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Does fish oil during pregnancy help prevent asthma in kids?

The evidence on fish oil has been mixed, but this study affirms its benefits—in certain women.

PRACTICE CHANGER

Fish oil supplementation taken by women in the third trimester of pregnancy can reduce the risk of persistent wheeze, asthma, and infections of the lower respiratory tract in their children.¹

STRENGTH OF RECOMMENDATION

B: Based on 2 double-blinded randomized controlled trials (RCTs).

Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med.* 2016;375:2530-2539.¹

ILLUSTRATIVE CASE

A 24-year-old G2P1 at 24 weeks' gestation presents to your clinic for a routine prenatal visit. Her older daughter has asthma and she is inquiring as to whether there is anything she can do to lower the risk of her second child developing asthma in the future. What do you recommend?

Asthma is the most common chronic disease in children in resource-rich countries such as the United States.² The Centers for Disease Control and Prevention (CDC) reported that 8.4% of children were diagnosed with asthma in 2015.³

Omega-3 fatty acids, found naturally in fish oil, are thought to confer anti-inflammatory properties that offer protection against asthma. Clinical trials have shown that fish oil supplementation in pregnancy results in higher levels of omega-3 fatty acids, along with anti-inflammatory changes, in off-

spring.⁴ Previous epidemiologic studies have also found that consumption of omega-3 fatty acids decreased the risk of atopy and asthma in offspring.^{5,6}

■ A Cochrane review published in 2015, however, concluded that omega-3 supplementation during pregnancy had no benefit on wheeze or asthma in offspring.⁷ Five RCTs were included in the analysis. The largest trial by Palmer et al, which included 706 women, showed no benefit for omega-3 supplementation.⁸ The second largest by Olsen et al, which included 533 women, did show a benefit (hazard ratio [HR]=0.37; 95% confidence interval [CI], 0.15-0.92; number needed to treat [NNT]=19.6).⁹

These results, however, were limited by heterogeneity in the amount of fish oil supplemented and duration of follow-up. For example, the children in the Palmer study were followed only until 3 years of age, which is around the time that asthma can be formally diagnosed, potentially leading to under-reporting.⁸ In addition, the diagnosis of asthma was based on parent report of 3 episodes of wheezing, use of daily asthma medication, or use of a national registry—all of which can underestimate the incidence of asthma. The reported rate of childhood asthma with IgE-sensitization (they did not report the rate without sensitization) was 1.8% in both arms, which is much lower than the CDC's rate of 8.4%, suggesting under-diagnosis.^{3,8} Due to these biases and other potential confounders, no firm conclusions can be drawn from the Cochrane review.

STUDY SUMMARY

Maternal fish oil supplementation reduces incidence of asthma in children

This single-center, double-blinded RCT of 736 pregnant women evaluated the effect of 2.4 g/d of n-3 long-chain polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or placebo (olive oil), starting at an estimated gestational age of 24 to 26 weeks, on wheeze or asthma incidence in their offspring.¹

Eligible women were between 22 and 26 weeks' pregnant at the time of recruitment. Exclusion criteria included supplementation of 600 IU/d or more of vitamin D, or having any endocrine, cardiac, or renal disorders. The investigators randomized the women in a 1:1 ratio to either fish oil or placebo. Maternal EPA and DHA blood levels were tested at the time of randomization and one week after birth.

■ **The primary outcome** was persistent wheeze or asthma (after 3 years of age, the diagnosis of persistent wheeze was termed asthma) based on daily diary recordings of 5 episodes of troublesome lung symptoms within the last 6 months (each lasting for at least 3 consecutive days), rescue use of inhaled beta₂-agonists, and/or relapse after a 3-month course of inhaled glucocorticoids. Secondary outcomes included lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization.

In total, 695 offspring were included in the study with 95.5% follow-up at 3 years and 93.1% follow-up at 5 years. The children had scheduled pediatric visits at 1 week; 1, 3, 6, 12, 18, 24, 30, and 36 months; and at 4 and 5 years, and acute visits for any pulmonary, allergic, or dermatologic symptoms that arose.

■ **Results.** The investigators found that the children of the mothers who received the fish oil had a lower risk of persistent wheeze or asthma at ages 3 to 5 years compared to those who received placebo (16.9% vs 23.7%; HR=0.69; 95% CI, 0.49-0.97; *P*=.035; NNT=14.7). But the effect of the fish oil supplementation was significant only in the children of the mothers with baseline EPA and DHA levels in the lowest third (17.5% vs 34.1%; HR=0.46; 95% CI, 0.25-0.83; *P*=.011; NNT=5.6). Similarly, in mothers who consumed the least EPA and DHA before the start

of the study, fish oil supplementation had a greater benefit in terms of decreased wheeze and asthma (18.5% vs 32.4%; HR=0.55; 95% CI, 0.30-0.98; *P*=.043; NNT=7.2).

As for the secondary outcomes, only a reduction in lower respiratory tract infections was associated with the fish oil supplementation vs the control (38.8% vs 45.5%; HR=0.77; 95% CI, 0.61-0.99; *P*=.041; NNT=14.9). There was no reduction in asthma exacerbations, eczema, or risk of sensitization in the fish oil group.

WHAT'S NEW?

Study adds fuel to the fire

This study strengthens the case for fish oil supplementation during pregnancy to reduce the risk of asthma in offspring, despite the recent Cochrane review that showed no benefit.^{1,7} The Palmer study used a much lower amount of omega-3s (900 mg/d fish oil vs 2400 mg/d in the current trial).^{1,8} Olsen et al supplemented with a greater amount of omega-3s (2700 mg/d) and did find a benefit.⁹ The NNT from the Olsen study (19.6) is consistent with that of the current investigation, suggesting that a higher dosage may be necessary to prevent the onset of asthma.

Additionally, this study followed children for a longer period than did the Palmer study, which may have led to more accurate diagnoses of asthma.^{1,8} Lastly, the diagnosis of asthma in the Palmer study was based on parent survey data and use of daily asthma medicine rather than on daily diary cards, which are often more accurate.

■ **Consider fish consumption.** Both this study and the Olsen trial were performed in Denmark.^{1,9} While Denmark and the United States have had a relatively similar level of fish consumption since the 1990s, women in Denmark may eat a higher proportion of oily fish than women in the United States, given the more common inclusion of mackerel and herring in their diet.¹⁰ Thus, the effect of supplementation may be more pronounced in women in the United States.

CAVEATS

Questions remain: Ideal dose and which women to treat?

The US Food and Drug Administration cur-



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rently recommends 8 to 12 ounces of fish per week for pregnant women, but there are no guidelines on the ideal amount of fish oil to be consumed.¹¹ The Palmer study,⁸ using 900 mg/d fish oil, did not show a benefit, whereas there did appear to be benefit in this study (2400 mg/d)¹ and the Olsen study (2700 mg/d).⁹ Further research is needed to determine the optimal dosage.

The decreased risk of persistent wheeze or asthma was seen only in the children of the women whose EPA and DHA blood levels were in the lowest third of the study population. Thus, only women whose blood levels are low to begin with will likely benefit from this intervention. Currently, EPA and DHA levels are not routinely checked, but there may be some benefit to doing so.

One proxy for blood levels is maternal intake of fish at baseline. The investigators found that there was an association between dietary intake of fish and blood levels of EPA and DHA ($r=0.32$; $P<.001$).¹ Therefore, additional screening questions to determine fish consumption would be useful for identifying women most likely to benefit from supplementation.

CHALLENGES TO IMPLEMENTATION

Multiple pills and additional cost

Since omega-3 fatty acids are relatively safe and the NNT in the general population is low, it may be worth supplementing all pregnant women, even without a commercially-available blood test for EPA or DHA. Nevertheless, some women may find it challenging to take up to an additional 4 pills/d for

13 or more weeks. Also, there is an associated cost with these supplements, although it is low.

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➤ Only women whose blood levels of EPA and DHA are low to begin with will likely benefit from this intervention.

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