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Omega-3 Fatty Acid Supplementation During Pregnancy and Respiratory Symptoms in Children

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BACKGROUND: Prenatal consumption of omega-3 fatty acids can act as an adjuvant in the development of the immune system and affect the inflammatory response of neonates.

METHODS: We conducted a double-blind, randomized, placebo-controlled trial in Cuernavaca, Mexico. We randomly assigned 1,094 pregnant women (18-35 years of age) to receive 400 mg/d of algal docosahexaenoic acid (DHA) or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes and respiratory symptoms information until 18 months were available for 869 mother-child pairs. Questionnaires were administered, and maternal blood samples were obtained at baseline. Maternal atopy was based on specific IgE levels. During follow-up, information on infants' respiratory symptoms was collected through questionnaires administered at 1, 3, 6, 9, 12, and 18 months of age. Negative binomial regression models were used to evaluate the effect of supplementation on respiratory symptoms in infants.

RESULTS: Among infants of atopic mothers, a statistically significant protective effect of DHA treatment was observed on phlegm with nasal discharge or nasal congestion (0.78; 95% CI, 0.60-1.02) and fever with phlegm and nasal discharge or nasal congestion (0.53; 95% CI, 0.29-0.99), adjusting for potential confounders.

CONCLUSIONS: Our results support the hypothesis that DHA supplementation during pregnancy may decrease the incidence of respiratory symptoms in children with a history of maternal atopy.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00646360; URL: www.clinicaltrials.gov

CHEST 2014; 146(2):373-382

Manuscript received June 20, 2013; revision accepted February 24, 2014; originally published Online First March 13, 2014.

ABBREVIATIONS: DHA = docosahexaenoic acid; IMSS = General Hospital of the Mexican Social Security Institute/Instituto Mexicano del Seguro Social; INSP = National Institute of Public Health/Instituto Nacional de Salud Pública; IR = incidence rate; IRR = incidence rate ratio; Th = T helper

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FUNDING/SUPPORT: This study was supported by the National Council of Sciences and Technology CONACYT [Grant 87121] and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [Award R01HD058818].

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DOI: 10.1378/chest.13-1432

Allergy and asthma affect > 350 million people worldwide and are responsible for increased respiratory symptoms in children and adults.[1] In 2009, asthma was the 15th leading cause among the 20 leading causes of illness in Mexico, and it was ranked 13th in the state of Morelos (Mexico), with incidence rates of 348.8 per 100,000 inhabitants for the general population, 382.7 per 100,000 for infants < 1 year of age, and 742.5 per 100.000 for children 1 to 4 years of age.[2]

Immune system deficiencies and the presence of diseases such as respiratory infections trigger the presence of respiratory signs and symptoms.[3] It is currently well known that the regulation of tolerance and immune system activation is crucial to health, and failure in the regulation of these responses can lead to recurrent infections, inflammatory diseases, and allergic reactions. Furthermore, many allergic and inflammatory processes in adulthood are believed to originate during fetal and neonatal periods, since these periods are key to immune adaptation.[4] Different studies have also shown that immune abnormalities precede the development of allergic diseases.[5] Since the maternal diet can affect neonatal immune development and subsequently alter the allergic response in infants, the consumption or supplementation with omega-3 polyunsaturated fatty acids may play an important role, especially for the most susceptible individuals.[6-8] However, the results of previous studies using omega-3 supplementation are inconsistent.

Because of the negative impact of respiratory disease on the quality of life and the high cost of long-term treatment of signs and symptoms, further research is needed to prevent such diseases.[9] This study assesses whether supplementation with omega-3 fatty acids during pregnancy reduces the incidence of respiratory symptoms in children up to 18 months of age using data from a double-blind randomized placebo-controlled clinical trial in Cuernavaca, Mexico. We hypothesize that omega-3 fatty acid intake during pregnancy plays an important role in preventing the development of respiratory symptoms and allergic diseases in infants whose mothers have a history of atopy.

Materials and Methods

Experimental Design

A randomized, double-blind controlled trial was conducted. A total of 1,094 pregnant women were randomly assigned to receive 400 mg of docosahexaenoic acid (DHA) or placebo daily from midpregnancy (18-22 weeks of gestation) to delivery (National Institute of Public Health/Instituto Nacional de Salud Pública [INSP] Mexico: CI-011 in clinicaltrials.gov: NCT00646360). DHA was chosen as the supplement, as the aim of the original trial was to determine potentially beneficial effects of omega-3 fatty acid supplementation during pregnancy on infant neurodevelopment; DHA is the most abundant omega-3 fatty acid in the mammalian CNS.[10] Of the 1,094 women randomized, 1,040 started treatment, and 973 completed the study. Five had stillbirths, and there were 968 live-born infants (963 single and five pairs of twins); for the present analysis, 869 mother-child pairs were included to have complete information from pregnancy until 18 months of follow-up (Fig 1). This study was conducted in collaboration with the Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia; INSP, Mexico; and the General Hospital of the Mexican Social Security Institute/Instituto Mexicano del Seguro Social (IMSS) in Cuernavaca, Mexico. The protocol was approved by the institutional review board at Emory University (CI:418) and by ethics and biosafety committees at the INSP. All procedures were explained to the participants, who signed an informed consent. The study data were reviewed periodically by an external data and safety monitoring committee.

Study Setting and Population

Participants were recruited at the General Hospital of the IMSS in Cuernavaca, Mexico, and three small health clinics within the IMSS system in Morelos, Mexico, during routine prenatal care visits between February 2005 and February 2007. In general, IMSS enrollees are from middle to low socioeconomic status.[10] Using data from a major study,[10] we estimated that a final sample of 338 infants per group would have at least 90% power to detect an effect size ≥ 0.25 SD for the major outcomes at the end of the study, assuming a significance level of $\alpha = 0.05$ for a two-tailed test. We, therefore, planned to recruit at least 994 pregnancies, assuming a 15% loss to follow-up during pregnancy and a further 20% loss in infancy, to have 393 births and 338 mother-child pairs per group complete the study at 18 months of age. This sample size would allow us to detect differences in the symptoms of one for each 1,000 (1 SD) with at least 80% power. However, for the present report, we included 869 mother-child pairs (429 from DHA group and 440 from placebo group). This sample size would allow us to detect differences in all symptoms (except in coughing and coughing with phlegm) of one for each 1,000 (1 SD) and a power of 90% (Fig 1). Only 869 mother-child pairs (Fig 1) were included in the present report by having all the information from birth until 18 months of follow up, including laboratory results.

Eligibility Criteria

The women included in the clinical trial were between 18 and 35 years of age and were recruited between 18 and 22 weeks of gestation. All participants expressed their willingness to breastfeed exclusively or predominantly during at least the first 3 months of life of the newborn and stated their intention to live in their area of residence for at least 2 years after delivery. Exclusion criteria were women with high-risk pregnancies (pregnancy complications, including premature placental abruption, preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy) or lipid absorption disorders, or who regularly consumed fish oil or DHA supplements or chronically used certain medications (eg, drugs for epilepsy).

Randomization and Blinding

We used block randomization to randomly create balanced replication of four treatments (two colors for DHA and two for control subjects) using a block size of eight. The list was generated for a sample size of 1,104. The assignment codes were placed in sealed envelopes at the beginning of the study. All study participants and members of the study team remained blinded to the treatment scheme throughout the intervention period of the study. Data were unblended for the analytical study team after the last baby in the study was born and had reached 6 months of age, at which time the participants were no