First Year Growth of Preterm Infants Fed Standard Compared to Marine Oil n-3 Supplemented Formula[1]

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Very low birth weight (VLBW) infants (748–1390 g, n = 65) were randomly assigned to receive control or marine oil-supplemented formula when they achieved intakes >454 kJ (110 kcal)/kg/d of a formula designed for VLBW infants. Study formulas with or without marine oil were provided until 79 wk of postconceptional age (PCA), first in a formula designed for preterm infants followed by a formula designed for term infants. Infants were studied at regular intervals through 92 wk PCA. Weight, length, and head circumference were determined by standardized prodedures and normalized to the National Center for Health Statistics figures for growth of infants born at term of the same age and gender. Mean normalized weight, weight-to-length, and head circumference were greatest at 48 wk and decreased thereafter. The decline in normalized weight was greater in infants fed the marine oil-supplemented formula. Beginning at 40 wk, marine oil-supplemented infants compared to controls had significantly poorer Z-scores for weight, length and head circumference. In addition, birth order (negatively) and maternal height (positively) influenced weight and length achievement in infancy as shown previously in infants born at term.
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The purpose of this study was to compare growth in preterm infants who were randomly assigned to receive either commercially available formulas or experimental formulas (also prepared commercially) which included a low level of marine oil. The marine oil was added experimentally to test the hypothesis that membrane phospholipid docosahexaenoic acid (DHA, 22:6n-3) could be maintained in a physiological range (1,2) and the development of visual acuity enhanced (3) compared to controls. The experimental formulas provided 0.2% of total fatty acids as DHA, the amount reported in milk of American women delivering prematurely (1,4). The marine oil added to the experimental formulas also provided 0.3% of total fatty acids as eicosapentaenoic acid (EPA, 20:5n-3). This EPA concentration is higher than generally found in human milk (1,4) without regular fish (5) or fish oil (6) consumption. Together, DHA and EPA provided 0.5% of total fatty acids (approximately 0.25% of dietary energy) in the experimental formulas.

Two studies in rodents had shown that marine oil reduced weight gain during periods of rapid growth and development (7,8). In both of these studies, marine oil provided a much greater proportion of total energy than in the present infant study. On the other hand, the rodent studies were of only 2 to 3 wk duration whereas preterm infants were fed the marine oil-supplemented formula for many months. Consequently, we monitored growth in these infants to assure that growth was not adversely affected by the low levels of marine oil included in the experimental formulas. The results of this study show that low levels of marine oil supplementation reduced growth in very low birth weight (VLBW) preterm infants compared to controls beginning approximately 8 wk after feeding.

METHODS

Selection of patients. Infants selected for this study were admitted to the Newborn Center at the University of Tennessee, Memphis, TN. Although infants weighed between 748 and 1390 g at birth, they had no risk factors for poor growth other than prematurity, *i.e.,* they were not severely growth retarded *in utero* (weight less than the 5th percentile for their gestational age), and did not require long-term mechanical ventilation or gastrointestinal surgery after birth. Other exclusion criteria (intraventricular/periventricular hemorrhage > grade 2, retinopathy of prematurity > stage 2, history of maternal cocaine use) were designed to eliminate risk factors for cognitive and visual development. Infants developing problems after enrollment were replaced with another infant assigned to the same formula.

Study design. The study was designed to test the effects of marine oil-supplementation on biochemistry, visual acuity, cognition and growth in the first year of life. This paper deals with the effects on growth. Infants were eligible for enrollment when they had reached intakes of a nutrient enriched formula designed for preterm infants >454 kJ (110 kcal)/kg/d. Parental consent was obtained according to an Institutional Review Board-approved protocol, and infants were randomized to receive either the standard or the marine oil-supplemented formula. Infants were assigned a postconceptional age (PCA) in weeks by averaging the obstetric assessments of age (dates and ultrasound). If there was a discrepancy of >2 wk between these and the pediatric assessment of PCA based on physical and neurological maturity (9), all assessments were averaged.

Infants were considered study completers if they remained in the study through 57 wk PCA. A total of 79 patients were enrolled, ten to replace infants who did not complete the study through 57 wk for a variety of reasons. Four additional infants were excluded for receiving enteral nutrition other than study formulas through 57 wk. The profile of the 65 infants who completed the study is shown in Table 1. All 65 infants remained in the study through 68 wk. At 79 wk, 31 control and supplemented infants returned for followup. At 92 wk, 28 infants in each group returned for followup.

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Abbreviations: AGA, appropriate-for-gestational age; ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PCA, postconceptional age; SGA, small for gestational age; VLBW, very low birth weight.

TABLE 1

Neonatal and Perinatal Characteristics of the Study Population of Preterm Infants by Formula[a,b]

	Control (n = 34)	Marine supplemented (n = 31)
Birth weight (g)	1074 ± 193 (740–1398)	1147 ± 154 (833–1350)
Gestational age (wk)	29 ± 2 (26–32)	29 ± 2 (26–32)
Enrollment weight (g)	1304 ± 183 (1072–1730)	1330 ± 129 (1040–1652)
Enrollment age (d)	25 ± 10 (10–44)	22 ± 8 (9–40)
Log ventilator (h)	1.10 (0–2.775)	0.775 (0–2.547)
Log oxygen (h)	1.76 (0–2.919)	1.66 (0.48–3.196)
First formula fed (h)	78 ± 55 (32–310)	79 ± 54 (27–272)
I.V.[c] nutrition (d)	18 ± 9 (7–41)	18 ± 8 (8–38)
Size at birth (AGA/SGA)[d]	31/3	31/2
BPD[e] (no/yes)	33/1	30/2
Birth order (no.)	2.5 ± 1.4 (1–6)	2.3 ± 1.1 (1–6)
Maternal height (cm)	163.1 ± 7.7 (149–180)	164.8 ± 7.9 (152–184)

[a]Mean ± SD (range).
[b]Significant differences between dietary groups did not occur for any descriptor.
[c]Intravenous.
[d]Appropriate for gestational age (AGA or small for gestational age [SGA]).
[e]Bronchopulmonary dysplasia.

TABLE 2

Fatty Acid Composition[a] of Standard (control) and Experimental (marine oil-supplemented) Preterm (PT) and Term (T) Formulas

	Preterm formulas		Term formula	
Fatty acid	Control-PT	Experimental-PT	Control-T	Experimental-T
	g/100 g total fatty acid			
6:0	0.3	0.3	0.1	0.1
8:0	28.8	28.8	2.3	2.2
10:0	14.5	14.2	2.0	2.0
12:0	10.0	9.7	17.2	16.9
14:0	4.3	4.2	7.2	7.2
16:0	6.3	6.2	9.9	10.0
16:1	0.2	0.3	n.d.[b]	n.d.
17:0	0.1	0.1	n.d.	n.d.
18:0	3.1	3.0	4.7	4.6
18:1	9.9	9.8	17.1	17.0
18:2n-6	19.1	18.7	33.2	32.6
20:0	0.3	0.3	0.6	0.6
18:3n-3	3.0	3.1	4.8	4.9
22:0	0.2	0.2	0.3	0.3
20:5n-3	n.d.	0.3	n.d.	0.3
24:0	0.1	0.1	0.1	0.1
22:6n-3	n.d.	0.2	n.d.	0.2
C_{18} n-6/n-3	6.4	6.0	6.9	6.6
$\geq C_{20}$ n-3	0	0.5	0	0.5

[a]Provided by Ross Laboratories, Columbus, OH. [b]Not detected.

From enrollment until discharge (1800 g) infants were fed a preterm formula with or without marine oil supplementation. From discharge until 79 wk, infants received a formula designed for term infants with or without marine oil supplementation according to their original assignment. The fatty acid composition of control and experimental preterm and term formulas is shown in Table 2. Formula A and A-T were commercially available; Formula B and B-T were experimental.

Infants were studied at the following ages adjusted for early delivery: term (38 ± 2 wk PCA, mean ± SD), 2 mon (48 ± 2 wk), 4 mon (57 ± 2 wk), 6.5 mon (68 ± 2 wk), 9 mon (79 ± 2 wk) and 12 mon (93 ± 2 wk). Nutrition counseling at each visit emphasized methods for assuring that infants were fed as much formula as desired without overfeeding or underfeeding. A history of dietary intake was obtained. All except one infant consumed at least 0.72 L of formula per day through 79 wk PCA.

Reported mean energy intakes from formula (kcal/day; kcal/kg/d) were not affected by dietary assignment or gender at 48 and 57 wk PCA. At 68 wk PCA, infants consuming the marine oil-supplemented formula had significantly higher energy intakes from formula (kcal/day; kcal/kg/d) compared to infants fed standard formula (Table 3).

Measurement of growth. Infants were weighed undressed on a calibrated infant balance. Length was determined in the supine position to the nearest 0.1 cm by two individuals using an infant measuring board (Jim's Instrument Manufacturing, Inc., Coralville, IA). Head circumference was measured at the largest occipitofrontal circumference with a non-stretchable paper tape. Individual size determinations were made at each age and group data expressed as mean ± SD for a given PCA with the exception of 40 wk PCA which was interpolated from sizes at the 38 and 48 wk measurements. The growth of individual preterm infants was also normalized to that of term infants of the same gender and precise age (10) using data from the National Center for Health Statistics (Hyattsville, MD) (11) to generate percentiles for norms. The growth index generated was an approximate Z-score which indicated the SD from the fiftieth percentile (+ or −).

Statistical methods. The effects of formula on normalized first year growth were evaluated by a repeated measures analysis of variance (ANOVA) for the effects of time and marine oil supplementation (Fig. 1). A similar analysis was done for each diet-gender group to compare absolute measures of size, but this data should be interpreted with caution since the numbers of infants in each diet-gender group are not adequate to eliminate a Type II error. Preplanned comparisons between least-squares means were made using Fisher's Least Significant Difference (12). Stepwise multiple linear regression was used to determine the independent factors which affect normalized growth at each age. In addition to marine oil-supplementation (shown here to affect growth), maternal height and birth order (shown previously to affect growth in term infants, 13) were included. All statistical analyses used software from SAS Institute Inc. (Cary, NC) (14) and the mainframe computer at University of Tennessee.

RESULTS

Population of infants studied. Thirty-four control and 31 marine oil-supplemented infants completed the study. The groups were statistically similar with regard to all descriptors (Table 1) and were not at risk for poor growth. Infants with chronic lung disease (bronchopulmonary dysplasia, BPD) are known to have poorer growth (15–17). Although three of the final 65 infants were diagnosed with BPD, all of these infants were weaned from oxygen before discharge and had growth indistinguishable from their dietary group. Intrauterine growth retarded infants are also known to have poorer growth achievement in the first year of life (18). Most of the infants who completed the study (= 60) were appropriately grown (>10th percentile for gestational age), and the remaining five infants were mildly growth retarded at birth (*i.e.*, between the 5th and 10th percentile.

Weight achievement. At enrollment, all diet-gender groups had the same absolute weight (1.3 ± 0.13 to 0.18 kg, mean ± SD) (Table 4). Likewise, at the term visit (38 ± 2 wk PCA), diet-gender differences were not seen: male control 2.25 ± 0.21 kg; male marine oil-supplemented, 2.44 ± 0.41 kg; female control, 2.42 ± 0.34 kg; female marine oil-supplemented, 2.28 ± 0.20 kg (mean ± SD). However, by 40 wk, and continuing throughout infancy, infants supplemented with marine oil had lower normalized weight than those fed standard formula by Fisher's Least Squares Difference (Fig. 1A). The Z-scores depicted in Figure 1A are the most valid measure of comparison as they are adjusted for gender differences, making the number of infants per group large enough to avoid Type II errors. In addition, the Z-score is calculated for the precise age of each infant at the time of growth assessment. Although absolute and normalized weight by age, diet and gender are included in Table 4 as a basis for comparison with the data of others, they do not meet these criteria and a null hypothesis is not necessarily correct.

Length achievement. Normalized lengths were significantly lower in marine oil-supplemented infants compared to controls by 40 wk PCA ($P < 0.05$) and remained lower ($P < 0.01$) for the remainder of infancy (Fig. 1B). As with weight, the only truly valid comparison between formulas is seen in Figure 1B. The mean absolute and normalized values for length by formula, time and gender are shown in Table 5 for comparison with the data of others. Infants returning for their term visit (38 ± 2 wk PCA) were 44.1 ± 1.3, 45.6 ± 1.8, 45.4 ± 1.8 and 44.5 ± 1.0 cm long (mean ± SD; male control, male marine, female control and female marine, respectively).

TABLE 3

Mean Reported Energy Intake from Formula of Infants Fed Standard (control) and Marine Oil-Supplemented Formula at 48, 57 and 68 Wk Postconceptional Age

		48 Wk		57 Wk		68 Wk	
Formula	Gender	kcal	kcal/kg/d	kcal	kcal/kg/d	kcal	kcal/kg/d
Control	male	718	150	759	112	627	80
	female	599	129	649	108	650	90
Marine	male	599	126	712	113	764	104
	female	592	138	692	127	712	108
ANOVA[a]	formula	n.s.[b]	n.s.	n.s.	n.s.	$P < 0.04$	$P < 0.01$
	gender	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

[a]Analysis of variance. [b]Not significant ($P > 0.05$).

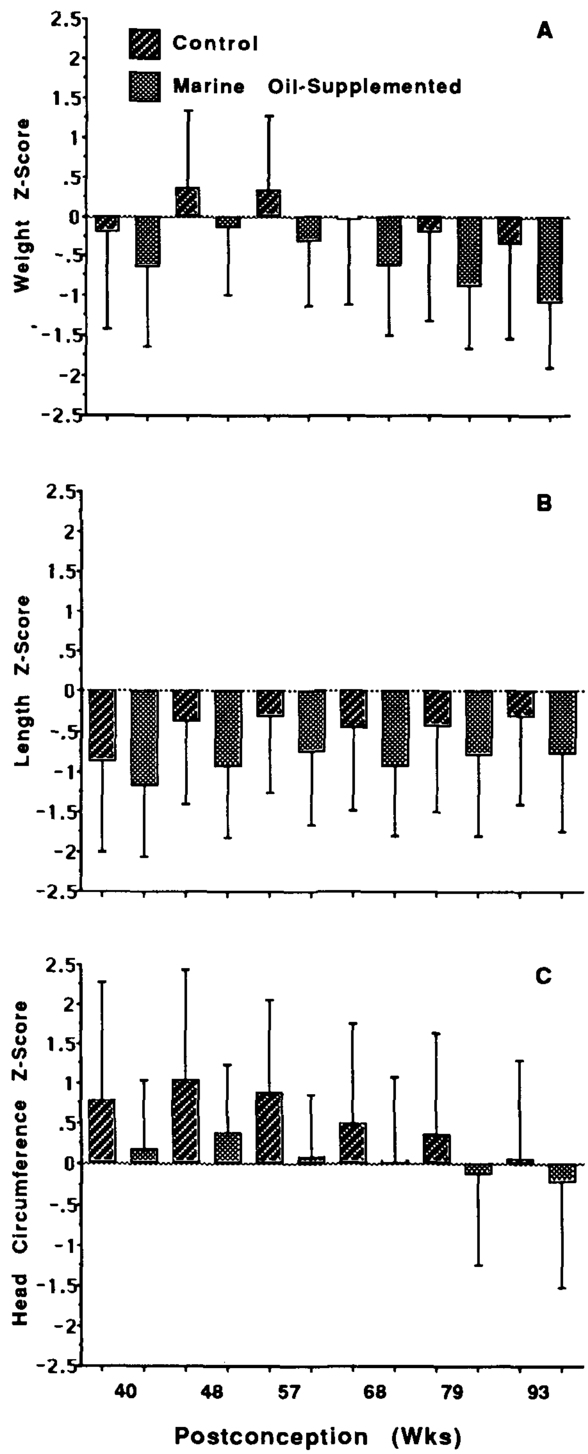

FIG. 1. Normalized growth of control and marine oil-supplemented infants at regular intervals from 40 to 93 wk postconception (mean ± SD). Individual comparisons were made between formulas using Fisher's Least Squares Difference (12). Control infants fed commercially available formulas were larger than marine oil-supplemented infants at all ages beginning at 40 wk ($P < 0.01$). The only exceptions were length at 40 wk and head circumference at 93 wk which were significant at $P < 0.05$. Analysis of variance of Z-score by formula and time: A. Weight: Formula, $P < 0.04$; time, $P < 0.001$; formula by time, n.s.; B. Length: Formula, $P < 0.08$; time, $P < 0.001$; formula by time, n.s.; C. Head circumference: Formula, $P < 0.056$; time, $P < 0.001$; formula by time, n.s.

Weight-to-length ratio. Independent of formula, the normalized weight-to-length ratio decreased significantly over time ($P < 0.0001$, Table 6). Marine oil supplementation did not affect weight-to-length ratios by ANOVA, but individual means for marine oil-supplemented infants at 79 and 93 wk PCA were lower than in the controls ($P < 0.01$). These data are not shown.

Head circumference. Head circumference Z-scores were significantly influenced by time and marine oil supplementation. Z-scores declined over time and were significantly lower in infants fed the experimental formulas compared to the standard formulas at all ages (Fig. 1C). Head circumference was the only measurement in which gender differences were seen after data were normalized to the size of term infants of the same age and gender: males had a normalized head circumference smaller than that of females at 68, 79 and 93 wk PCA (ANOVA by gender and formula, $P < 0.01$). Absolute and normalized values for head circumference by formula, time and gender are given in Table 7. As with absolute measurements of weight and length, these values are presented primarily for purposes of comparison with the data of others.

Factors affecting growth achievement. Marine oil supplementation negatively affected first year growth in these preterm infants. Previously, maternal height and birth order have been shown to affect first year growth of term infants (13). The effects of these independent variables (maternal height, birth order and marine oil supplementation) on first year growth were studied by stepwise multiple regression. Length was positively associated with maternal height, but negatively associated with marine oil supplementation; weight was negatively associated with both birth order and marine oil supplementation (Table 8).

DISCUSSION

Studies of VLBW infants cared for in neonatal intensive care centers in the late 1980s have repeatedly shown that growth in the first year of life, even when corrected for prematurity, is not equivalent to that of infants born at term. Karniski *et al.* (18) demonstrated that growth of appropriate-for-gestational age (AGA) VLBW infants appeared to be catching-up to that of infants born at term when expressed by chronological age, but not when normalized for age and gender. Georgieff *et al.* (19) also showed that VLBW infants (mean birth weight 1143 g) did not reach term-equivalent growth by 92 wk PCA, and an eight-site collaborative study of <1250 g birthweight infants concluded that normalized growth did not catch up by the 12-mon examination (20).

Infants enrolled in our study were a select group of VLBW infants without prolonged ventilator requirements or other serious illness which would limit energy intake or growth, and without evidence of chronic illness after discharge. Their parents received counseling about appropriate feeding at regular intervals during their first year at home to insure that intakes of formula were voluntary and unlimited. Growth achievement in these infants was excellent compared to published data of first year growth, *i.e.*, despite their very low birth weight (mean 1074 g), they achieved weights, lengths and head circumferences in the first year of life equivalent to much larger male and female infants (mean birth weight 1690 g)

TABLE 4

Absolute (kg) and Normalized (Z-score) Weight Achievement[a] of Very Low Birth Weight Infants in Year One by Formula and Gender

Postconceptional age (wk)	Control Male (n = 11) kg	Control Male (n = 11) Z-score	Control Female (n = 23) kg	Control Female (n = 23) Z-score	Marine supplemented Male (n = 13) kg	Marine supplemented Male (n = 13) Z-score	Marine supplemented Female (n = 18) kg	Marine supplemented Female (n = 18) Z-score
33 ± 2	1.31	—	1.29	—	1.33	—	1.33	—
40	3.03	−0.61	3.13	−0.13	2.87	−0.60	2.94	−0.68[c]
48 ± 2	4.65	−0.07	4.63	0.51	4.84	−0.05	4.23[c]	−0.23[c]
57 ± 2	6.43	−0.10	6.12	0.41	6.40	−0.18	5.63[c]	−0.42[c]
68 ± 2	7.91	−0.32	7.40	−0.03	7.58	−0.46	6.77[c]	−0.73[c]
79 ± 2	9.06	−0.37	8.24	−0.24	8.21[c]	−0.84[b]	7.70[c]	−0.84[c]
93 ± 2	10.08	−0.33	9.13	−0.50	8.78[c]	−1.14[c]	8.61[c]	−0.90[c]
ANOVA[d]	Male (kg)		Male (Z-score)		Female (kg)		Female (Z-score)	
Formula	n.s.[e]		n.s.		$P < 0.02$		$P < 0.02$	
Time	$P < 0.0001$		$P < 0.0001$		$P < 0.0001$		$P < 0.0001$	
F by T	$P < 0.0001$		n.s.		n.s.		n.s.	

[a]Least-squares means for gender-formula subgroups. [b]$P < 0.05$ and [c]$P < 0.01$ compared to controls of the same gender and time by Fisher's Least Significant Difference. [d]Analysis of variance. [e]Not significant ($P < 0.05$).

TABLE 5

Absolute (cm) and Normalized (Z-score) Length Achievement[a] of Very Low Birth Weight Infants in Year One by Formula and Gender

Postconceptional age (wk)	Control Male (n = 11) cm	Control Male (n = 11) Z-score	Control Female (n = 23) cm	Control Female (n = 23) Z-score	Marine supplemented Male (n = 13) cm	Marine supplemented Male (n = 13) Z-score	Marine supplemented Female (n = 18) cm	Marine supplemented Female (n = 18) Z-score
40	47.5	−1.09	48.1	−0.83	47.6	−1.06	47.1[b]	−1.27[c]
48 ± 2	53.7	−0.83	54.6	−0.25	54.8[b]	−0.88	53.0[c]	−0.99[c]
57 ± 2	60.9	−0.70	60.4	−0.21	61.3	−0.72	59.4[b]	−0.79[c]
68 ± 2	66.7	−0.62	65.6	−0.39	65.6[b]	−1.05[b]	64.1[c]	−0.89[c]
79 ± 2	69.9	−0.84	69.4	−0.25	69.4	−0.89	68.2[c]	−0.75[c]
93 ± 2	74.4	−0.59	73.7	−0.28	73.1[b]	−0.96	72.3[c]	−0.63[b]
ANOVA[d]	Male (kg)		Male (Z-score)		Female (kg)		Female (Z-score)	
Formula	n.s.[e]		n.s.		$P < 0.08$		$P < 0.07$	
Time	$P < 0.0001$		n.s.		$P < 0.0001$		$P < 0.0001$	
F by t	$P < 0.02$		n.s.		n.s.		n.s.	

[a]Least-squares means for gender-formula subgroups. [b]$P < 0.05$ and [c]$P < 0.01$ compared to controls of the same gender and time by Fisher's Least Significant Difference. [d]Analysis of variance. [e]Not significant, or with a trend toward significance ($P > 0.10$).

TABLE 6

Normalized (Z-score) Weight-to-Length Ratios[a] of Very Low Birth Weight Infants in Year One by Formula and Gender

Postconceptional age (wk)	Control Male (n = 11) Z-score	Control Female (n = 23) Z-score	Marine supplemented Male (n = 13) Z-score	Marine supplemented Female (n = 18) Z-score
48 ± 2	1.03	0.73	0.85	0.61
57 ± 2	0.80	0.65	0.44	0.25[c]
68 ± 2	0.39	0.37	0.38	−0.03[b]
79 ± 2	0.60	0.07	−0.15[c]	−0.21
93 ± 2	0.46	−0.16	−0.60[c]	−0.48[b]
ANOVA[d]	Male (Z-score)		Female (Z-score)	
Formula	n.s.[e]		n.s.	
Time	$P < 0.0001$		$P < 0.0001$	
F by T	n.s.		n.s.	

[a]Least-squares means for gender-formula subgroups. [b]$P < 0.05$ and [c]$P < 0.01$ compared to controls of the same gender and time by Fisher's Least Significant Difference. [d]Analysis of variance. [e]Not significant ($P > 0.05$).

TABLE 7

Absolute (kg) and Normalized (Z-score) Head (occipitofrontal) Circumference Ratios[a] of Very Low Birth Weight Infants in Year One by Formula and Gender

	Control				Marine supplemented			
	Male (n = 11)		Female (n = 23)		Male (n = 13)		Female (n = 18)	
Postconceptional age (wk)	cm	Z-score	cm	Z-score	cm	Z-score	cm	Z-score
40	35.0	0.05	35.3	1.13	34.7	0.18	35.0	0.20[c]
48 ± 2	38.6	0.33	38.9	1.38	39.2[b]	0.41	37.9[c]	0.39[c]
57 ± 2	41.8	0.06	41.8	1.16	41.8	0.06	40.7[c]	0.12[c]
68 ± 2	44.3	−0.03	43.7	0.76	43.9	−0.06	42.9[c]	0.10[c]
79 ± 2	45.7	−0.09	45.0	0.58	45.1[b]	−0.32	44.3[b]	−0.02[c]
93 ± 2	46.8	−0.26	46.0	−0.25	46.1[b]	−0.55	45.7	0.00

ANOVA[d]	Male (cm)	Male (Z-score)	Female (cm)	Female (Z-score)
Formula	n.s.[e]	n.s.	$P < 0.07$	$P < 0.03$
Time	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
F by T	$P < 0.04$	n.s.	n.s.	$P < 0.01$

[a]Least-squares means for gender-formula subgroups. [b]$P < 0.05$ and [c]$P < 0.01$ compared to controls of the same gender and time by Fisher's Least Significant Difference. [d]Analysis of variance. [e]Not significant or with a trend toward significance ($P > 0.10$).

TABLE 8

Normalized Growth Achievement in the First Year of Life. Multiple Regression Analysis Included Birth Weight (forced),[a] Maternal Height, Birth Order and Marine Oil Supplementation (marine oil)

Dependent variable	Age[b]	Independent variable	F	Probability	Model r^2[c]
Weight	40	marine oil (−)[d]	4.73	0.03	0.13
	48	marine oil (−)	14.13	0.001	
		maternal height (+)	6.19	0.02	0.28
	57	marine oil (−)	15.43	0.001	
		birth order (−)	8.12	0.006	0.33
	68	marine oil (−)	12.88	0.001	
		birth order (−)	7.17	0.01	0.30
	79	marine oil (−)	10.28	0.002	0.17
	93	marine oil (−)	8.84	0.005	
		birth order (−)	4.48	0.04	0.24
Length	40	no variable met the $P < 0.05$ level of significance			
	48	maternal height (+)	9.26	0.004	
		marine oil (−)	11.87	0.001	0.29
	57	maternal height (+)	13.21	0.001	
		marine oil (−)	10.07	0.003	
		birth order (−)	4.73	0.03	0.36
	68	marine oil (−)	10.69	0.002	
		maternal height (+)	7.89	0.007	
		birth order (−)	8.55	0.005	0.35
	79	maternal height (+)	10.16	0.003	
		marine oil (−)	6.70	0.01	0.22
	93	maternal height (+)	13.71	0.001	
		marine oil (−)	7.24	0.01	0.28
Head circumference	40	marine oil (−)	4.15	0.05	0.08
	48	marine oil (−)	6.33	0.02	0.12
	57	marine oil (−)	9.40	0.01	0.16
	68	marine oil (−)	4.13	0.05	0.07
	79	no variable met the $P < 0.05$ level for entry into the model			
	93	no variable met the $P < 0.05$ level for entry into the model			

[a]Birth weight was forced into each analysis, but did not reach significance for any dependent variables.
[b]Postconceptional age (wk).
[c]Proportion of the variance predicted by the significant independent variables.
[d]The sign indicates if the association with height is negative (−) or positive (+).

in an eight-center survey (20). Nevertheless, infants supplemented with marine oil compared to controls had significantly lower Z-scores for weight and length by 40 wk PCA; these lower Z-scores continued throughout the first year of life. The lower normalized growth in marine oil-supplemented infants was not related to lower energy intakes compared to controls (Table 3).

Infants fed both standard and marine oil-supplemented formulas achieved weights closest to standards for infants born at term when they were 48 and 57 wk PCA. After this age, their normalized weights fell consistently to the end of infancy as has been reported by others (18,19). The decline in weight in late infancy was greater in marine oil-supplemented infants compared to those infants fed standard formulas, and appeared to be responsible for the significantly lower weight-to-length ratio seen in the supplemented compared to the control infants at 79 and 93 wk PCA.

The mechanisms by which growth of VLBW infants falls progressively farther behind that of term infants in the last half of infancy is not known. This pattern of growth is more consistent with a response to some extrinsic factor, *e.g.*, the quality and quantity of nutritional intake, than with failure to recover from the insults of the neonatal intensive care period. The mechanism by which such low levels of marine oil supplementation might influence growth in preterm infants is also not known. Marine oil has been reported to slow weight gain in rodents during periods of rapid growth (7,8). Although these rodent studies were of only two to three weeks duration, they provided more dietary energy from EPA and DHA than the 0.25% of energy fed to preterm infants in this study. We recently reported a positive correlation between arachidonic acid status and growth in VLBW infants fed standard formulas (21). Since marine oil supplementation decreased the concentration of plasma arachidonic acid further (2), it is tempting to speculate that a common mechanism related to arachidonic acid status is involved in both the decline in normalized growth of preterm infants in the last half of infancy (18,19) and the greater decline in normalized growth in infants randomized here to receive marine oil-supplemented formula compared to standard formula.

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REFERENCES

1. Carlson, S.E., Rhodes, P.G., and Ferguson, M.G. (1986) *Am. J. Clin. Nutr. 45,* 798–804.
2. Carlson, S.E., Cooke, R.J., Rhodes, P.G., Peeples, J.M., Werkman, S.H., and Tolley, E.A. (1992) *Pediatr. Res. 30,* 404–412.
3. Neuringer, M., Connor, W.E., Van Petten, C., and Barstad, L. (1984) *J. Clin. Invest. 73,* 272–276.
4. Bitman, J., Wood, L., Hamosh, M., Hamosh, P., and Mehta, N.R. (1983) *Am. J. Clin. Nutr. 38,* 300–312.
5. Innis, S.M. (1989) in *Dietary Omega-3 and Omega-6 Fatty Acids: Biological Effects and Nutritional Essentiality,* NATO ASI Series, Series A. Life Sciences (Galli, C., and Simopoulos, A.P., eds.) Vol. 171, pp. 135–146, Plenum Press, New York.
6. Harris, W.S., Connor, W.E., and Lindsey, S. (1984) *Am. J. Clin. Nutr. 40,* 780–785.
7. Cunnane, S.C., McAdoo, K.R., and Horrobin, D.F. (1986) *Br. J. Nutr. 56,* 87–95.
8. Clarke, S.D., Benjamin, L., Bell, L., and Phinney, S.D. (1988) *Am. J. Clin. Nutr. 47,* 828–835.
9. Dubowitz, L., Dubowitz, V., and Goldberg, C. (1970) *J. Pediatr. 77,* 1–10.
10. Dibley, M.J., Goldsby, J.B., Staehling, N.W., and Trowbridge, F.L. (1987) *Am. J. Clin. Nutr. 46,* 5736–5748.
11. Hamill, P.V., Drizd, T.A., Johnson, C.L., Reed, R.B., Roche, A.S., and Moore, W.M. (1979) *Am. J. Clin. Nutr. 32,* 607–629.
12. Sokol, R.R., and Rohlf, F.J. (1981) *Biometry,* 2nd edn., pp. 232–262, W.H. Freeman, New York.
13. Wingerd, J. (1972) *Hum. Biol. 42,* 105–131.
14. SAS Institute, Inc. (1985) *User's Guide: Statistics Version,* 5th edn., p. 956, SAS Institute, Inc., Cary.
15. Markestad, T., and Fitzhardinge, P.M. (1981) *J. Pediatr. 98,* 597–602.
16. Suave, R.S., and Singhal, N. (1985) *Pediatrics 76,* 725–733.
17. Groothuis, J.R., and Rosenberg, A.A. (1987) *Am. J. Dis. Child. 141,* 992–995.
18. Karniski, W., Blair, C., and Vitucci, J.S. (1987) *Am. J. Dis. Child. 141,* 520–526.
19. Georgieff, M.K., Mills, M.M., Zempel, C.E., and Chang, P-N. (1989) *J. Pediatr. 114,* 288–292.
20. Casey, P.H., Kraemer, H.D., Bernbaum, J., Tyson, J.E., Clifford Sells, J., Vogman, M.W., and Bauer, C.R. (1990) *J. Pediatr. 117,* 298–307.
21. Carlson, S.E., Werkman, S.H., Peeples, J.M., Cooke, R.J., Tolley, E.A. and Wilson, W.M., III (1992) in *Essential Fatty Acids and Eicosanoids: Proceedings of the Third International Congress* (Gibson, R.A., and Sinclair, A.J., eds.) American Oil Chemists' Society, Champaign, pp. 192–196.

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