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Consumption of fish and long-chain n-3 polyunsaturated fatty acids during pregnancy: has the tide turned?

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Keywords

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Omega-3 (also known as n-3) polyunsaturated fatty acids (PUFA) are essential nutrients, which means that they are necessary for normal biological function, yet we cannot synthesize them in sufficient quantity, and so we need to consume them in our diet.

Most essential nutrients were identified in the process of investigating the etiology of a disease – for example, the cause of rickets is insufficient intake of vitamin D, the cause of scurvy vitamin C deficiency. This connection between an essential nutrient and an identifiable constellation of symptoms has historically been extremely tight; in fact, the definition I find in my nutritional epidemiology textbook states that “the essential nutrients... have little in common except that insufficient intake results in predictable clinical signs and symptoms of deficiency.”¹

However there is no human disease described that has been found to derive from a lack of omega-3 PUFA in a regular diet.² Clinically manifest abnormalities result only from experimental manipulations of laboratory animals, or among children on long-term total parenteral nutrition.³ This is probably because the sources of omega-3 fatty acids are so varied, including vegetable oils, grain, nuts, eggs, meat, and fish, that it is difficult to consume an insufficient amount.

Nevertheless, concern has existed that the metabolic process of converting the parent short-chain n-3 PUFA (alpha-linolenic acid [ALA]), to the more biologically active long-chain (LC) n-3 PUFA (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) is inefficient, and thus that intake of some long-chain n-3 PUFA is needed for optimal function. Since the main dietary source of n-3 LCPUFA is seafood, people who do not eat fish frequently tend to have very low intake of DHA and EPA⁴ – they are called the ‘marine’ fatty acids for good reason. This concern is especially acute for pregnant and lactating mothers, since DHA is a major structural component of neurons in the brain and retina, and its incorporation primarily occurs in late gestation and the first few months of postnatal life. Some evidence also suggests that more DHA might be associated with slower early growth, although observed effects have been small and their clinical significance unclear.² Additionally, n-3

LCPUFA are implicated in the development of the immune system, risk for atopic disease, and timing of delivery.

The first big wave of research into health effects of n-3 LCPUFA was focused on supplementation of infant formula. More recently, the focus has moved into the prenatal period, and the literature now includes numerous observational studies of prenatal fish or fatty acid consumption as well as randomized trials. Briefly summarised, while several observational studies have found associations of fish consumption or dietary fatty acid intake with relevant outcomes including lower preterm birth or improved offspring cognition, fewer have found associations of fatty acid biomarkers with these outcomes (e.g. see Oken and colleague⁵). Meta-analyses of randomised trials have not supported benefits of n-3 LCPUFA supplementation for cognitive and visual development,⁶ preterm delivery⁷ or BMI in childhood.⁸

In this issue of *Paediatric and Perinatal Epidemiology*, Mohanty et al.⁹ present observational associations of maternal peri-conceptional shell, lean, fatty, and total fish intake with infant size at birth, based on an analysis of the Omega study cohort. They found that intake of lean fish >1 serving/week (versus <0.2 servings/month) was associated with a 2.2-fold (95% CI 1.2, 4.1) higher risk of low birth weight, whereas shellfish intake of >1 serving/week (versus <0.2 servings/month) was associated with a 0.6 kg/m³ (95% CI 0.0, 1.2) higher mean ponderal index. However, total seafood intake was not related to any outcomes, and most notably the fatty fish - those with the highest DHA and EPA contents – also were not related to the outcomes. Furthermore, maternal red blood cell DHA and EPA concentration, while correlated with diet, was also not related to size at birth.

If we believe that the health effects of fish consumption derive from n-3 LCPUFA, why did this and other studies see no evidence of effects of the fatty acids themselves? Certainly, confounding may be a reasonable explanation; although we did not see strong evidence for sociodemographic confounding in our own prior observational work,⁵ residual confounding certainly can remain. The possibilities for confounding with fish intake go far beyond sociodemographic characteristics, however, which is why the path to the right answer about optimal prenatal fish consumption has been so thorny.¹⁰

One key ingredient missing from this analysis (and many others), is the lack of information on exposure to environmental contaminants – most notably methylmercury. Dietary fish intake is the major source of exposure to methylmercury. Mercury is most famous as a neurotoxicant, and the fetal brain is the most sensitive end-organ for its effects;¹¹ also a very limited literature suggests that prenatal exposure to methylmercury even at low levels might have effects on other birth outcomes including fetal growth and risk for preterm delivery.¹² So, the n-3 LCPUFA and the methylmercury found in the same fish might act on the exact same endpoints.

A relatively understudied possibility is confounding by the beneficial nutrients in fish other than n-3 LCPUFA – e.g. selenium, iodine, vitamin D – although none of these seems to have all of the the health effects attributed to the n-3 LCPUFA. Or maybe it is the n-3 LCPUFA in combination with the other nutrients that confers a benefit, although I am aware of no

sound biological justification for such an argument. Also, we may be using the wrong biomarker, as the fatty acids bound within red cell membranes may not be available to cross the placenta and reach the fetus; although this explanation would not explain the null trials.

I had high hopes that the Salmon in Pregnancy Study (SiPS) would provide some clear answers. In this trial, 123 women with low habitual oily fish consumption were randomly assigned at 20 weeks gestation to continue their habitual diet or were provided with 2 weekly portions of farmed salmon. The study intervention resulted in improved DHA and EPA status in mother and baby, as well as 5 days longer gestation, but no differences in infant size at birth.¹³ While some markers of infant immune response were changed in the intervention group, clinical measures of atopy did not differ.¹⁴ I am not aware of any publications on postnatal growth or cognitive function from this group.

So, has the tide turned on the benefits of prenatal fish or n-3 LCPUFA consumption during pregnancy? Given the small sample size and limited follow up of the SiPS study, I think there is still a role for a well designed and powered randomised trial of fish consumption that addresses multiple relevant endpoints before we conclude that fish and marine fatty acids are not essential components of a pregnant woman's diet. Also, as far as I am aware, none of the randomised trials have begun before pregnancy or early in the first trimester. It is possible that the n-3 LCPUFA must be present from very early gestation or even before conception. Since habitual consumption likely tracks over time, observational studies probably cannot adequately account for the timing of exposure.

Debate about the optimal amount and type of fish intake during pregnancy is ongoing and passionate. To usefully inform policy, it is essential that all studies of dietary fish consumption assess and carefully account for important confounders, including nutrients and contaminants. It is also incumbent on investigators to interpret their own findings within the larger body of the observational and interventional literature.

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Biography

About the author

Dr. Oken's research focuses on the influence of nutrition and other modifiable factors during pregnancy and early childhood on long-term maternal and child health, especially cardiometabolic health and cognitive development. Her work on the toxicant risks and nutrient benefits of prenatal fish consumption has influenced national guidelines for fish consumption during pregnancy. She participated in the deliberations of the FDA's Risk Communication Advisory Committee on methods for effective risk communication of the 2014 draft updated advice for fish consumption. She completed clinical training in internal medicine and pediatrics.

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