) were administered at 6 and 12 months to assess motor and cognitive development (Psychomotor Developmental Index; Mental Developmental Index, respectively).

Language

The infant version of the MacArthur Communicative Development Inventories,[40] a standardized parent-report instrument, was completed at 9 and 14 months. This checklist of words, phrases, gestures, and actions provides information about comprehension vocabulary (words and phrases the child understands), and expressive vocabulary (words and phrases the child says). Percentile scores were computed from gender-specific norms and transformed to standard scores by convention.

Temperament

The Infant Behavior Questionnaire[41] was completed by the parent(s) at 6 and 12 months. This standardized 94-item questionnaire measures activity level, distress to novel stimuli, distress to limitations, soothability, smiling and laughter, and duration of orienting. Infant temperament was also assessed using the Behavior Rating Scale of the Bayley Scales[39], an index of the examiner's overall impression of the child's behavior.

Statistical Methods

Power analysis estimated that 54 infants (27 male, 27 female) in each of the 3 randomized formula groups were needed to detect a 1 SD difference in growth for each gender with 90% power. An additional sample size estimate was based on the results of a previous study showing lower vocabulary scores in 14-month-old infants fed a DHA-supplemented formula than in infants fed human milk or a control formula, respectively[12]. This power analysis estimated that 47 infants per group were needed to detect a 0.75 SD difference in vocabulary scores with 90% power. Blood samples from approximately 27 infants per group were needed to detect a 1 SD difference (90% power) in the levels of the fatty acids, AA and DHA.

All analyses controlled for site (ie, site was used as a covariate) to minimize the potential confounding effect of intersite variability. Comparisons among the 3 formula groups and between the 2 BF groups were done twice, once with no additional covariates and once with additional covariates selected a priori. Analyses reported are without the additional covariates; in all cases covariate analyses showed similar results. Categorical variables were analyzed using χ^2 or Cochran-Mantel-Haenszel tests and continuous variables by analysis of variance (analysis of variance) and/or analysis of covariance. Repeated measures analyses were used for data collected at >1 time period. Post hoc comparisons of formula-fed and BF infants were done using the BF and corresponding formula groups to provide the greatest power to detect differences between these cohorts.

RESULTS

Two hundred ninety-four (73%) of the 404 enrolled infants completed the study. The most common reasons for exiting the study early were reported intolerance for the formula groups (n = 16, 13, and 14 for the control, egg-DTG, and fish/fungal groups, respectively) and cessation of breastfeeding and/or formula feedings started before 3 months for the BF groups (n = 10 and 9 for the BF/control and BF/AA+DHA groups, respectively). The distribution of infants across groups, the primary reasons for early exit, and the numbers of days in the study did not differ across groups for those who exited early.

Infant and family sociodemographic characteristics were not different among the formula groups or between the BF groups, with the exception of inconsequential statistical differences between the BF/control and BF/AA+DHA groups for infant gestational age (39.2 ± 1.2 vs 39.6 ± 1.3 weeks, respectively) and for maternal age (29.1 ± 5.2 vs 30.8 ± 4.6 years, respectively). The demographic characteristics of the study population as a whole are generally similar to those described for the US population.[42] The average daily caloric intake of formula and measures of formula tolerance (eg, frequency of spitting up and/or vomiting; consistency of stools) did not differ among groups within each cohort (data not shown).

Comparisons between the formula-fed and BF groups showed the formula groups with a larger percentage of mothers having no postsecondary education (39, 33, 21, and 19% in the control, AA+DHA [egg-DTG], BF/control, and BF/AA+DHA groups, respectively; P = .024) and a higher prevalence of smoking (Table 2). Although breastfeeding rates in the present study declined after 3 months, the rates were higher than the national averages in the mid-1990s. In the present study, 36% of mothers were exclusively breastfeeding at 6 months with another 30% providing breast milk for some of the daily feedings. The national breastfeeding rates are about 10% and 15%, respectively, for mothers with similar demographics[43] (AS Ryan, personal communication).

AA and DHA

The average levels of AA and DHA in breast milk at 4 months were 0.51% (range: 0.27%–0.93%) and 0.12% (range: 0.04%–0.34%), respectively. Infants fed the AA+DHA supplemented formulas, independent of the source (egg-DTG or fish/fungal), had significantly higher levels of AA and DHA in red blood cell phospholipids than those fed the control formula ($P < .0001$; Table 3). In the BF groups, red blood cell phospholipid levels of AA and DHA were not different at 4 months, but at 12 months infants fed the AA+DHA formula had about 40% higher levels of DHA than those fed the control formula (P = .03). Comparisons between the BF and corresponding formula groups found lower AA and DHA levels in red blood cells of infants fed the unsupplemented control formula than those fed the supplemented formula and/or human milk (Table 3).

Growth

There were no overall or gender specific differences for increases in weight, length, or head circumference among groups during the 12-month study (Fig 1). Weight gain from enrollment to 12 months was 17.7 ± 2.6, 17.8 ± 2.4, and 17.3 ± 2.6 g/d ($P >$ .05) for infants fed the control, AA+DHA (fish/fungal), and AA+DHA (egg-DTG) formulas and 17.4 ± 2.6. and 18.0 ± 3.1 g/d ($P >$ .05) for infants in the BF/control and BF/AA+DHA groups, respectively. Weight gain for male infants between enrollment and 4 months, but not between enrollment and 12 months, was greater for the AA+DHA (fish/fungal) group than the control group (31.4 ± 4.6 g/d and 27.8 ± 4.2, respectively; $P < .05$). Weight gain for infants fed AA+DHA from egg-DTG (29.1 ± 5.1 g/d) was not greater than the control group over the same period. Similarly, there were no differences in length or head circumference gains between enrollment and 4 months. Gains in weight, length, and head circumference between 0 and 4 months and 0 and 12 months were not different between the BF/control and BF/AA+DHA groups. No differences in growth between the BF and corresponding formula groups were found.

Visual Acuity

Visual acuity results (cyc/deg) were log-transformed according to convention[44] before analysis, and the geometric mean values (cyc/deg) are reported with SD in octaves. Visual acuity was in the normal range for each group at all ages tested[45,46] and was not different in relation to supplementing

TABLE 2. Infant and Family Sociodemographic Characteristics

Cohort	Formula Groups			Breastfed Groups	
	Control	AA+DHA (Egg-DTG)	AA+DHA (Fish/Fungal)	Control	AA+DHA (Egg-DTG)
n	77	80	82	82	83
Infant characteristics					
Birth weight, kg	3.45 ± 0.44	3.39 ± 0.47	3.41 ± 0.41	3.49 ± 0.48	3.54 ± 0.41
Birth length, cm	50.8 ± 2.5	50.3 ± 2.6	50.6 ± 2.1	50.9 ± 2.4	51.1 ± 2.6
Gestational age, wks*	39.4 ± 1.2	39.0 ± 1.3	39.3 ± 1.2	39.2 ± 1.2†	39.6 ± 1.3†
Gestational appropriateness, *n* (%)					
AGA	66 (85.7)	69 (86.3)	71 (86.6)	72 (87.8)	69 (83.1)
SGA	2 (2.6)	2 (2.5)	0	1 (1.2)	1 (1.2)
LGA	8 (10.4)	9 (11.0)	8 (9.8)	8 (9.8)	13 (15.7)
Unknown	1 (1.3)	0	3 (3.7)	1 (1.2)	0
Apgar, 5 min	9.1 ± 0.4	9.1 ± 0.4	9.1 ± 0.5	9.1 ± 0.4	9.1 ± 0.7
Males, *n* (%)	37 (48.1)	39 (48.7)	40 (48.8)	42 (51.2)	43 (51.8)
Birth order, *n* (%)					
1	30 (39.0)	22 (27.5)	29 (35.4)	32 (39.0)	32 (38.6)
2	25 (32.5)	36 (45.0)	38 (47.5)	27 (32.9)	30 (36.1)
≥3	22 (28.6)	22 (27.5)	14 (17.1)	23 (28.0)	21 (25.3)
Ethnicity, *n* (%)					
European American	61 (79.2)	70 (87.5)	72 (87.8)	67 (80.7)	74 (90.2)
African American	3 (3.9)	2 (2.5)	3 (3.7)	4 (4.8)	0 (0.0)
Hispanic American	2 (2.6)	4 (5.0)	4 (4.8)	6 (7.2)	3 (3.7)
Asian American	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other/missing‡	10 (13.0)	4 (5.0)	3 (3.7)	6 (7.2)	5 (6.1)
Family characteristics					
Maternal age, y§	28.1 ± 5.9	29.0 ± 5.1	29.2 ± 5.0	29.1 ± 5.2†	30.8 ± 4.6†
Smoking, *n* (%)					
During pregnancy‖	12 (15.6)	16 (20.0)	15 (18.5)	7 (8.5)	6 (7.2)
In household¶	16 (20.8)	26 (32.5)	14 (17.3)	11 (13.4)	7 (8.4)
Parental education, y					
Mother	13.7 ± 2.1	14.2 ± 1.9	14.1 ± 2.5	15.1 ± 2.3	15.3 ± 2.4
Father	13.8 ± 2.0	14.0 ± 2.1	14.6 ± 2.1	15.0 ± 2.4	15.3 ± 2.6
Maternal marital status, *n* (%)					
Married	60 (77.9)	63 (78.6)	68 (82.9)	70 (85.4)	80 (96.3)
Single	14 (18.2)	15 (18.8)	14 (17.0)	10 (12.2)	3 (3.6)
Separated-divorced	3 (3.9)	2 (2.5)	0	2 (2.4)	0

Values are mean ± SD unless noted otherwise. Within each cohort, values with different superscripts are statistically different.
AGA indicates appropriate-for-gestational age; SGA, small-for-gestational age (<10th percentile); LGA, large-for-gestational age (>90th percentile).
† $P < .05$.
‡ Other category includes Native American and mixed ethnicities. Significant differences in post hoc comparisons between the breastfed and corresponding formula groups: * $P = .006$ for gestational age, BF/AA+DHA (egg/DTG) group versus AA+DHA (egg-DTG) formula group; § $P = .001$ for maternal age, BF/AA+DHA (egg-DTG) group versus control formula group; ‖ $P = .054$ for maternal smoking during pregnancy, breastfed versus formula groups; ¶ $P = .001$ for prevalence of smoking in the household, breastfed versus formula groups.

infant formula with AA+DHA (Fig 2). Visual acuity was not different between the BF and corresponding formula groups.

Information Processing

Infant information processing, assessed as novelty preference, was also in the normal range at the 2 ages tested.[36,47,48] Scores did not differ between infants in the formula control and AA+DHA groups or between BF/control and BF/AA+DHA groups (Table 4). Look duration during the familiarization and testing periods, thought to index the rate of information processing,[37,38] similarly did not differ in relation to adding AA and DHA to formula (data not shown). Novelty preference and look duration also were not different between the BF and corresponding formula groups.

Bayley Scales

Infants in all groups scored in the normal ranges on both the psychomotor and mental development indices of the Bayley Scales.[39] Neither index at 6 or 12 months differed among the formula control and the AA+DHA groups or between the BF/control and BF/AA+DHA groups (Table 4). No differences emerged in the percentages of infants who scored <70 or 71 to 84 (data not shown). There were no differences in mental or motor scales between the BF and corresponding formula groups.

Language

Children scored in the normal range of the vocabulary comprehension and expression at the ages tested.[40] Vocabulary comprehension did not differ among the three formula groups or between the BF groups, but at 14 months, infants fed the AA+DHA (fish/fungal) formula had a slightly, but significantly, higher vocabulary expression score than those fed the AA+DHA (egg-DTG) formula (Table 4). However, neither AA+DHA group was significantly different from the control formula group, and there were no differences between the BF and corresponding formula groups.

TABLE 3. AA and DHA Levels in Red Blood Cell Phospholipids (g/100 g) in Infants Fed Formulas With or Without AA+DHA or Breastfed for at Least the First 3 Months After Which Formula With or Without AA+DHA May Have Been Fed as a Supplement or Weaning Formula

	Formula Groups			Breastfed Groups	
	Control	AA+DHA (Egg-DTG)	AA+DHA (Fish/Fungal)	Control	AA+DHA (Egg-DTG)
Red blood cell phosphatidylethanolamine					
AA (20:4n-6)†‡					
4 mo	23.3 ± 2.1	25.4 ± 1.8	25.9 ± 2.1	26.7 ± 3.3	27.5 ± 2.3
12 mo	23.2 ± 1.9	25.0 ± 2.9	25.7 ± 2.4	25.1 ± 2.6	25.1 ± 2.7
Significance*	a	b	b	**NS**	
DHA (22:6n-3)†‡					
4 mo	4.3 ± 0.7	6.5 ± 1.1	7.0 ± 0.8	6.9 ± 1.6	6.7 ± 1.2
12 mo	3.2 ± 0.6	6.3 ± 1.2	6.6 ± 0.9	4.3 ± 1.4	5.6 ± 1.2
Significance	a	b	b	**NS**	
Red blood cell phosphatidylcholine					
AA (20:4n-6)†‡					
4 mo	5.0 ± 0.9	7.8 ± 1.0	8.0 ± 1.0	7.8 ± 1.9	8.3 ± 1.3
12 mo	5.1 ± 1.3	7.1 ± 1.4	7.6 ± 1.9	6.2 ± 1.5	6.7 ± 1.6
Significance*	a	b	b	**NS**	
DHA (22:6n-3)†‡					
4 mo	0.9 ± 0.2	1.8 ± 0.4	1.9 ± 0.3	1.8 ± 0.7	1.7 ± 0.4
12 mo	0.8 ± 0.3	1.7 ± 0.5	1.9 ± 0.5	1.1 ± 0.5	1.5 ± 0.5
Significance*	a	b	b	d	e

NS indicates not significantly different.
Values are mean ± SD. Sample sizes (4, 12 months) for the control, AA+DHA (egg-DTG), and AA+DHA (fish/fungal) formula groups were (32, 22), (33, 26), and (30, 32), respectively, and for the BF/control and BF/AA+DHA groups were (41, 31) and (40, 38), respectively.
* Statistically significant differences within each cohort by repeated measures analysis ($P < .01$) are shown by letter notation. Unlike letter notations for AA and DHA within each lipid class indicate significant differences within each cohort; Bonferonni adjusted P values for pairwise comparisons: a, b ($P \leq .0001$); d, e ($P \leq .005$). Post hoc analyses of the breastfed and corresponding formula groups found lower 20:4n-6 and 22:6n-3 in both RBC-PC and -PE from infants in the formula control group than in the AA+DHA (egg-DTG), BF/control, and BF/AA+DHA groups; $P = .001$. Additionally, infants in the BF/control group had lower RBC-PE 22:6n-3 and RBC-PC 22:6n-3 than those in the formula AA+DHA (egg-DTG) group.

Temperament

No differences emerged among the groups for 5 of the 6 dimensions of the Infant Behavior Questionnaire (Table 4). The smiling and laughter score for the control formula group was slightly but statistically significantly higher than for the AA+DHA (Egg-DTG) formula group. No differences emerged on any score between the BF/control and the BF/AA+DHA groups. The percentages of infants with Behavior Rating Scale facet scores (motor quality, orientation/engagement, emotional regulation) on the Bayley Scales at or below the lowest 10th percentile of the reference population did not differ among any groups in relation to AA+DHA supplementation (data not shown). No differences emerged between the BF and corresponding formula groups on the dimensions of Infant Behavior Questionnaire or on the facet scores of the Bayley Scales.

DISCUSSION

This is the largest randomized, prospective, longitudinal, and multivariate study to compare AA+DHA-supplemented formulas with an unsupplemented control formula fed to term infants for the first year after birth. Infants in all groups developed normally on multiple indices of development over the first 14 months after birth. AA+DHA supplementation predictably increased the levels of these fatty acids in plasma and red cells, but multiple measures of growth, visual acuity, information processing, general development, language, and temperament assessed using masked clinical tests and by parent report instruments through 14 months of age were not different among infants who were fed AA+DHA-supplemented and control formulas. The variance in the visual and developmental tests was not increased with multiple testers at multiple sites, evidence that the sensitivity of the tests was not compromised in this multicenter trial. The variances were those expected[36,39,40] with the standard deviations for the visual acuity and Bayley Scales assessments similar to[10,13,16,26–28] or less than[15,17] those reported in similar single-center studies. The comparisons in this trial were adequately powered, and the overall patterns of results were the same when covariates with high potential to influence developmental outcomes were included in the statistical models.

The visual and neurodevelopmental results of the present study are consistent with those of a previous study for which the control formula was the same as in this study except that it did not contain added nucleotides.[11,12] The levels of AA and DHA in milk from women in the present study were also similar to those previously reported by many,[10–12,31–32] but not all,[13,16] contemporaneous studies in the United States including samples from Portland, Oregon[31,32] where DHA levels would be expected to be higher.[49] Furthermore, the demographics of the sample studied here (Table 2) were generally comparable to the

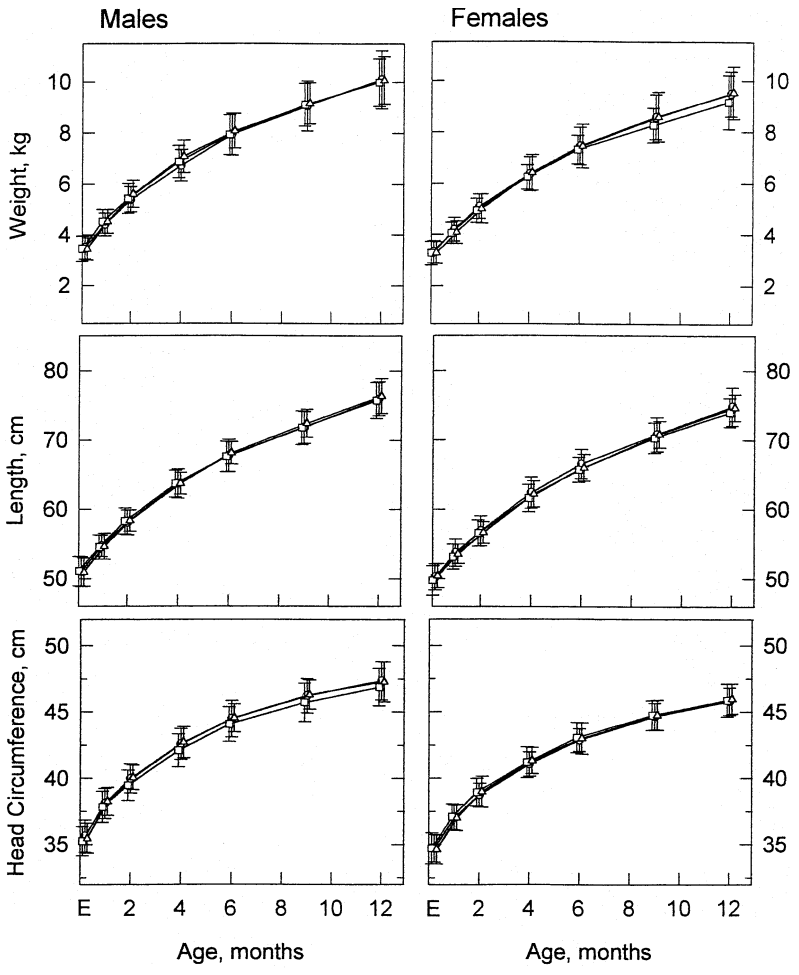

Fig 1. Weight, length, and head circumference in healthy term infants fed formulas with or without AA+DHA from enrollment (E; median, 2 days of age) to 12 months of age. A) Males. B) Females. ○, control formula; □, AA+DHA (egg-DTG); △, AA+DHA (fish/fungal). Values are mean ± SD. No differences among groups for overall growth by repeated-measures analyses were found.

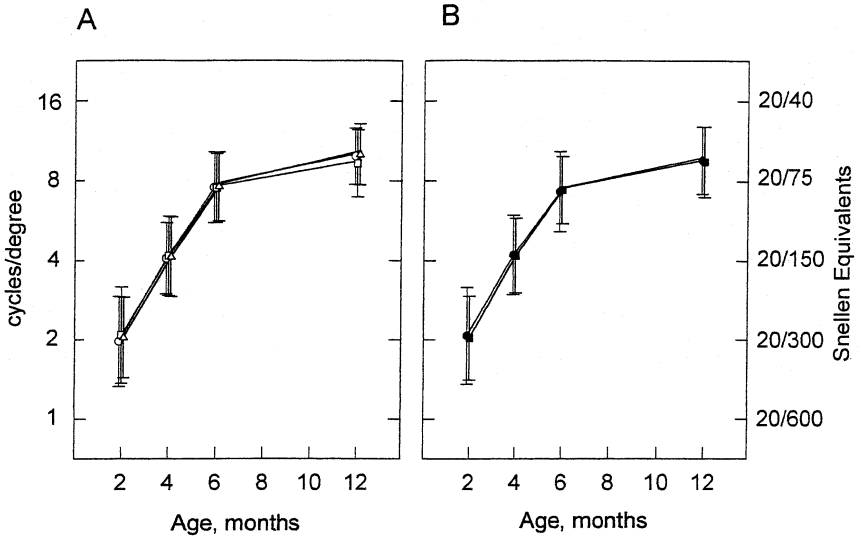

Fig 2. Visual acuity measured by the acuity card procedure for infants fed formulas with or without AA+DHA or BF for at least the first 3 months after which formula with or without AA+DHA may have been fed as a supplement or weaning formula. A) Formula groups: ○, control formula; □, AA+DHA (egg-DTG) supplemented formula. △, AA+DHA (fish/fungal) supplemented formula. B) BF groups: ●, BF/control formula; ■, BF/AA+DHA (egg-DTG) supplemented formula. Data are shown on the left axis as mean (cycles/degree; cy/deg) ± SD (octaves). No differences in visual acuity among groups by repeated-measures analysis were found.

US population,[42] thus allowing us to generalize the results to healthy term infants in the US.

Published studies in which formulas containing sources of DHA or both AA and DHA were fed to term infants have reported mixed outcomes in terms of the potential advantages of supplementation.[8–17] Several explanations for this variance are possible, including differences in the amount of the α-linolenic acid (precursor to DHA), the source or amount of the AA- and/or DHA-enriched ingredient (eg, fish oil, egg lipid, algal oil, fungal oil), other differences in formula composition, the outcomes studied, the testing procedures used, the number of months of formula feeding, and/or the number of infants studied. Additionally, the influence of genetic and specific socioenvironmental factors on developmental measures may be greater than previously recognized.[50,51] This lack of consistency in the extant literature to-

TABLE 4. Development, Cognition, Vocabulary, and Temperament in Infants Fed Formulas With or Without AA+DHA or Breastfed for at Least the First 3 Months After Which Formula With or Without AA+DHA May Have Been Fed as a Supplement or Weaning Formula

	Formula Groups				Breastfed Groups		
	Control	AA+DHA (Egg-DTG)	AA+DHA (Fish/Fungal)	F(df)	Control	AA+DHA (Egg-DTG)	t(df)
Fagan Test of Infant Intelligence							
n (6, 9 mo)	(34, 32)	(43, 42)	(36, 37)		(47, 44)	(48, 45)	
Novelty Preference, %				0.16 (2,117)			0.06 (99)
6 mo	59.0 ± 6.1	58.2 ± 6.5	59.7 ± 6.1		58.6 ± 6.0	59.5 ± 6.2	
9 mo	57.1 ± 5.3	58.1 ± 7.4	57.4 ± 5.9		57.7 ± 5.0	57.1 ± 6.6	
Look Duration During Familiarization, s				0.08 (2,118)			0.00 (99)
6 mo	1.96 ± 0.68	2.04 ± 0.95	1.91 ± 0.62		2.15 ± 0.84	1.89 ± 0.65	
9 mo	1.51 ± 0.45	1.48 ± 0.46	1.46 ± 0.43		1.45 ± 0.33	1.59 ± 0.52	
Look Duration During Testing, s				0.89 (2,118)			0.18 (99)
6 mo	1.60 ± 0.58	1.62 ± 0.49	1.72 ± 0.61		1.87 ± 0.62	1.66 ± 0.64	
9 mo	1.17 ± 0.28	1.22 ± 0.32	1.05 ± 0.28		1.16 ± 0.27	1.22 ± 0.38	
Bayley Scales of Infant Development							
n (6, 12 mo)	(49, 48)	(62, 60)	(55, 57)		(65, 61)	(69, 65)	
Psychomotor Development Index				0.98 (2,166)			0.00 (130)
6 mo	99.1 ± 12.3	98.5 ± 11.1	97.1 ± 11.3		100.2 ± 10.2	100.2 ± 10.5	
12 mo	94.6 ± 12.5	96.0 ± 13.8	91.9 ± 12.7		96.1 ± 11.4	97.1 ± 12.9	
Mental Development Index				0.66 (2,166)			1.34 (130)
6 mo	100.4 ± 5.0	99.5 ± 6.6	99.8 ± 5.6		101.1 ± 5.3	100.4 ± 5.4	
12 mo	97.8 ± 8.3	95.7 ± 10.0	97.8 ± 8.5		101.3 ± 7.8	98.6 ± 9.7	
MacArthur Communicative Development Inventories							
n (9, 14 mo)	(47, 39)	(58, 49)	(58, 51)		(59, 53)	(63, 59)	
Vocabulary Comprehension				0.14 (2,161)			0.15 (121)
9 mo	101 ± 17	103 ± 19	98 ± 17		99 ± 16	98 ± 21	
14 mo	100 ± 11	100 ± 13	103 ± 17		103 ± 15	101 ± 14	
Vocabulary Expression*				4.23 (2,133)			0.31 (107)
14 mo	99 ± 12[a,b]	96 ± 18[a]	104 ± 13[b]		98 ± 15	96 ± 19	
Infant Behavior Questionnaire†							
n (6, 12 mo)	(50, 46)	(63, 59)	(59, 56)		(65, 61)	(70, 68)	
Activity level				0.28 (2,166)			1.83 (130)
6 mo	4.39 ± 0.85	4.41 ± 0.72	4.28 ± 0.84		4.46 ± 0.94	4.24 ± 0.82	
12 mo	4.40 ± 0.89	4.51 ± 0.88	4.56 ± 0.82		4.44 ± 0.94	4.30 ± 0.81	
Distress to novel stimuli				0.79 (2,166)			1.63 (130)
6 mo	2.55 ± 0.85	2.60 ± 0.81	2.57 ± 0.85		2.52 ± 0.76	2.40 ± 0.78	
12 mo	2.84 ± 0.72	3.09 ± 0.78	2.88 ± 0.73		3.04 ± 0.79	2.87 ± 0.69	
Distress to limitations				0.59 (2,166)			1.33 (130)
6 mo	2.89 ± 0.73	3.13 ± 0.74	3.05 ± 0.73		3.21 ± 0.86	3.18 ± 0.76	
12 mo	3.49 ± 0.77	3.50 ± 0.72	3.58 ± 0.78		3.71 ± 0.87	3.49 ± 0.74	
Soothability				0.69 (2,165)			0.00 (130)
6 mo	5.50 ± 0.91	5.41 ± 0.84	5.20 ± 0.81		5.23 ± 0.81	5.29 ± 0.64	
12 mo	5.27 ± 0.90	5.15 ± 0.78	5.25 ± 0.90		5.34 ± 0.86	5.24 ± 0.88	
Smiling and laughter‡	a	b	a,b	3.06 (2,166)			0.01 (130)
6 mo	5.58 ± 0.73	5.39 ± 0.79	5.40 ± 0.88		5.45 ± 0.78	5.39 ± 0.79	
12 mo	5.66 ± 0.60	5.29 ± 0.71	5.44 ± 0.79		5.35 ± 0.73	5.37 ± 0.73	
Duration of orienting				0.36 (2,166)			0.37 (130)
6 mo	4.29 ± 1.22	4.13 ± 1.17	4.32 ± 1.00		4.13 ± 1.08	4.23 ± 1.01	
12 mo	3.70 ± 1.03	3.58 ± 1.06	3.62 ± 1.14		3.45 ± 1.02	3.59 ± 0.87	

Values are mean ± SD. *n* = numbers of participants at the designated study visits. Unless otherwise noted, no significant differences were found within the formula-fed or BF groups or between the BF and corresponding formula groups.

* Unlike letter notations within the formula-fed groups indicate significantly different Bonferonni adjusted pairwise comparisons (a,b, $P < .05$).

† A 7-point scale was used; 1 = never, 2 = very rarely, 3 = less than half the time, 4 = about half the time, 5 = more than half the time, 6 = almost always, 7 = always. Comparisons between the BF and corresponding formula groups by repeated-measures analysis found no significant differences with or without adjustment for covariates.

‡ Values were significantly different by repeated-measures analysis with or without adjustments for covariates for the formula control group versus the AA+DHA (Egg-DTG) group, $P = .05$.

gether with the comprehensiveness of the present report casts doubt on any certain advantage of adding DHA and AA to infant formula.

The fact that no consistent differences emerged for any of several diverse measures of infant development and functioning between infants fed the supplemented formulas also suggests that differences in the triglyceride fatty acid distribution between fish and fungal compared with egg-DTG are of little or no consequence, at least for the outcomes studied.

The absence of significant and/or consistent effects of the AA+DHA formulas on multiple measures of general development, including growth, visual acuity, information processing, language, and temperament over the first 14 months after birth, together with the fact that all assessments, test re-

sults, and variances fell within normal ranges, despite higher AA and twofold increases in red blood cell levels of DHA, point to the conclusion that there would be no demonstrable advantage to infant development from the widespread addition of AA+DHA to infant formula. This conclusion is further supported by the absence of advantages to breastfeeding on the visual and developmental outcomes tested despite the expected differences in family demographics and red blood cell AA and DHA levels. It may be possible that differences (advantages or disadvantages) of AA+DHA supplementation do not appear until after the first year, that they may be present in domains of development not measured here, that they only appear in more differentiated and subtle assessments, or that they only become apparent in direct response to cognitive or social stressors. However, at the average levels of AA and DHA in human milk reported in the United States and for common standardized and robust developmental measures, dietary supplementation with AA+DHA seems to pose no demonstrable benefits for infant development in a study population similar to the overall US population.

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TRAINED AND SOCIALIZED TO ACT

Occasionally I read in articles by medical professionals that their patients fear uncertainty. No doubt true at times, and surely part of being human—and unwell. But assertions about patients' fear of uncertainty are often used to justify the overprovision of treatments. Less occasionally, I read that clinicians also fear uncertainty and that they are trained and socialized to act at all costs.

Hill S. From our coordinating editor, *Cochrane Consumers and Communicating Review Group Newsletter,* January 2001

Submitted by Student

Growth and Development in Term Infants Fed Long-Chain Polyunsaturated Fatty Acids: A Double-Masked, Randomized, Parallel, Prospective, Multivariate Study

Nancy Auestad, Robin Halter, Robert T. Hall, Mark Blatter, Margaret L. Bogle, Wesley Burks, Julie R. Erickson, Kathleen M. Fitzgerald, Velma Dobson, Sheila M. Innis, Lynn T. Singer, Michael B. Montalto, Joan R. Jacobs, Wenzi Qiu and Marc H. Bornstein

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