

# Growth to Age 18 Months Following Prenatal Supplementation with Docosahexaenoic Acid Differs by Maternal Gravidity in Mexico<sup>1–4</sup>

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## Abstract

Little is known about the long-term effects of DHA intake during pregnancy. Offspring of primigravid Mexican women who received 400 mg/d DHA from wk 20 of gestation through delivery were heavier and had larger head circumferences at birth than children whose mothers received placebo; no effect was observed in offspring of multigravidae. We have followed these children ( $n = 739$ ; 76% of the birth cohort), measuring length, weight, and head circumference at 1, 3, 6, 9, 12, and 18 mo. At 18 mo, intent-to-treat differences between placebo and DHA, adjusted for maternal height and child sex and age at measurement, were: length,  $-0.21$  cm (95% CI =  $-0.58, 0.15$ ); weight,  $-0.03$  kg (95% CI =  $-0.19, 0.13$ ); and head circumference,  $0.02$  cm (95% CI =  $-0.18, 0.21$ ) (all  $P > 0.05$ ). There was heterogeneity of associations by maternal gravidity for weight ( $P < 0.08$ ), length ( $P < 0.02$ ), and head circumference ( $P < 0.05$ ). Among offspring of primigravid women, length at 18 mo was increased by  $0.72$  cm (95% CI =  $0.11, 1.33$ ) following DHA supplementation, representing  $0.26$  length-for-age Z-score units; among offspring of multigravidae, the estimate was  $-0.13$  cm (95% CI =  $-0.59, 0.32$ ) ( $P > 0.5$ ). Maternal DHA supplementation during the second half of gestation may enhance growth through 18 mo of children born to primigravid women. J. Nutr. 141: 316–320, 2011.

## Introduction

The long-chain PUFA DHA is proposed to be limiting to the growth and development of infants and young children (1). Maternal diets high in fish are associated with increased offspring cognitive development (2). Maternal breast milk DHA concentration has been associated with infant size at 5 mo in Congo and Burkina Faso (3) but not in the Netherlands (4). Intervention studies in which women have been provided fish oil (which contains DHA and EPA) during and after pregnancy have yielded inconsistent findings (5–8), likely due to small sample sizes and heterogeneity in the underlying distribution of long-chain PUFA intakes.

From a programmatic perspective, it is important to determine whether supplementation of the mother during pregnancy alone can provide adequate amounts of DHA, to the fetus via placental transfer and to the infant via breast milk, to permit improved growth and development. It is also critical to determine whether the limiting nutrient is DHA or other

constituents of fish oil are relevant. Here, we report on a large study in which maternal supplementation with algal DHA was provided solely during pregnancy.

## Materials and Methods

**Study setting and design.** We conducted a double-blind, randomized, placebo-controlled trial in Cuernavaca, Mexico. The results reported here constitute 1 of 2 primary outcomes to be ascertained at 18 mo. The study design and the impact of the intervention on offspring size at birth have been reported (9). The study protocol was approved by the Emory University Institutional Review Board and by the Instituto Nacional de Salud Pública Research, Biosafety and Ethics Commissions and all women provided written informed consent for themselves and for their infants.

**Study setting.** Women were recruited at the Mexican Institute of Social Security (IMSS)<sup>8</sup> General Hospital I, a large hospital located in Cuernavaca, Mexico, and 3 small health clinics within the IMSS system in Cuernavaca during routine prenatal care visits between February 2005 and February 2007. Generally, the women who use the hospital are of medium-to-low socioeconomic status and either they and/or their husbands are employed.

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<sup>3</sup> This trial was registered at clinicaltrials.gov as NCT00646360.

<sup>4</sup> Supplemental Figure 1 and Supplemental Table 1 are available with the online posting of this paper at [jn.nutrition.org](http://jn.nutrition.org).

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<sup>8</sup> Abbreviations used: BMIZ, BMI-for-age Z-score; HAZ, height-for-age Z-score; IMSS, Mexican Institute of Social Security; LAZ, length-for-age Z-score; WAZ, weight-for-age Z-score.

**Prenatal supplementation.** Eligible women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery. Women were randomized to receive either 400 mg of algal DHA daily or placebo until delivery. Study participants and members of the study team remained unaware of the treatment scheme throughout the intervention period of the study. The supplements (Martek Biosciences) were in color-coded bottles (2 colors/treatment arm) and were distributed by trained field workers during weekly visits at the participant's homes and/or work place. The DHA capsules contained 200 mg DHA derived from an algal source. The placebo capsules contained olive oil and were similar in appearance and taste to the DHA capsules. Women were instructed to take 2 capsules daily, together, at the same time each day. During each weekly home visit, participants received 14 capsules in a precoded container; the capsules remaining from the prior visit were counted. Supplements were provided for more than 1 wk in cases where the participant planned to travel. Women ceased supplement ingestion at delivery. Of the 1094 women randomized, 1040 started treatment and 973 completed the study; 5 had stillbirths, and 968 delivered 973 live-born infants, 963 singletons, and 5 pairs of twins.

**Compliance with study intervention and change in DHA status.** We calculated compliance as the total number of capsules actually consumed during pregnancy expressed as a percentage of the total number expected to be consumed. The 739 women followed to 18 mo consumed 230 capsules, on average, representing 88.9% compliance in both groups. DHA concentrations in maternal plasma at delivery and cord blood were higher ( $P < 0.05$ ) in the intervention group compared with the control group in a random subsample of study participants (9).

**Maternal and offspring diet.** At randomization, we administered a 110-item FFQ to ascertain maternal diet in the 3 mo prior to randomization, i.e. in early gestation (10). Among women whose children remained in the study through the 18-mo follow-up, intakes of preformed DHA were very low (median intake, 55 mg/d; IQR, 37, 99 mg/d) with no difference between treatment groups. At offspring ages 12 and 18 mo, we administered to the mothers a 70-item FFQ, derived from the instrument used in the Mexican National Nutrition Survey (11), assessing the child's consumption in the previous month. There were no significant differences in reported consumption of any DHA-source foods by offspring between treatment groups at either time point. We did not assess the mothers' diet after delivery.

**Postnatal anthropometry.** Birth weight was measured using a pediatric scale to the nearest 10 g. Birth length and head circumference were measured to the nearest 1 mm using a portable anthropometer with a fixed head piece and a flexible tape, respectively, using standard procedures (9). We obtained weight and length at 1, 3, 6, 9, 12, and 18 mo; head circumference was not obtained at 9 mo. We measured length and head circumference (each to 1 mm) using a calibrated length board and a flexible tape, respectively, and weight (to 10 g) using a pediatric scale (10). All postnatal measurements were obtained by trained study personnel at the study headquarters located at IMSS General Hospital I. We calculated age at measurement from the date of birth and the date of measurement and computed BMI ( $\text{kg}/\text{m}^2$ ). We converted the anthropometric measures to Z-scores using the 2006 WHO reference standards (12).

**Data analysis.** We retained in the analysis the 739 children for whom data on anthropometric measurements at 18 mo were available. All analyses were implemented in SAS version 9.1 (SAS Institute). To identify potential sources of selection bias, we compared the final analytic sample to those infants lost to follow-up on these same baseline characteristics and birth outcomes. For these analyses, we used Student's  $t$  test for normally distributed continuous variables and chi-square tests for categorical variables.

Our primary outcome measure was size at 18 mo. We also examined the associations of exposure to supplementation with postnatal anthropometric measurements for each prior age period (1, 3, 6, 9, and 12 mo)

considered separately by using data from all individuals who were assessed at that age. We considered  $P < 0.05$  to be significant for comparisons between treatment groups. We controlled for child sex and age at measurement and maternal height (which differed between treatment groups in the analytic sample).

We previously reported that gravidity modified the effect of DHA supplementation on weight and head circumference at birth (9). To assess whether this interaction persisted through age 18 mo, we examined the coefficient of the interaction term between gravidity and intervention group on weight, length, BMI, and head circumference at 18 mo. We also tested whether the interaction was significant (at  $P < 0.10$ ) in models that also included the same measure of size at birth. Values in the text are means  $\pm$  SD unless otherwise indicated.

## Results

At 18 mo, we obtained data on 739 children (76.0% of the birth cohort; **Supplemental Fig. 1**). Loss to follow-up did not differ by treatment assignment. At birth, children subsequently lost to follow-up were 132 g lighter ( $P < 0.005$ ), had 0.4 cm smaller head circumference ( $P < 0.01$ ), and were more likely to have a low birth weight ( $P < 0.05$ ) compared with those with anthropometric measurements at 18 mo of age.

In the analytic sample, mothers who received DHA were 0.9 cm shorter ( $P < 0.05$ ) than mothers who received placebo; all other examined maternal and child characteristics were similar between the 2 groups (**Table 1**). Given the importance of maternal size as a predictor of child growth, we therefore controlled for maternal height in all analyses. The groups did not differ in breast-feeding. Overall, over 95% of the mothers breast-fed, with a mean duration of 10 mo.

**Results by randomization group.** In both the DHA and placebo groups, children experienced a decline in length-for-age Z-score (LAZ), which was counterbalanced by elevations in mean BMI-for-age Z-score (BMIZ), resulting in weight-for-age Z-scores (WAZ) that were close to the reference (**Supplemental Table 1**). At 18 mo, children whose mothers had received placebo had a weight of  $10.4 \pm 1.2$  kg (WAZ,  $-0.24 \pm 0.94$ ; BMIZ,  $0.30 \pm 0.88$ ), a length of  $79.5 \pm 2.8$  cm [height-for-age Z-score (HAZ),  $-0.75 \pm 0.95$ ], and a head circumference of  $47.0 \pm 1.4$  cm. In analyses controlling for maternal height and age at measurement and sex of the child, the between-group intent-to-treat differences (DHA – placebo) at 18 mo did not differ between the treatment groups (all  $P > 0.05$  by  $t$  test) (**Table 2**). Weight, length, and head circumference did not differ between treatment groups at any age measured (**Supplemental Table 1**).

**Interactions with gravidity.** At 18 mo, the treatment by gravidity interaction was significant for weight ( $P < 0.08$ ), length ( $P < 0.02$ ), HAZ ( $P < 0.02$ ), and head circumference ( $P < 0.05$ ), but not for WAZ or BMI (**Table 3**). Among children born to primigravida mothers, children whose mothers received DHA were 0.7 cm taller (95% CI = 0.1, 1.3;  $P = 0.02$ ) than children whose mothers received placebo. Additional adjustment for birth length did not alter these estimates (data not shown), but control for birth weight attenuated the estimate to 0.6 cm (95% CI =  $-0.0$ , 1.1;  $P = 0.07$ ). Among children born to multigravida women, no effect of maternal DHA supplementation was observed. The heterogeneity of effects on length was also observed at 3, 9, and 12 mo (**Fig. 1**). Gravidity-specific estimates for weight and head circumference at 18 mo were in the same direction but were not significant ( $P = 0.13$ – $0.41$ )

**TABLE 1** Selected maternal characteristics at randomization and child characteristics at birth among 739 children born to women who participated in a trial of 400 mg/d DHA during pregnancy and who were followed through 18 mo, by intervention group<sup>1</sup>

Variables	<i>n</i>	Placebo	<i>n</i>	DHA	<i>P</i> <sup>2</sup>
Maternal characteristics at randomization					
Age, <i>y</i>	369	26.3 ± 4.6	367	26.4 ± 4.9	0.74
Gestational age, <i>wk</i>	369	20.5 ± 2.1	367	20.5 ± 2.0	0.83
Socio-economic status	369	0.0 ± 1.0	367	0.0 ± 1.0	0.92
Schooling (High school or more), %	368	60.6	367	56.9	0.31
Ravens score	369	41.4 ± 9.1	367	40.8 ± 8.8	0.39
Primgravid, %	369	39.8	367	37.1	0.44
Weight, <i>kg</i>	369	63.5 ± 11.4	367	62.5 ± 11.5	0.22
Height, <i>cm</i>	369	155.8 ± 5.7	367	154.9 ± 5.6	0.04
BMI, <i>kg/m</i> <sup>2</sup>	369	26.2 ± 4.4	367	26.0 ± 4.3	0.61
Child characteristics at birth					
Weight, <i>g</i>	370	3220 ± 475	369	3242 ± 441	0.51
Length, <i>cm</i>	369	50.4 ± 2.5	369	50.3 ± 2.3	0.51
Head circumference, <i>cm</i>	320	34.3 ± 1.8	323	34.5 ± 1.5	0.14
Low birth weight (<2500g), %	370	5.4	369	4.3	0.50
Gestational age, <i>wk</i>	368	39.1 ± 1.6	369	39.1 ± 1.8	0.90
Preterm (<37 <i>wk</i> ), %	368	8.2	369	8.9	0.70
Sex (male), %	370	54.3	369	54.2	0.97
IUGR, <sup>3</sup> %	368	10.3	369	10.6	0.91
Placenta weight, <i>g</i>	311	656 ± 123	315	656 ± 139	0.96

<sup>1</sup> Values are mean ± SD or percent.

<sup>2</sup> *t* test for comparison of means and chi-square test for comparison of proportions.

<sup>3</sup> IUGR, Intrauterine growth retardation: birth weight for gestational age < 10th percentile Williams reference.

(Table 3), and the interaction terms became nonsignificant (*P* > 0.15) with further adjustment for these measures at birth. Among the 626 children with data on placental weight, further adjustment for placental weight did not alter any estimates substantively (data not shown).

## Discussion

We conducted a placebo-controlled, randomized, controlled trial of supplementation with 400 mg/d algal DHA restricted to the second half of pregnancy. We found no overall effect of supplementation on measures of size at 18 mo or any intervening age. At 18 mo of age, specifically, the overall estimates were very close to zero and were accompanied by tight CI. Offspring of

primagravid women supplemented with DHA were taller at 18 mo than offspring of primagravid women supplemented with placebo.

The women in our study had low baseline intakes of DHA (13) and were highly compliant with the study intervention (9), and the intervention raised cord blood levels of DHA (9) and breast milk concentrations at 1 mo postpartum (Beth Imhoff-Kunsch, Emory University, personal communication). All researchers and field staff and the participating women were unaware of treatment group, and postnatal feeding behaviors did not differ by treatment allocation. Thus, we conclude that the study was appropriately designed and well conducted.

We are aware of only 1 other study that has followed infants whose mothers received DHA in pregnancy (6). In that study, conducted in Norway, 590 mothers were randomized to receive

**TABLE 2** Anthropometric measures at age 18 mo among 739 children born to women who participated in a trial of maternal supplementation with 400 mg/d DHA during pregnancy, by treatment group<sup>1,2</sup>

Outcome variables	Placebo	DHA	<i>P</i> <sup>3</sup>	Adjusted difference (95% CI) <sup>4</sup>
Weight, <i>kg</i>	10.4 ± 1.2	10.4 ± 1.1	0.99	−0.03 (−0.19,0.13)
WAZ	−0.24 ± 0.94	−0.24 ± 0.91	0.97	−0.03 (−0.16,0.10)
Length, <i>cm</i>	79.5 ± 2.8	79.6 ± 2.8	0.63	−0.21 (−0.58,0.15)
LAZ	−0.75 ± 0.95	−0.73 ± 0.98	0.79	−0.07 (−0.20,0.06)
WHZ <sup>5</sup>	0.16 ± 0.91	0.14 ± 0.85	0.80	0.01 (−0.12,0.14)
BMIZ	0.30 ± 0.88	0.29 ± 0.82	0.78	0.02 (−0.10,0.15)
Head circumference, <i>cm</i>	47.0 ± 1.4	47.0 ± 1.5	0.65	0.02 (−0.18,0.21)

<sup>1</sup> Values are mean ± SD, *n* = 370 (placebo) or 369 (DHA).

<sup>2</sup> Z-scores derived from (11).

<sup>3</sup> *P*-value from *t* test to compare mean difference.

<sup>4</sup> Model adjusted for maternal height, child sex, and child age at measurement.

<sup>5</sup> Weight-for-height Z-score.

**TABLE 3** Effect of maternal prenatal supplementation with 400 mg/d DHA on selected measures of size at 18 mo among 739 children, by maternal gravidity<sup>1</sup>

	Primigravid			Multigravid		
	Estimate	95% CI	P-value <sup>2</sup>	Estimate	95% CI	P-value <sup>2</sup>
Weight, kg	0.18	−0.09, 0.44	0.19	−0.08	−0.29, 0.12	0.41
Length, cm	0.72	0.11, 1.33	0.02	−0.13	−0.59, 0.32	0.57
LAZ	0.26	0.04, 0.47	0.02	−0.05	−0.22, 0.11	0.54
Head circumference, cm	0.26	−0.11, 0.62	0.17	−0.17	−0.40, 0.05	0.13

<sup>1</sup> Estimates are differences between the DHA and placebo groups and are derived from general linear regression models, controlling for age at measurement, sex, and maternal height. 95% CI are presented.

<sup>2</sup> P-value for effect of treatment. Test for heterogeneity by gravidity (Wald score) had  $P < 0.10$  for each outcome measure.

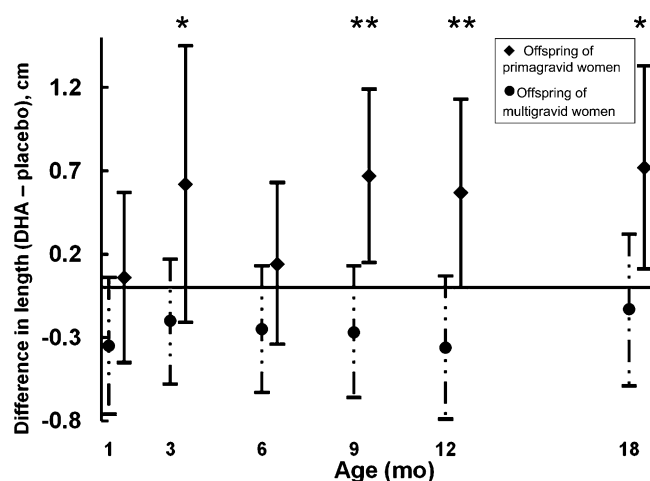
10 mL/d cod liver oil or corn oil from mid-gestation through 3 mo postpartum, and 288 of the 341 infants were followed through 12 mo of age, at which time there was no difference between the groups in measures of length, weight, or head circumference. Our study confirms that general finding and extends it by: 1) isolating the potential effect of prenatal supplementation; 2) isolating the potential effect of DHA provided as the sole supplement; 3) increasing 2.5-fold the number of children studied, thus enhancing study power; and 4) adding a different context, in which maternal DHA intakes are low (13).

In our earlier report, we identified an interaction with gravidity, such that DHA supplementation enhanced birth weight and head circumference specifically among children born to primigravid women (9). In that study, we did not observe an interaction on length. Without control for size at birth, attained weight, length, and head circumference at 18 mo were all elevated among children of primigravid women who received DHA in pregnancy compared with those in the placebo group, whereas there was no effect of maternal DHA supplementation among children born to multigravid women. For weight and head circumference, this interaction disappeared when the models were further adjusted for size at birth, suggesting that the effect of DHA on postnatal growth specif-

ically was not modified by maternal gravidity. For length, however, the heterogeneity remained significant even after adjustment for length at birth but was attenuated with control for birth weight. However, we recognize that control for birth length, which was recorded by delivery ward staff rather than by our research team, may not be optimal and there may be residual confounding. Taken together, these data suggest sustained effects on length and head circumference at least through age 18 mo of prenatal supplementation with DHA in primigravid women. In our study, primigravid women were, on average, younger than the multigravid women (9) and it is possible that their own body stores of DHA were not as well established and thus not as available to the fetus and infant. It will be of interest to further study these children as they grow.

We provided algal DHA to our study participants. Other studies investigating this question have supplied fish oil (which contains EPA as well as DHA) or have been observational and hence could not completely control for potential confounding. It is possible that isolated DHA acts differently from fish oil and EPA may hamper the efficacy of DHA. Other components of fish oil may have functions that are unknown at this time. It is also possible that in the context of urban Mexico, where  $\alpha$ -linolenic acid intakes are relatively high (13) but intakes of some micronutrients may be deficient, DHA in the diet of pregnant women is not the only limiting factor for offspring growth. Micronutrients such as zinc, iron, and vitamin B-12, which are often lacking in Mexican diets (14), may be important. Our recent meta-analysis (15) shows that whereas single nutrient interventions such as iron, zinc, and vitamin A may not improve growth, multiple micronutrient interventions that contain several vitamins and minerals do improve growth, indicating the role of diet quality and nutrient interactions. If this is the case, then subsequent studies would need to ensure that a comprehensive nutritional intervention, perhaps through a micronutrient supplement, accompanies a trial of DHA supplementation.

The children in our study experienced modest growth faltering over the study period, with HAZ in the placebo group declining 0.27 SD units from −0.48 at 1 mo to −0.75 at 18 mo. We note that our estimated effect of DHA supplementation on length among offspring of supplemented primigravid women represents 0.26 HAZ units. These offspring, therefore, avoided much of the postnatal growth failure observed in our cohort. In terms of weight for age, there was little change from birth onwards; 5% of the placebo group had birth weights < 2500 g, and by 18 mo the mean WAZ was −0.24. The observation that the WAZ is closer to zero than is the HAZ highlights the rising BMIZ in this population. Mexico is experiencing an epidemic of child obesity (16). In our study, mean BMIZ increased from



**FIGURE 1** Difference in length among 739 children born to women who participated in a trial of DHA in pregnancy and who were followed through 18 mo of age, by treatment assignment and maternal gravidity. Data are differences attributable to DHA and 95% CI and are adjusted for maternal height and offspring sex and age at assessment. \* $P < 0.05$ ; \*\* $P < 0.01$  for heterogeneity of estimates by parity.

−0.03 at 1 mo to 0.30 at age 18 mo, but BMIZ did not differ between the supplemented and placebo control groups. We thus do not confirm a report by Lauritzen et al. (8), who observed an increase in BMI among infants whose mothers received fish oil during lactation.

We conclude that DHA supplementation of primagravid women during the second half of gestation may enhance the linear growth of their children through 18 mo. Most of this impact may have occurred during gestation. Further study of child development is needed to assess whether the low DHA in the diets of pregnant women is limiting to the overall development of human capital in Mexico.

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