Fish Oil Supplementation in Pregnancy

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

**CASE VIGNETTE**

**A Pregnant Woman Considering n−3 Long-Chain Polyunsaturated Fatty Acid Supplementation**

Ramya Ramaswami, M.B., B.S., M.P.H.

Ms. Franklin is a 30-year-old woman who is 20 weeks pregnant with her second child and is seeing you today for a routine prenatal visit. She is a healthy woman with a history of well-controlled asthma. She reports no current symptoms and is using no asthma medications now; she used no asthma medications during her previous pregnancy. Ms. Franklin takes a prenatal vitamin daily and has no allergies. Her first-trimester ultrasound screening showed no fetal anomalies. She lives in the central United States with her partner and 4-year-old son, Charlie. She eats a well-balanced diet that includes lean meats and occasional fish.

Charlie is seen frequently in the emergency department for episodes of persistent wheezing and lower respiratory tract infections, and Ms. Franklin wants to discuss with you today the risks of similar symptoms in her unborn child. She asks you about the results of a recently published randomized, controlled trial that investigated the effect of supplementation with n−3 long-chain polyunsaturated fatty acids (n−3 LCPUFAs) on pregnant women and their offspring. The trial concluded that n−3 LCPUFA supplementation in the third trimester of pregnancy reduced the risk of asthmatic symptoms and lower respiratory tract infections in children. Ms. Franklin asks your opinion — should she start taking n−3 LCPUFA supplements?

**TREATMENT OPTIONS**

Which of the following options would you recommend for this patient?

1. Start n−3 LCPUFA supplementation.
2. Do not start n−3 LCPUFA supplementation.

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which option would you choose? Make your choice, vote, and offer your comments at NEJM.org.

**OPTION 1**

**Start n−3 LCPUFA Supplementation**

Charles N. Serhan, Ph.D., D.Sc., and Bruce D. Levy, M.D.

Ms. Franklin is worried about symptoms of asthma in her unborn child; therefore treatment with n−3 LCPUFAs is a potential therapeutic option. The n−3 LCPUFAs — mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) — are the active components of fish oils. These n−3 LCPUFAs are substrates for biosynthesis of potent mediators that resolve inflammation and infection. These specialized pro-resolving mediators are present in placenta and human milk and, in preclinical experimental models, two types of these pro-resolving mediators, resolvins and protectins, decrease airway inflammation, mucus metaplasia, and hyperreactivity and promote host defense against respiratory infection. Airway mucosal levels of n−3 LCPUFAs are lower in patients with asthma than in those without asthma, and pro-resolving mediators within the lung are underproduced in patients with severe and uncontrolled asthma.
The n−3 LCPUFAs are essential, and since humans do not produce them to any great extent, they must be added to our diet. Ms. Franklin has a diet low in marine products and is probably relatively deficient in this nutrient. Although the general public believes that fish oils are beneficial, there is some controversy among experts regarding their usefulness in specific disease indications. Epidemiologic studies have linked maternal fish intake during pregnancy to reductions in allergic disorders in their offspring. With broad consensus regarding the nutritional value of fish for a fetus’s growth and development in utero and for an infant’s early immune system, the Food and Drug Administration and the Environmental Protection Agency issued a joint statement in June 2014 to recommend that pregnant women eat two to three servings of seafood that is low in mercury each week (200 to 300 g per week).

In contrast to findings in epidemiologic studies, results from intervention trials evaluating fish oil consumption by pregnant women have been less convincing; however, many of these trials were underpowered or had methodologic limitations. Evidence in support of potential benefits includes findings that fish oil supplementation during pregnancy results in higher n−3 LCPUFAs levels in infants that are associated with beneficial changes in immune responses; in addition, several studies have shown a lower incidence of allergic sensitization among infants born to mothers who supplemented with fish oil than among infants born to mothers who did not, as well as a lower prevalence of allergic disorders, including food allergies, atopic dermatitis, and wheezing illnesses in the first year of life, with possible persistence until later in life. A negative trial failed to show protection, but it is important to note that it was not associated with clinically significant adverse outcomes.

In this issue of the Journal, Bisgaard et al. provide new data that support the use of n−3 LCPUFAs during pregnancy. They show that the offspring of women who received 2.4 g per day of n−3 LCPUFAs from 24 weeks of gestation until 1 week after delivery had a lower risk of asthmatic symptoms and fewer respiratory infections than the offspring of women who were assigned to placebo. The number of women who would need to be treated to prevent one case of persistent wheezing or asthma was 14.6 among women in the entire cohort and 5.6 among women in the lower third of preintervention EPA and DHA levels.

Thus, there is benefit and little risk associated with n−3 LCPUFA supplementation. Even though we do not know Ms. Franklin’s EPA and DHA levels, there is likely to be a benefit for her child, at little risk, cost, or inconvenience. She should start taking n−3 LCPUFA supplements.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**Option 2**

**Do Not Start n−3 LCPUFA Supplementation**

Maria Makrides, B.N.D., Ph.D.

Ms. Franklin should not start prenatal fish oil supplements on the basis of the results of a single study. Clinical practice decisions are best made in accordance with practice guidelines based on well-conducted systematic reviews, preferably of several randomized, controlled trials. In the area of marine oil supplementation during pregnancy, there have been in excess of 50 randomized, controlled trials assessing the effects of the bioactive n−3 LCPUFAs on outcomes as diverse as pregnancy duration, the risk of prematurity, infant birth weight, maternal depression, and childhood neurobehavioral outcomes, as well as allergy and asthma outcomes.

The trials assessing the effect of prenatal n−3 LCPUFA supplementation on childhood allergy and asthma outcomes have been driven largely by the plausible hypothesis that diets high in n−3 LCPUFAs may modulate the development of immunoglobulin E–associated allergic disease. There is some supportive evidence from a Cochrane systematic review that showed that at least 1 g of n−3 LCPUFA supplementation daily during pregnancy resulted in rates of atopic eczema in the first 3 years of life and of sensitization to allergens during the first year of life among children with a higher-than-normal risk of allergic dis-
ease that were lower than the rates among children whose mothers did not receive n−3 LCPUFA supplementation. The review showed no clear effects on asthma or wheezing outcomes. The two largest and highest-quality trials show contrasting results. Bisgaard et al. found a 31% lower rate of persistent wheezing or asthma at 3 to 5 years among infants whose mothers received n−3 LCPUFA supplementation than among infants whose mothers did not receive the supplementation, with no significant effects on eczema or allergic sensitization; in contrast, Palmer et al. found lower rates of allergic sensitization and atopic eczema at 1 year that were no longer evident at 3 or 6 years; there were no significant effects of n−3 LCPUFA supplementation on wheezing or asthma at 3 and 6 years. These inconsistencies are perplexing and may be related to differences in the populations studied or in the definitions used to diagnose asthma. Asthma can be difficult to diagnose accurately in early childhood, and not all persistent wheezing is asthma. Children may have 10 or more virus-related colds in a year, and respiratory symptoms may last for 2 or more weeks. An unexpected finding reported by Bisgaard et al. was that prenatal n−3 LCPUFA supplementation was also associated with a lower risk of lower respiratory tract infections in children. How the symptoms of persistent wheezing or asthma were related to the occurrence of respiratory tract infections and whether the frequency of respiratory tract infections was also related to the higher-than-anticipated rate of persistent wheezing or asthma are not clear.

In considering outcomes beyond allergy and asthma, there is consistent evidence that prenatal n−3 LCPUFA supplementation extends the length of pregnancy, which is associated with a lower rate of early preterm birth (<34 weeks of gestation) as well as a higher rate of obstetrical intervention because of prolonged gestation. While we work to reconcile all relevant data for fish oil supplementation in pregnancy in a way that is useful for clinical decision making, it seems prudent to advise Ms. Franklin to follow standard-of-care surveillance for persistent wheezing and asthma in her child after birth.