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Fish Consumption, Erythrocyte Fatty Acids, and Preterm Birth

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Abstract

Objective—To estimate the association between fish consumption and erythrocyte omega-3 long chain polyunsaturated fatty acids and preterm birth in a high-risk cohort.

Methods—This was an ancillary study to a randomized trial of omega-3 supplementation to prevent preterm birth in women with at least one prior spontaneous preterm delivery. Dietary fish intake was assessed by questionnaire and erythrocyte fatty acids were measured at enrollment (16 to 21 completed weeks of gestation). The association between fish consumption and preterm delivery was modeled with linear and quadratic terms.

Results—The probability of preterm birth was 48.6% among women eating fish less than once a month and 35.9% among women eating fish more often ($p<0.001$). The adjusted odds ratio for preterm birth among women reporting moderately frequent fish consumption (three servings per week) was 0.60 (95% confidence interval 0.38 – 0.95), with no further reduction in preterm birth among women who consumed more than three servings of fish per week. Erythrocyte omega-3 levels correlated weakly but significantly with frequency of fish intake (Spearman $r=0.22$, $p<0.001$); women in the lowest quartile of erythrocyte omega-3 levels were more likely to report consuming less than one fish meal per month (40.3%) than were women in the highest three quartiles (26.3%, $p<0.001$).

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Conclusion—Moderate fish intake (up to three meals per week) prior to 22 weeks of gestation was associated with a reduction in repeat preterm birth. More than moderate consumption did not confer additional benefit. These results support the recommendations of the U.S. Food and Drug Administration and the American Congress of Obstetricians and Gynecologists for fish consumption during pregnancy.

Introduction

Eating fish has been associated with reductions in preterm birth, increased duration of pregnancy, or both reductions in preterm birth and increased duration of pregnancy in some, (1-4) but not all studies;(5-8) most studies have been conducted in unselected or low-risk women. Several reports have found the association between fish consumption and pregnancy outcome to be non-linear. In one study mean birthweight increased up to 3 fish dinners per week, but leveled off or decreased thereafter.(9) In another study, gestational age was shortened and preterm birth was increased(2) only among women who consumed no fish. However, among women who ate fish, frequency of consumption was not associated with these outcomes, suggesting a threshold for fish intake. One study reported that, among women with high marine omega-3 fatty acid consumption, the ratio of omega-3 fatty acids to arachidonic acid in erythrocytes was not associated with shortened gestation, while among women with lower fish consumption gestation was prolonged with increases in this ratio. These results suggest that any benefit of increasing omega-3 long chain polyunsaturated fatty acid levels may occur only in gravidas with chronically low intake and have no impact in those with chronically high intake.(10)

We recently conducted a randomized, double-blind placebo-controlled clinical trial of omega-3 supplementation, beginning at 16-21 weeks' gestation, for the prevention of recurrent preterm birth in a group of high risk women.(11) We were interested in estimating the association between omega-3 fatty acids early in pregnancy prior to study enrollment and preterm birth, and if this exposure modified the response to supplementation. Omega-3 exposure was estimated by dietary history of fish intake (including tuna and shellfish) at study enrollment and by erythrocyte omega fatty acid levels collected at study enrollment.

Materials and Methods

The data for this report are from the NICHD Maternal-Fetal Medicine Units Network randomized clinical trial of omega-3 long chain polyunsaturated fatty acid supplementation to prevent recurrent preterm birth.(11) The trial recruited (at 13 Network centers from January 2005 to October 2006) women who had a history of at least one previous spontaneous singleton preterm birth and randomized 434 women to receive daily supplementation of 1200 mg eicosapentaenoic acid (EPA, 20:5n-3) and 800 mg of docosahexaenoic acid (DHA, 22:6n-3); and 418 to matching placebos, beginning at 16 to $21^{6/7}$ weeks' gestation and continuing until $36^{6/7}$ weeks' gestation or delivery, whichever occurred first. As part of the trial, all enrolled women also received weekly injections of 17 alpha-hydroxyprogesterone caproate. Women currently taking fish oil or omega-3 supplements were ineligible for the trial; detailed inclusion and exclusion criteria are reported elsewhere.(11) Delivery before 37 completed weeks' gestation occurred to 37.8% and 41.6% of women randomized to omega-3 supplementation and placebo, respectively. (11) Omega-3 supplementation was associated with a significant change in plasma levels of DHA, EPA and arachidonic acid from baseline to 25-28 weeks' gestation compared with placebo.(11) The study was approved by the IRBs of the biostatistical coordinating center and all participating clinical centers and this secondary analysis was determined to be exempt from IRB review by the Office of Human Subjects Research, NIH; all enrolled women gave written informed consent.

At randomization, women underwent an interview, including a four item food frequency questionnaire designed to assess fish intake during the time from last menstrual period to randomization. The four items were dark-meat fish, canned tuna, other fish and shellfish; (12) response options for frequency of consumption were never or <1 serving per month, 1-3 servings/month, 1 serving/week, 2-4 servings/week, 5-6 servings/week, 1 serving/day, 2-3 servings/day, 4-5 servings/day, and 6 or more servings/day. In this analysis, intake of each type of fish was converted to servings per week, and all 4 were summed and considered as fish intake. When the response option was a range, the midpoint was used; 1-3 servings/month was assumed to represent 0.5 servings/week; never or less than 1 serving/month was assumed to represent 0 servings/week. Due to small numbers, the 4 individual types of fish were not considered separately. Women received no specific dietary advice as part of this study, although taking non-study omega-3 supplements or prenatal vitamins containing omega-3 long chain polyunsaturated fatty acids was prohibited during the trial.

Blood was collected at randomization, before dispensing study drug. Erythrocytes were separated from plasma, snap frozen and shipped to a central laboratory for fatty acid analysis by gas chromatography. Individual polyunsaturated fatty acids were assayed using previously-described methods and expressed as percent of total fatty acids.(13) Erythrocyte measures studied were the sum of omega-3 fatty acids, DHA and EPA; the sum of omega-6 polyunsaturated fatty acids, linoleic acid (LA) and arachidonic acid (AA); and the ratio of these 2 sums.

Gestational age at birth was determined from the sonographically-confirmed gestational age at randomization and the elapsed time from randomization to delivery;(11) preterm birth was defined as birth at <37 completed weeks (259 days) of gestation. The associations between preterm birth and fish intake and erythrocyte polyunsaturated fatty acids were evaluated graphically by LOESS plots.(14) LOESS (locally weighted scatterplot smoothing) is a form of data smoothing and plotting that performs locally-weighted regression of preterm birth on fish intake at every point of fish intake and combines the regressions to form a curve. It is thus a ‘nonparametric’ regression that does not constrain the association between fish intake and preterm birth to take any prespecified mathematical relationship. We employed this technique to evaluate whether the association between preterm birth and fish intake appeared linear, and if not then how best to model the association. Continuous variables were compared using the Wilcoxon or Kruskal-Wallis test and categorical variables were compared using the chi-square test. When categories were ordered, significance was assessed with the Cochran-Armitage test for trend.(15) We tested whether the effect of omega-3 supplementation on preterm birth differed according to baseline erythrocyte fatty acid concentration using the Breslow-Day test (16). Multiple logistic regression was used to adjust the association between fish intake and preterm birth for confounders selected *a priori*: study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index, race and ethnicity. When we considered linear and quadratic terms in evaluation of dose-responses, we used the likelihood ratio test with 1 and 2 degrees of freedom, respectively, to determine statistical significance. Tests for interaction between fish consumption as both a linear and quadratic term and study treatment assignment utilized the likelihood ratio test with 2 degrees of freedom. Statistical significance was defined as a two-tailed p-value <0.05, with no adjustment for multiple comparisons. Data were analyzed using SAS (SAS Institute, Cary, NC) and R (www.r-project.org).

Results

Gestational age at delivery and baseline (16-21 completed weeks) fish consumption were available for all 852 randomized women. There were 253 (29.7%) women who reported consuming fish never or less than once per month; 524 (61.5%) who consumed 0.5 – 3 servings per week, and 75 (8.8%) who consumed fish more than 3 times per week. The association between fish consumption and characteristics of the study population is presented in Table 1. Because the association between fish consumption and the study outcomes appeared U-shaped (see below), fish consumption is presented in Table 1 as none or <1/month, 0.5 – 3 servings/week, and >3 servings/week. However, in subsequent modeling, fish consumption was considered as a continuous variable. African-American and Hispanic women ate fish more frequently than non-African American and non-Hispanic women, respectively. Fish consumption did not differ significantly by any of the other characteristics in Table 1.

Preterm birth occurred to 48.6% of the 253 women who ate fish once/month or less as reported at 16-21 weeks' gestation, versus 35.9% of the 599 women who ate fish more often ($p<0.001$). LOESS plots of the association between servings/week of fish and preterm birth (Figure 1) demonstrated that the probability of preterm birth declined with increasing fish consumption and then increased again, although few women ate fish more than several times/week and thus the confidence bands around the association were wide for women eating fish very frequently. The shape of the association was similar among women assigned to omega-3 supplements and to placebo (data not shown). Because of this U-shape, fish intake was modeled as both a linear and a quadratic term. In unadjusted analysis, both linear and quadratic terms for fish intake were statistically significant ($p<0.001$ and $p=0.001$, respectively), and a model with a term for $(\text{number of fish servings})^2$ fit the data significantly better than one containing only a linear term for number of fish servings. In addition the p-value for the 2 terms taken together was also significant ($p=0.002$).

In a model adjusting for study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index, race and ethnicity, the combination of linear and quadratic terms for fish consumption in the first half of pregnancy remained statistically significant ($p=0.02$). Both the linear ($p=0.01$) and quadratic terms ($p=0.008$) were individually statistically significant and were therefore retained in calculation of odds ratios. Furthermore, the association between fish consumption and preterm birth was similar among women receiving omega-3 supplementation or placebo (p-value for the interaction between treatment and fish consumption=0.95).

The modeled odds ratios and their 95% confidence intervals for the association between total fish consumption and preterm birth are presented in Table 2. Note that the odds ratios in Table 2 are derived from modeling the entire dose-response curve for fish consumption and preterm birth rather than directly from the individual reported amounts. Increasing fish consumption was associated with a decreasing odds ratio for preterm birth, reaching a predicted minimum of 0.6 at approximately 3 servings of fish per week. The modeled odds ratio rose as fish consumption increased beyond this point, reaching the value observed in non-consumers at approximately 7 servings per week, although the confidence limits were wide.

Red cell fatty acid values at baseline were available for 701 (82.3%) of the 852 women. The mean RBC omega-3 fatty acids as a percentage of all fatty acids was 3.55% for women randomized to omega-3 supplements and 3.73% for women randomized to placebo ($p=0.59$). A LOESS plot of the association between preterm birth and erythrocyte DHA

+EPA was generated (not shown). Due to the irregularity of the curve, erythrocyte fatty acids were analyzed as quartiles. Table 3 shows the association between quartiles of erythrocyte DHA+EPA and preterm birth. Women in the lowest quartile had an increased risk of preterm birth (47.2%) compared with women in the 3 highest quartiles combined (38.1%, p=0.03) but there was no consistent trend among women in the higher quartiles; the overall association (by chi-square test) between all 4 quartiles of erythrocyte DHA+EPA and preterm birth was of borderline statistical significance (p=0.054). After adjusting for study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index, race and ethnicity the odds ratio for preterm birth among women in the lowest quartile compared with women in the 3 highest quartiles combined was 1.41 (0.97 – 2.05). When the top 3 quartiles were compared individually to the lowest quartile, the adjusted odds ratio for women in quartile 2 indicated a statistically significant reduction, but quartiles 3 and 4 were not significantly different from quartile 1 (Table 3).

Compared with placebo, the effect of omega-3 supplementation was similar among women in the lowest quartile of erythrocyte omega-3 (45.2% versus 48.9%, respectively, p=0.63) and among women in the top 3 quartiles of erythrocyte omega-3 (35.7% versus 40.6%, respectively, p=0.24). The p-value for interaction between treatment assignment and erythrocyte omega-3 was 0.86 (Breslow-Day test for homogeneity of the odds ratios).

The odds ratios for quartiles of erythrocyte omega-6 fatty acids and preterm birth were not statistically significant. Results for quartiles of the omega3/omega-6 ratio were similar to those for omega-3, but of slightly smaller magnitude. In no case did the interaction between treatment assignment and any of the measures of erythrocyte fatty acids (omega-3, omega-6 or the ratio of omega-3/omega-6) approach statistical significance (lowest p-value for interaction=0.27).

Erythrocyte DHA+EPA levels correlated weakly but significantly with reported frequency of fish intake (Spearman r=0.22, p<0.001). Women in the lowest quartile of DHA+EPA were more likely to report consuming fish never or less than once/month (40.3%) than were women in the highest 3 quartiles (26.3%, p<0.001). When actual omega-3 intake was estimated according to the formula of Hu,(12) the correlation between omega-3 intake and erythrocyte DHA+EPA was essentially identical (Spearman r=0.22, p<0.001).

Discussion

Our findings may be summarized as follows: 1) In our high-risk population of women with a prior preterm birth, those who reported the lowest fish consumption at 16-21 weeks' gestation were at elevated risk of recurrent preterm birth compared with comparable women who ate fish more frequently. 2) However, the “dose-response” of fish consumption for preterm birth was statistically significantly non-linear. The lowest occurrence of preterm birth was seen among women who ate fish approximately 2-3 times/week. More frequent fish consumption was not associated with further reductions in preterm birth, and our data indicate that preterm birth might become more common with further increases in fish consumption, although our estimates were imprecise. Similarly, the lowest occurrence of preterm birth was observed among women in the second quartile of erythrocyte omega-3 levels. 3) The lack of benefit of omega-3 polyunsaturated fatty acid supplementation was similar regardless of either baseline fish consumption or erythrocyte omega-3 concentration.

The association between low fish consumption and preterm birth was of similar magnitude among women assigned to omega-3 supplementation (47.6% versus 33.9%, p=0.008) or placebo (49.6% versus 38.1%, p=0.03); the Breslow-Day p-value for homogeneity was 0.74.

(11) Why should moderate fish intake and higher erythrocyte omega-3 concentration in the first half of pregnancy be associated with a reduced recurrence of preterm birth while omega-3 supplementation did not reduce the recurrence? One reason for our discrepant findings might be the timing of supplementation. Our erythrocyte omega-3 measures were obtained at 16 to $21^{6/7}$ weeks' gestation and reflect omega-3 status over two to three months; (18) the fish questionnaire asked about consumption from conception to randomization. Thus, both measures reflect exposure around conception and during early gestation. In contrast, supplementation began from 16 to $21^{6/7}$ weeks' gestation. Even though supplementation raised plasma omega-3 concentrations(11) it is possible that low early-pregnancy levels are associated with preterm birth and supplementation occurred too late to have an impact. Olsen, et al(2) also noted that seafood consumption assessed at 16 weeks' gestation, but not at 30 weeks(7) was associated with preterm birth, providing support for this explanation.

A second possible explanation for the result is that another nutrient contained in fish, thus sharing a dietary source with DHA and EPA, is responsible for the reduction in preterm birth. Several types of fish are rich dietary sources of vitamin D,(19) deficiency of which has been associated with preterm birth(20) and preeclampsia.(21) A third explanation is that supplementation does not alter dietary habits and individuals who do not eat seafood may have higher dietary intake of omega-6 fatty acids,(12) the precursors of the uterotonic prostaglandins, leukotrienes and thromboxanes involved in cervical ripening and myometrial contraction.(22) A fourth explanation is that there may be unmeasured characteristics of women who do not consume seafood (or consume very little dietary DHA and EPA) that are the true cause of the increase in preterm birth. We found few differences between women who ate fish rarely/never, occasionally or frequently and Oken, et al(23) reported similar results in a cohort of pregnant women in Boston. Nevertheless, our measure of socioeconomic status was limited to education and we did not collect data on other components of diet, behavioral factors such as physical activity, psychosocial characteristics or genital tract infection that might be associated with fish consumption and preterm birth.

We also observed that preterm birth may increase at high levels of fish consumption, and failed to decrease further beyond the second quartile of erythrocyte omega-3 long chain polyunsaturated fatty acids. Our results of a non-linear association between fish intake and preterm birth are similar to those of Olsen, who reported that gestational age was shorter and preterm birth increased(2,9) only among women who consumed little or no fish, but among women who ate fish, the actual frequency of consumption was not strongly associated with these outcomes. Olsen also reported that mean birthweight increased with increasing fish consumption up to 3 meals per week, but leveled off or decreased with more frequent consumption.(9) In addition to being a source of nutrients, many types of fish contain environmental contaminants such as methylmercury(24) and polychlorinated biphenyls(25) which have been associated in some studies with shortened gestation.(26) Fish is a rich source of protein, and high-protein supplementation was associated with increased occurrence of preterm birth in a randomized trial conduced among women in Harlem.(27)

Our study has limitations. In addition to having few measures of socioeconomic factors that might be associated with fish consumption, we collected no data on diet other than frequency of fish consumption up to the time of randomization; nor did we assess biomarkers of environmental contaminants or nutrients other than omega-3 and omega-6 fatty acids. Thus we cannot evaluate what other components or correlates of fish intake might account for the associations we observed with preterm birth. Fish consumption is likely to reported with error, although since the report was obtained before the outcome of the pregnancy was known the error is likely to be unbiased with respect to preterm birth. As part of the trial protocol, all women received weekly injections of 17 alpha-

hydroxyprogesterone caproate and all women had a previous spontaneous preterm birth. Therefore, our population was at unusually high risk of having a preterm infant and our results may not apply to other populations of pregnant women.

However, from a clinical perspective our data suggest that DHA and EPA supplementation cannot take the place of fish consumption with respect to any benefits there might be for preterm birth. Our results also support the recommendations of both the American Congress of Obstetricians and Gynecologists (28) and the Food and Drug Administration(29) for consumption of up to 2 servings of fish per week.

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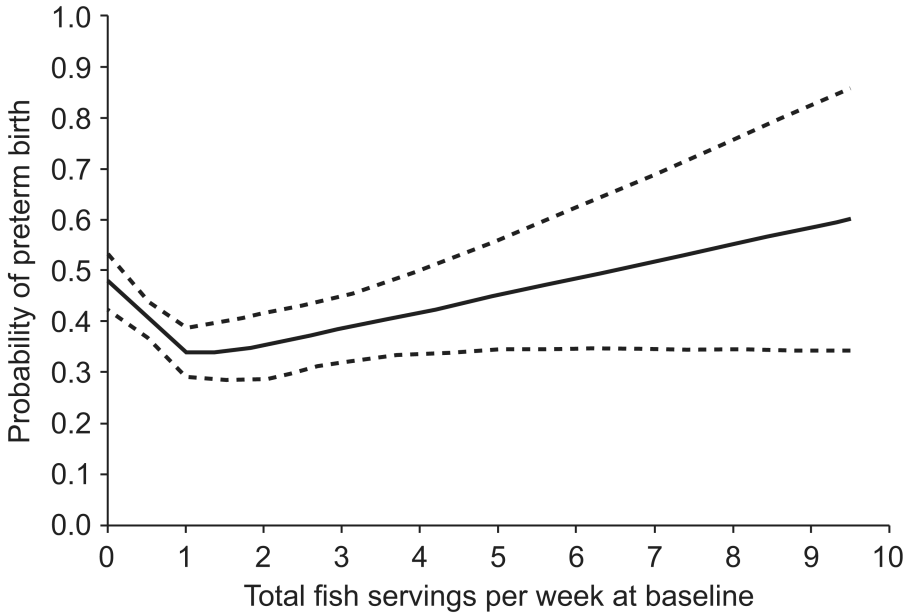

Figure 1. Probability (solid line) and 95% confidence limits (dashed lines) of preterm birth by frequency of fish consumption

Table 1

Fish Consumption According to Selected Characteristics

		Fish consumption (servings)			
Characteristic	**N**	**<1/month**	**0.5 – 3 per week**	**>3 per week**	**p-value**
Treatment					0.60
Omega3	434	28.6%	63.1%	8.3%	
Placebo	418	30.9%	59.8%	9.3%	
Smoking					0.24
Yes	136	35.3%	55.2%	9.6%	
No	716	28.6%	62.7%	8.7%	
Education (years)					0.06
<12	164	26.2%	62.2%	11.6%	
12	237	28.3%	59.9%	11.8%	
>12	451	31.7%	62.1%	6.2%	
Race/ethnicity					<0.001
African-American	288	20.1%	67.0%	12.9%	
Other	563	34.6%	58.6%	6.8%	
Hispanic ethnicity					0.014
Yes	121	22.3%	62.8%	14.9%	
No	730	31.0%	61.2%	7.8%	
Age (years, mean(SD))		27.1 (5.6)	28.0 (5.6)	27.3 (5.7)	0.09
BMI (kg/m^2 mean(SD))		25.9 (7.0)	26.9 (6.8)	26.9 (7.3)	0.10
Number of previous spontaneous preterm infants (mean (SD))		1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	0.96
Gestation of most severe prior preterm infant (weeks, mean (SD))		30.0 (4.7)	30.2 (4.7)	29.5 (5.1)	0.48

Table 2

Adjusted* Odds Ratios for Preterm Birth by Number of Servings of Fish Eaten per Week

	Preterm Birth		
Servings of fish	**Odds Ratio**	**95% CI**	**p-value**
<1 per month	1	-	-
1 per week	0.76	0.61 - 0.94	0.01
2 per week	0.64	0.45 - 0.92	0.02
3 per week	0.60	0.38 - 0.95	0.03
4 per week	0.62	0.37 - 1.04	0.07
5 per week	0.70	0.40 - 1.24	0.23
6 per week	0.89	0.46 - 1.71	0.72
7 per week	1.24	0.55 - 2.82	0.60
8 per week	1.93	0.65 - 5.69	0.24

*Adjusted for study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index and ethnicity. Fish consumption modeled as linear and quadratic terms.

Table 3

Probability and Adjusted* Odds Ratio of Preterm Birth by Quartiles of Erythrocyte DHA+EPA**

	Quartile of DHA+EPA (1=lowest, 4=highest)				
	1 (n=176)	**2 (n=175)**	**3 (n=175)**	**4 (n=175)**	**p-value*****
	N (percent preterm)				
% of total fatty acids	<3.052	3.052–3.719	3.723–4.426	>4.426	
Number (%) of preterm infants	83 (47.2%)	61 (34.9%)	76 (43.4%)	63 (36.0%)	0.054
Adjusted odds	1.00	0.59	0.84	0.71	
Ratio (95% CI)		(0.37–0.94)	(0.53–1.32)	(0.45–1.15)	0.14

*Adjusted for study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index and ethnicity.

**DHA= docosahexaenoic acid, EPA= eicosapentaenoic acid, as percentage of total erythrocyte fatty acids.

***p-value for whether percentage preterm birth differs by erythrocyte DHA+EPA, or for whether addition of erythrocyte DHA+EPA significantly improves the adjusted model.

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