The Relationship Between Fish Oil Supplementation During Pregnancy and Incidence of Asthma in Children

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The Relationship Between Fish Oil Supplementation During Pregnancy and Incidence of Asthma in Children

Abstract
Background: The incidence of asthma is increasing in the United States. Some researchers believe this rise is due to higher levels of n-6 fatty acids in relation to n-3 fatty acids that are found in cold-water fish. Several studies over the years have tried to discern if increasing fish oil in the diet or by supplementation can decrease the incidence of asthma in children. However, the results of these studies are not in agreement.

Methods: A comprehensive search of available medical literature was performed using MEDLINE-Ovid, CINAHL, and Web of Science using the keywords: fatty acids, omega-3s, fish oil, LCPUFAs, wheezing, asthma, respiratory sounds, pregnancy, and perinatal. Studies were assessed for quality based on GRADE criteria.

Results: There were 264 articles that were screened, 5 of which applied to the clinical question with only 2 articles meeting the eligibility criteria. One study found a significant decrease in the incidence of asthma in children when mothers were supplemented with high dose fish oil during pregnancy. The other study found no significant difference in the incidence of asthma in children of mothers supplemented with fish oil during pregnancy when compared to the control group. Overall the quality of evidence is low and further research needs to be done to explore key findings.

Conclusion: Using fish oil supplements during pregnancy to prevent asthma in children cannot be strongly recommended at this time. However, it is reasonable for mothers to choose to supplement fish oil during pregnancy since the harm is low and the benefit may be great if further research can support recent findings.

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The Relationship Between Fish Oil Supplementation During Pregnancy and Incidence of Asthma in Children

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Biography

[redacted]
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Acknowledgements

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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

LCPUFA  Long-Chain Polyunsaturated Fatty Acids
EPA     Eicosapentaenoic Acid
DHA     Docosahexaenoic Acid
GRADE   Grading of Recommendations, Assessment, Development and Evaluations
RCT     Randomized Clinical Trial
The Relationship Between Fish Oil Supplementation During Pregnancy and Incidence of Asthma in Children

BACKGROUND

In 2010, 25.7 million people (8.4%) in the United States were living with a diagnosis of asthma. According to a National Health Interview Survey, this was an increase compared to the 20.3 million people with asthma in 2001. Of these 25.7 million Americans with asthma, 7 million of them were children. The United States has a higher prevalence of asthma when compared to the incidence of asthma worldwide, and some researchers have attributed this discrepancy to the American diet. Healthy fats are an important component of a well-balanced diet, but the American diet includes higher levels of n-6 polyunsaturated fatty acids that are more inflammatory than the long chain n-3 polyunsaturated fatty acids found in fish. There are a variety of long chain polyunsaturated fatty acids (LCPUFAs), but the two that are typically included in fish oil supplements are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

Over the last few decades, research has conflicted over the effect of fish oil in preventing and treating allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis. Support for fish oil supplementation was seen in a 2008 study by Olsen et al that consisted of a 16-year follow up of a randomized control trial. Olsen et al found that children born to mothers who received fish oil during pregnancy had a decreased incidence of asthma compared to the control
group. In a recent follow up of the same randomized control trial, the children in the treatment group continue to have less asthma-related medications prescribed to them. In contrast, a 2013 study by Miyake et al found no relationship between the ratio of dietary n-3 PUFA to n-6 PUFA and subsequent wheeze or eczema in children. A randomized control trial by D’Vaz et al in 2012 also found no significant reduction of allergic disease in children supplemented with fish oil after birth. While the previous two studies do not provide support for increasing dietary fish oil or taking fish oil supplements postnatally, there appears to be some promise in taking fish oil supplements during pregnancy. This particular supplementation strategy is worthy of further investigation to determine if it helps reduce the incidence of childhood asthma.

METHODS

A comprehensive database search was performed in CINAHL, MEDLINE-Ovid, and Web of Science with the search terms: fatty acids, omega-3s, fish oil, LCPUFAs, wheezing, asthma, respiratory sounds, pregnancy, and perinatal. Study eligibility criteria included: randomized clinical trials, supplementation of fish oil via capsules, studies published within the last 5 years, length of study at least 5 years, and studies published in the English language. Eligible studies were then assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria.
RESULTS

A search of MEDLINE-Ovid using the aforementioned search terms produced 116 articles, 3 of which applied to the clinical question with only 1 article meeting eligibility criteria. A subsequent search of CINAHL produced 45 articles, some of which were duplicates, with 1 article meeting eligibility criteria. A search of Web of Science produced 103 articles, some of which were duplicates, with none meeting eligibility criteria. After the database search was complete, 2 articles\textsuperscript{10,11} were chosen for this systematic review. See Table 1.

Bisgaard et al (2016)

This Copenhagen randomized clinical trial\textsuperscript{10} enrolled 736 pregnant women to receive a daily capsule of either 2.4 g of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) or placebo (olive oil) beginning at 24 weeks of gestation. Women were asked to return all unused capsules 1 week after delivery of their baby to determine adherence. Blood levels of fish-oil derived fatty acids (EPA and DHA) were drawn before starting the therapy and 1 week after birth. The study then followed the 695 children through age 3-5 years. Evaluation included 9 clinical visits to a pediatrician starting at 1 week of age and continuing to 36 months, followed by as needed appointments. Mothers were asked to take daily diary notes on any lung-related symptoms their child experienced, which were then reviewed by pediatricians. Follow-up is ongoing.\textsuperscript{10}

The primary endpoint was persistent wheeze or asthma which was defined as “diary recordings of 5 episodes of troublesome lung symptoms within the preceding 6 months, each lasting for at least 3 consecutive days; symptoms typical of asthma; the rescue use of inhaled
beta-agonist; and response to a 3 month course of inhaled glucocorticoids followed by relapse after the end of treatment.\textsuperscript{10}

The results showed a 16.9\% incidence of wheeze or asthma in the treatment group and a 23.7\% incidence in the control group, which corresponds to a hazard ratio of 0.69 (95\% CI, 0.49-0.97) and a relative risk reduction of 30.7\%.\textsuperscript{10} This effect was more pronounced in children born to mothers with blood levels of EPA and DHA in the lowest third of trial participants. In this subgroup, the incidence of wheeze or asthma was 17.5\% in the treatment group and 34.1\% in the control group, with a hazard ratio of 0.46 (95\% CI, 0.25-0.83) and a relative risk reduction of 54.1\%. The number needed to treat for the entire trial population was 14.6, and only 5.6 in the subgroup analysis.\textsuperscript{10}

\textbf{Best et al (2016)}

This study\textsuperscript{11} was a 6-year follow up of a randomized controlled trial conducted in Australia and New Zealand. In the original study by Makrides et al,\textsuperscript{12} 2399 women were enrolled to receive daily capsules of either 900 mg of fish-oil derived fatty acids (DHA and EPA) or placebo (vegetable oil) capsules starting at 21 weeks of gestation. Of the 726 children born to the women in the trial, 706 were invited to take part in a 6-year allergy follow-up study. The child attended an appointment prior to their 6\textsuperscript{th} birthday where an allergy skin prick test was administered using the following allergens: hen’s egg, peanut, cashew, rye grass pollen, olive tree pollen, \textit{Alternaria tenuis}, cat, dog, and two species of house mite (\textit{Dermatophagoides pteronyssinus} and \textit{Dermatophagoides farina}). An International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was completed to assess for asthma and allergy symptoms.\textsuperscript{11}
The primary outcome was the incidence of allergic disease symptoms (including IgE-associated wheeze) with a positive skin prick test to 1 or more of the above allergens. The study stated that, “IgE-associated wheeze was defined as a history of wheezing and/or whistling in the chest within the past 12 months with sensitization to at least 1 of the aeroallergens tested” using the ISAAC questionnaire and skin prick test to assess these parameters.\textsuperscript{11}

The results of the follow up indicated that there was no significant difference between the incidence of IgE-associated wheeze in the children born to mothers receiving fish oil during pregnancy compared to the control group. In a subgroup analysis, there was a significant decrease in the sensitization to the house dust mite \textit{Dermatophagoides farina} in the fish oil group compared to the control group, with an adjusted relative risk of 0.67 (95\% CI, 0.44-1.00).\textsuperscript{11}

**DISCUSSION**

**Clinical Relevance**

This systematic review attempted to bring forward additional information on whether supplementing fish oil during pregnancy can reduce the incidence of wheeze or asthma in children. However, these studies\textsuperscript{10,11} appear to conflict over the significance of this preventative treatment. Bisgaard et al\textsuperscript{10} demonstrated significant benefit in preventing childhood wheeze or asthma with a relative risk reduction of 30.7\% and a number needed to treat of 14.6 when mothers were supplemented with 2.4 g of n-3 LCPUFAs during pregnancy. This effect was seen more prominently in women with low blood levels of DHA and EPA at baseline, and in women with a variation in the FADS gene that predisposes them to low blood levels of DHA and EPA.
The relative risk reduction in this subgroup was 54.1% with a number needed to treat of 5.6. In contrast, Best et al\textsuperscript{11} showed no significant difference in preventing IgE-associated wheeze in children when mothers were supplemented with 900 mg of fish-oil derived fatty acids during pregnancy. The study did find a significant decrease in the incidence of sensitization to the \textit{Dermatophagoides farina} species of dust mite. However, since the Best et al study\textsuperscript{11} evaluated only one phenotype of asthma, their results may not measure asthma incidence completely.

The number needed to treat of 14.6 that was determined in Bisgaard et al\textsuperscript{10} has the potential to significantly impact clinical practice if future studies can support it. Despite contradictory findings by Best et al\textsuperscript{11}, the study by Bisgaard et al\textsuperscript{10} showed higher quality of evidence when analyzed for bias and limitations by GRADE criteria. Even with conflicting evidence, the low risk and other potential health benefits of fish oil may make supplementation worthwhile to patients. Fish oil supplementation is readily available and not cost prohibitive to women who can afford an extra supplement during pregnancy, which makes it a reasonable recommendation for parents who have histories of asthma. This recommendation may especially pertain to women with low levels of DHA and EPA or with the FADs genotype, as demonstrated in the post hoc analysis by Bisgaard at al.\textsuperscript{10}

The risks of taking fish oil supplements are minimal. The National Center for Complementary and Integrative Health (NCCIH) considers fish oil safe, but patients should avoid it if they have fish or shellfish allergies, or if they are on anticoagulation medications because it may extend bleeding time.\textsuperscript{4} The only other side effects are a fishy taste and indigestion. Despite limited evidence for the efficacy of fish oil, some patients find that the low
cost and minimal risk of using fish oil supplements make the potential benefits worthwhile. For instance, recent meta-analyses no longer support fish oil supplementation for preventing cardiovascular events, but other studies have shown that fish oil may be helpful in treating the symptoms of rheumatoid arthritis. The research being conducted on fish oil is extensive across a variety of disease states including macular degeneration, cystic fibrosis, and allergies.

**Study Limitations**

Both studies had limitations in their long-term double blinding procedure, the most significant of which was seen in Best et al. Prior to the follow-up by Best et al, 15.2% of mothers in the control group, and 9.9% of mothers in the experimental group asked to be unblinded. As a consequence, the answers given on the ISAAC questionnaire could have been influenced by whether the mother knew if her child was in the control group or experimental group. This is a serious bias limitation that resulted in a downgrade of the quality of the Best et al study according to the GRADE criteria. The unblinding also created a possible recruitment bias, since knowing what treatment group they were in may have been influenced whether a woman completed the 6-year follow up. However, implementing an intention to treat analysis that included women who did not complete the assessment helped with this concern. Bisgaard et al also had a portion of mothers that were unblinded, but this was done after the primary outcome was assessed by age 3-5 years old. Since the relative risk reduction and number needed to treat were calculated for the period of time that was double blinded, this did not require a
downgrade in the quality of the Bisgaard et al study.\textsuperscript{10} However, follow-up is ongoing and this may present as an issue during future analyses.

The Best et al\textsuperscript{11} study was also limited by their definition of IgE-associated wheeze, which required symptoms in the ISAAC questionnaire and a positive skin prick test. Although the ISAAC questionnaire is a validated assessment method, it is unclear how combining it with the skin prick test affects the validity. Most questions in the ISAAC questionnaire only applied to the allergic symptoms in the previous 12 months, and the questions that did cover longer periods of time relied on a parent’s recollection of the past 6 years. The parental reporting of child symptoms in Bisgaard et al\textsuperscript{10} had the potential for more accuracy, because parents were asked to keep daily notes on any symptoms from birth up until age 3-5. A positive skin prick test was the second component in the Best et al\textsuperscript{11} definition of IgE-associated wheeze and it too posed some issues. Although the allergens selected for the skin prick test reflected many of the most common triggers for wheeze, it did not cover all possibilities.

The two studies\textsuperscript{10,11} also differed in their dosage of fish oil. Bisgaard et al employed a much higher daily dose than Best et al (2400 mg vs. 900 mg, respectively). This could have large implications in the efficacy of fish oil in preventing asthma if larger doses are needed to elicit an effect.

**Further Studies**

Future research needs to be done to determine optimal dosing of fish oil. The high dose of fish oil (2.4 g) may have been a contributing factor in decreasing the incidence of wheezing and asthma in the Bisgaard et al cohort.\textsuperscript{10} The population studied by Best et al\textsuperscript{11} received 900 mg
of fish oil during pregnancy, which is a substantial difference between the two study protocols. It may also be worthwhile to vary the ratio between DHA and EPA to determine if that is an influential factor.

Subsequent studies may benefit from expanding upon the ethnic, geographical, and socioeconomic diversity of the population sample. Best et al\textsuperscript{11} did find a significant decrease in child sensitization to \textit{Dermatophagoides farina}, so it may be worthwhile to see if supplementing fish oil in pregnant mothers from areas where this species of dust mite is more prevalent results in a decrease in wheezing or asthma in those children.

\textbf{CONCLUSION}

The answer to whether supplementing fish oil during pregnancy decreases the incidence of asthma in children remains uncertain. Recent studies on this topic continue to show conflicting results; however, a high quality randomized control trial by Bisgaard et al has provided compelling evidence in support of the claim. While Best et al and other studies propose the contrary, it will be worthwhile to explore the effect of high dose fish oil supplementation, especially in mothers with baseline low levels of fish-oil derived fatty acids or in mothers with the FADS genotype that predisposes them to lower DHA and EPA levels. Although the evidence is still not clear, clinicians should feel comfortable recommending fish oil to pregnant mothers due to the low risk, low cost, and considerable potential benefit to both the mother and child.
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<sup>a</sup> Confidence intervals are wide  
<sup>b</sup> Unblinding of a small percentage of mothers prior to 6-year follow-up assessment  
<sup>c</sup> Allergic outcomes were defined as having a positive skin prick test to one or more designated allergens