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Maternal obesity, fish intake and recurrent spontaneous preterm birth

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Abstract

Objective: Moderate fish intake in early pregnancy is associated with decreased risk of preterm birth (PTB). Obesity during pregnancy is characterized by inflammation and insufficiency of essential fatty acids. The objective of this study was to measure the association between fish intake during pregnancy and risk of recurrent spontaneous (s)PTB among lean, overweight and obese women.

Design: This is secondary analysis of a randomized controlled trial of omega-3 fatty acid supplementation for recurrent PTB prevention, 2005–6. The primary exposure was fish intake at time of enrollment (16–22.9 weeks gestation). The primary outcomes were sPTB <37 weeks and sPTB < 35 weeks. Maternal pre-pregnancy body mass index was treated as an effect modifier.

Subjects: 852 women were included, 47% were lean, 25% overweight and 28% obese.

Results: In this cohort, among lean, but not overweight or obese women, ≥ 1 serving of fish per week was associated with decreased frequency of sPTB < 37 weeks compared with < 1 serving of fish per week (45.1 vs. 27.5%, $p = 0.001$) and spontaneous PTB < 35 (21.4 vs 11.6%, $p = 0.01$). In adjusted models, as fish intake increased, the predicted probability of sPTB decreased in lean women but increased in overweight and obese women (p for interaction <0.10).

Conclusion: Fish intake was associated with lower probability of sPTB in lean women and higher probability in obese women. These findings warrant further investigation to understand the dietary or metabolic factors associated with obesity that may modulate benefit of fish intake during pregnancy.

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Keywords

maternal obesity; preterm birth; fish intake; omega 3 fatty acids

Introduction

The American College of Obstetricians and Gynecologists (ACOG) recently revised guidelines to recommend 2–3 servings of low mercury fish and/or seafood per week for pregnant women and those who may become pregnant.[1] In observational studies, moderate fish intake (1–3 serving/weeks) has been associated with decreased risk of PTB[2, 3] and improved childhood neurodevelopmental outcomes.[4] However, randomized controlled trials (RCTs) of fish oil supplementation among women at high risk of recurrent PTB have shown conflicting results.[2, 5] Fish and fish oil intake have been hypothesized to improve perinatal outcomes through immunomodulation and anti-inflammatory characteristics of omega-3 fatty acids.[6–9] Maternal obesity during pregnancy is associated with a chronic, pro-inflammatory state and a circulating insufficiency of certain antioxidant dietary components, particularly essential fatty acids.[10–13] Thus, there is biologic plausibility that fish intake and omega-3 supplementation may impact pregnancy outcomes of obese women differently than non-obese women.

Given the paucity of data surrounding the relationship between maternal BMI, fish intake, omega-3 fatty acid status and pregnancy outcomes, we sought to examine whether maternal obesity or overweight modifies the association between fish intake and PTB risk. We hypothesized that obese and overweight women would need higher fish intake to obtain similar PTB risk reduction compared to lean women.

Methods

Study design

This is a secondary analysis of the Maternal Fetal Medicine Unit’s Omega-3 trial. This was a randomized, double-blind, placebo controlled trial of omega-3 fatty acid supplementation among women with one or more prior spontaneous PTB. The details of this study are described elsewhere.[2] Briefly, this trial was conducted at 13 U.S. sites from January 2005-October 2006. Women were included in the trial if they had a previous spontaneous PTB of a singleton infant between 20.0–36.9 weeks or preterm premature rupture of membranes (PPROM). Women were recruited for the trial at 16–22.9 weeks gestation. Women were excluded from the trial for major fetal anomaly, more than 500 mg of fish oil supplementation in the previous month, allergy to fish, major maternal medical co-morbidity, planned or current cerclage or planned delivery at an outside institution or prior to 37 weeks. All women in this trial were receiving weekly 250 mg 17-α progesterone injections for PTB prevention. Women were randomized to daily placebo or to the study drug, 1,200 mg eicosapentaenoic acid (EPA) and 800 mg docohexaenoic acid (DHA), for a total of 2000 mg of omega-3 long chain polyunsaturated fatty acids. At time of randomization and at 25–28 weeks, women were asked detailed information on frequency of fish intake using the same tool at both time points. At randomization, women were asked about fish intake since the beginning of pregnancy until randomization. At 25–28 weeks, women asked about fish intake from randomization. Questions were developed specifically for this study. During data collection, women reported frequency of serving of any type of fish as never or < one/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day or ≥6/day. After data collection, all responses were converted to servings/week. The questionnaire also assessed types of fish women consumed at randomization including canned tuna, dark meat fish, shellfish and other fish. Women self-reported their pre-pregnancy weight and height was abstracted from the medical chart and used to calculate pre-pregnancy BMI. We included women with known pre-pregnancy BMI, early pregnancy fish intake and gestational age at delivery.

Plasma samples (at randomization) were snap frozen and shipped to a central laboratory for individual measurement using previously described methods.[14] The concentrations of four omega-3 fatty acids (EPA, DHA, alpha-Linolenic acid, eicosatrienoic acid). The concentrations of four n3 FAs (EPA, DHA, alpha-Linolenic acid, eicosatrienoic acid) were assayed. Omega-3 fatty acids were calculated by adding the individual values of the constituent fatty acids.

Statistical analysis

Our primary exposure was self-reported fish intake (servings/week) in early pregnancy (< 22 weeks gestation) before randomization to study supplement. Our primary outcomes were spontaneous PTB < 37 weeks and spontaneous PTB <35 weeks. We categorized maternal pre-pregnancy BMI by World Health Organization standards as lean (BMI < 25 kg/m^2), overweight (25–29.9 kg/m^2) or obese (≥ 30 kg/m^2), and BMI category was treated as an effect modifier.

Klebanoff *et al* have previously described maternal demographics and clinical characteristics in this cohort by fish intake in early pregnancy.[6] To inform this analysis, we compared maternal demographics, clinical characteristics and fish intake in early pregnancy by BMI category. Categorical variables were assessed using chi square tests. We assessed normality of continuous variables using the Shapiro-Wilk test. We used ANOVA (for normally distributed outcomes) and Kruskal-Wallis (for non-normally distributed outcomes) to assess differences in continuous outcomes, as appropriate. To assess the association between fish intake, BMI and PTB, we constructed scatterplots for each BMI category. We plotted servings per day of fish on the x axis, and probability of PTB on the Y axis, using LOESS (local polynormial regression) curves. This methodology was previously utilized in a planned secondary analysis of this trial.[6]

Based on the appearance of the scatterplot and inflection points, we quantified the association between fish intake and outcomes using an adjusted multivariable logistic regression model with an interaction term between fish intake and BMI category. Interaction terms were considered significant if $p<0.1$.[15] Based on the previous secondary analysis of this trial which found that age, race, education, smoking in early pregnancy (categorically), number of prior previous PTB and gestational age at earliest PTB (continuously) were confounders of associations between fish intake and spontaneous PTB, we included these covariates in our model *a priori*.[6] Treatment group assignment (active supplement/placebo) was examined as an effect modifier, but the interaction p was not indicative of significant effect modification (p>0.1), so all analyses are presented with treatment groups combined, with additional adjustment for treatment group. We then determined predicted probabilities and 95% confidence intervals (CI) of PTB by fish intake within each BMI category.

We assessed the correlation of fish intake in early pregnancy (before randomization) and in late pregnancy (from randomization to 25–28 weeks) within each BMI category to determine if fish intake changed over course of pregnancy. We also assessed the correlation of early pregnancy fish intake and early pregnancy erythrocyte omega-3 fatty acid (as a percentage of all fatty acids) using Spearman's correlations (due to non-normal distribution of omega-3 fatty acid).

We used adjusted linear regression to assess the association between fish intake and omega-3 fatty acid stratified by BMI group. We then performed multivariable logistic regression to assess if omega-3 fatty acid and fish intake in early pregnancy were associated spontaneous PTB < 37 weeks, after adjustment for confounders. We tested whether fish intake modified the association of omega-3 fatty acids and PTB < 37 weeks stratified by BMI group using the Breslow Day test.

Analyses were performed using Stata 14.0 (College Station, Texas).

Results

Population

All women (n=852) in the parent study met inclusion criteria for our study. In the entire cohort, 47% of women were lean, 25% were overweight, and 28% were obese. Compared with lean women, obese and overweight women were more likely to be non-Hispanic black, have less than 12 years of education and to have gestational diabetes in the current pregnancy (p<0.001, Table 1). In their prior PTB, obese and overweight women had a lower median gestational age compared with lean women (p=0.002). The majority of women (70.3%) reported consuming some fish since the beginning of pregnancy; and nearly half of all women reported consuming at least one serving of fish per week. There was no difference by BMI category in women's intake of tuna, dark meat or shellfish per week. However, obese women had greater intake per week of "other fish" compared with overweight and lean women. "Other fish" may have included non-oily fish (e.g. cod, haddock, Pollack) and processed/fried fish, however, further characterization is not available.

Fish intake and PTB

Among lean women, at least one serving of fish per week (compared to less than one serving of fish per week) was associated with decreased frequency of spontaneous PTB < 37 weeks (<1 serving: 45.1% vs. ≥ 1 serving: 27.5%, p = 0.001) and spontaneous PTB < 35 weeks (21.4 vs 11.6%, p =0.01) (Table 2). However, neither the frequency of spontaneous PTB < 37 weeks nor < 35 weeks varied by fish intake among overweight or obese women.

In multivariable logistic regression models for spontaneous PTB, the likelihood ratio test for models with and without interaction terms between maternal BMI group and fish intake was significant (p=0.03). In pairwise comparisons, interaction term was significant for obese compared with lean women (p=.04), but not overweight women compared with lean women (p=0.19). In other words, the association between fish intake and spontaneous PTB is different for lean and obese women but not between lean and overweight women. To increase interpretability of our models, we present the predicted probability of spontaneous preterm < 37 weeks by fish intake among lean, overweight and obese women (Figure 1). Among lean women, increasing fish intake was associated with a lower predicted probability of spontaneous PTB<37 weeks. However, among obese women, the relationship was in the opposite direction – as fish intake increased, predicted probability of PTB < 37 weeks also increased. For example, among lean women who consumed no fish in early pregnancy, the predicted probability of spontaneous PTB < 37 weeks was 39% (95% CI 33–46%) compared with 31% (95% CI 23–39%) for overweight women and 29% (95% CI 21–37%) for obese women. At two servings of fish per week, predicted probability of spontaneous PTB was similar among lean (32%, 95% CI 24–38%), overweight (30%, 95% CI 23–38%) and obese women (33%, 95% CI 27–42%). However, at four servings of fish per week, predicted probability of spontaneous PTB continued to decrease among lean women (25%, 95% CI 14–35%), stayed approximately the same among overweight (30%, 95% CI 15–45%) and increased among obese women (41%, 95% CI 26–56%). These differences were more pronounced for predicted probabilities of spontaneous PTB < 35 weeks (Figure 2).

We further evaluated the association between fish intake and systemic fatty acid concentrations. Measures of fish intake at baseline and at the second study visit (25–28 weeks) were highly correlated (rho =0.66, p <0.001) and were similar in each BMI category. Of the entire cohort, 82% (n= 696) of women had available erythrocyte omega-3 fatty acid concentrations at baseline. Fish intake and erythrocyte omega-3 concentrations at baseline were correlated overall (rho = 0.22, p <0.001). When we stratified by BMI, we found correlations among lean women (rho=0.28, p<0.001) and overweight women (rho=0.17, p=0.03) but not among obese women (rho=0.12, p=0.10). In adjusted linear regression, higher fish intake was associated with higher omega-3 fatty acid concentrations in each BMI group, but to a lesser extent among obese women (lean β 0.23, 95% 0.11–0.35; overweight β 0.18 95% CI 0.03–0.34; obese β 0.13 95% CI 0.01–0.25). Although fish intake was associated with omega-3 fatty acid concentrations at baseline, these concentrations were not associated PTB in any BMI category (interaction terms all p>0.1).

Discussion

In women with a history of a prior spontaneous PTB, we found that increasing fish intake appears to have a protective association with recurrent PTB among lean women only. Among lean women, higher fish intake was associated with a reduced predicted probability of PTB < 37 weeks; among obese women greater fish intake was associated with higher predicted probability of PTB. These results are contrary to our initial hypothesis. With a higher dose of fish, lean women continued to have a decrease in recurrent PTB, overweight women had no change in recurrent PTB, and obese women had higher recurrent PTB risk.

These differences could be explained by underlying maternal metabolic milieu, or differences in type of fish consumed by lean, overweight and obese women.

Our findings confirm and extend earlier work on associations between fish intake and recurrent PTB. Previous studies, including the planned secondary analysis of this parent study, have found that moderate intake of fish in early pregnancy is associated with decreased risk of any PTB.[63, 7, 16] However, while the majority of these studies control for BMI, none of these studies investigate the extent to which BMI modifies the association between fish intake and PTB.

We and others have described the metabolic differences between obese and lean pregnant women, including higher inflammation, oxidative stress and lower omega-3 fatty acids and other nutritional antioxidant defenses.[10–13, 17] It is possible that the benefits of fish intake did not outweigh these metabolic risk factors in obese women, but did improve overall metabolic health in lean women. This is supported by our observation that fish intake in early pregnancy is associated with erythrocyte omega-3 fatty acid concentrations in lean and overweight, but not obese women. However, omega-3 concentration was not associated with odds of PTB, suggesting that fish intake may be acting through a pathway other than omega-3 fatty acid levels. It has been postulated that other constituents of fish, such as selenium, iodine or vitamin D, may cumulatively or individually confer benefit.[17] Another potential explanation of our findings was that although obese women ate more fish in early pregnancy than lean women, the types of fish or fish preparations that obese women consumed did not have anti-inflammatory properties or metabolic health benefits. For example, farmed salmon cooked with dry heat (grilling, pan-frying, broiling, oven baking) contains 4023 mg of omega-3 fatty acids and 1185 mg of omega-6 fatty acids while fried catfish contains 501 mg of omega-3 fatty acids and 2276 omega-6 fish acids.[18, 19, 19] The omega-6 to omega-3 fatty acid ratio is an established marker of systemic inflammatory status.[20, 21] The metabolism of omega-6 fatty acids (linoleic acid and arachidonic acid) increases the release of pro-inflammatory eicosanoids into systemic circulation; in contrast, metabolism of omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) increases anti-inflammatory lipid mediators.[22] It is plausible that if obese women are consuming higher amounts of fish that are higher in omega-6 FAs (e.g. farmed tilapia or catfish) and/or cooking with methods such as frying in omega-6 rich oils, this may increase their omega-6/omega-3 ratio and potentially explain the observed association of fish intake and PTB in obese women. Future studies should seek to delve more deeply into the metabolic and dietary mechanisms that may underlie the observed associations.

Our study has several strengths. The parent study included a racially and geographically diverse population of women with a history of PTB receiving standard-of-care 17-alpha hydroxyprogesterone caproate, increasing generalizability. The design of the parent study allowed detailed prospective collection of data regarding our exposure and outcome, including careful differentiation between spontaneous and indicated PTB. We have complete data on fish intake, pre-pregnancy BMI and gestational age at delivery for all women included in the trial, reducing the risk of selection bias. Perhaps our study's most important strength is our inclusion of maternal BMI as an effect modifier; other studies assessing the relationship between fish intake and PTB have either not included maternal BMI in their models or adjusted for BMI as confounder.[2,5,7,20,21] In contrast to other studies of fish intake and PTB,[3, 7, 16] we also have baseline assessments of omega-3 erythrocyte percentage.

Our findings must be interpreted in the context of the study design. Because this cohort of women all had a prior spontaneous PTB, these results may not be generalizable to women who have not had a previous PTB. Data on fish intake were self-reported. We do not have information about how fish were prepared (ie baked, broiled, fried) or types of oils used. Our study also did not assess mercury levels, which have been associated with PTB in other studies.[16] We also do not have detailed information about other foods such as processed fatty foods and sugars or indicators of overall diet quality including amounts of fresh fruit and vegetable intake, which may mediate the associations that we observed.

We found that among lean pregnant women at high risk of recurrent PTB, higher fish intake was associated with a lower risk of PTB. This protective association was not observed among overweight and obese women. Our study does not address the pathophysiological mechanism underlying the effect modification of maternal BMI on fish intake and recurrent spontaneous PTB. We suggest that, in light of our findings, future studies may seek to understand these mechanisms including the contribution of certain types of fish or other dietary components to an altered omega3/6 ratio, the role of mercury and other environmental contaminants and nutrients such as vitamin D, iodine and selenium. Our findings suggest that future studies should carefully examine dietary and metabolic factors associated with obesity to better understand how maternal obesity may affect risk for spontaneous PTB. If our findings are replicated, this research could support more targeted dietary recommendations regarding choice of fish and fish preparation for obese women.

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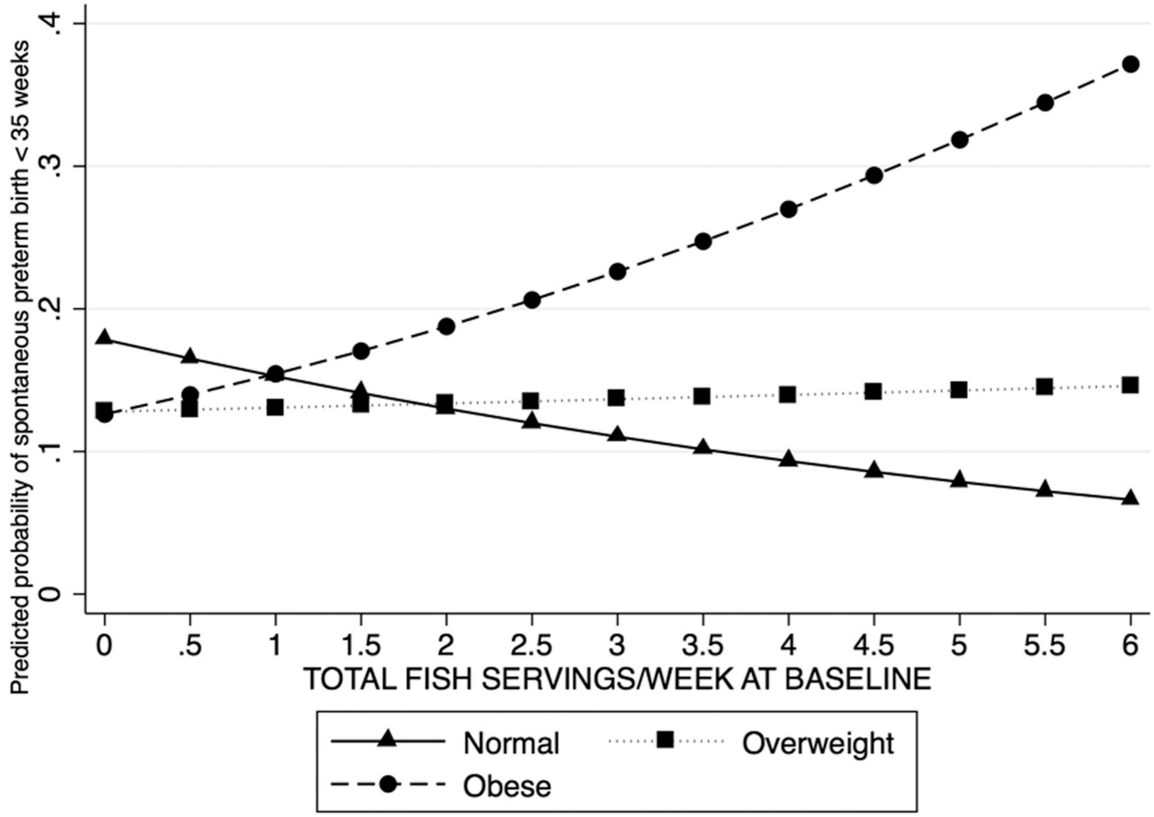

Figure 1:
Adjusted predicted probability of spontaneous preterm birth <35 weeks and fish intake among lean, overweight and obese women (n=852). Models include maternal age, race, education, smoking, number of prior previous PTB, gestational age at earliest PTB and treatment group, with predictors held at the mean. P value for interaction = 0.04

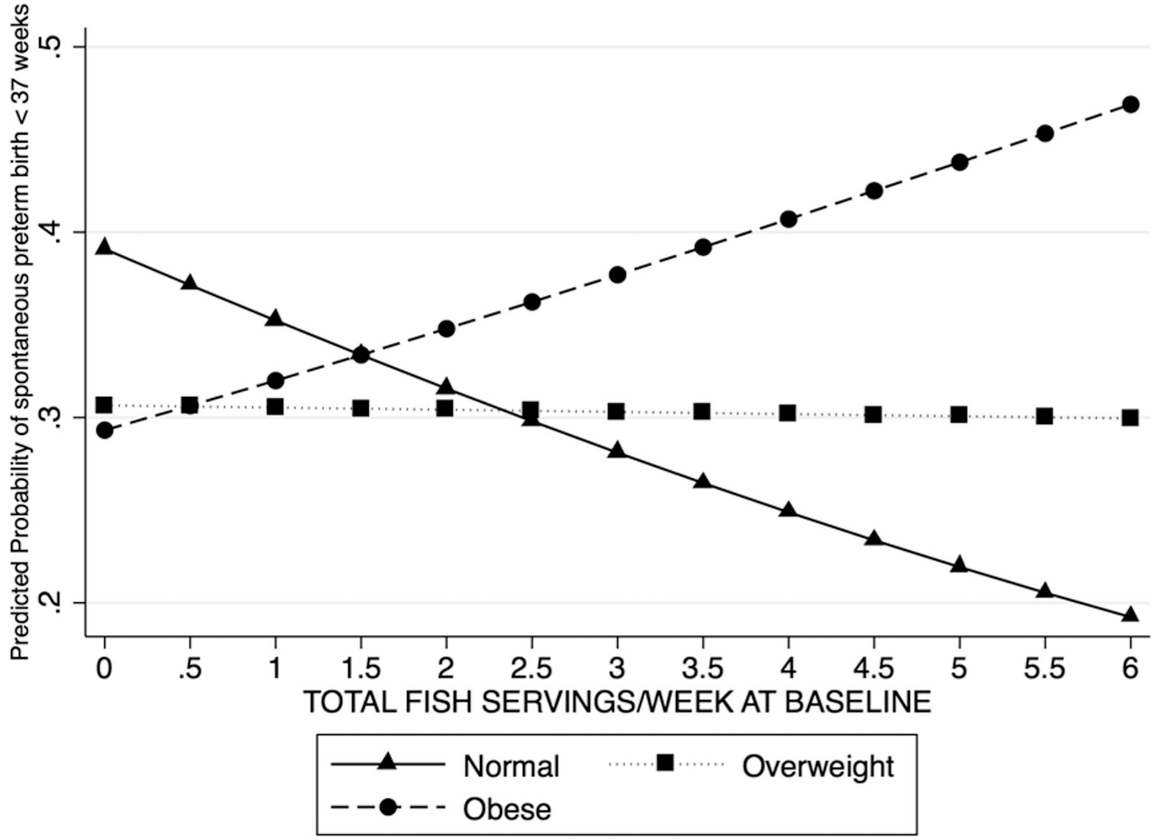

Figure 2:

Adjusted predicted probability of spontaneous preterm birth <37 weeks and fish intake among lean, overweight and obese women (n=852). Models include maternal age, race, education, smoking, number of prior previous PTB, gestational age at earliest PTB and treatment group with predictors held at the mean. P value for interaction = 0.03

Table 1.

Maternal characteristics by pre-pregnancy obesity in MFM Omega-3 Trial (n=852)

		Maternal pre-pregnancy BMI (kg/m^2)			P value[#]
	Total	< 25	25–29.9	≥30	
	N=852	N=404	n=208	n=240	
Maternal characteristic					0.94
Age at delivery (years) N (%) <20 20–24 ≥35	89 (1.5) 677 (79.5) 86 (10.01)	41 (10.2) 324 (80.2) 39 (9.7)	23 (11.1) 161 (77.4) 24 (11.5)	25 (10.4) 192 (80.0) 23 (9.6)	
Race/ethnicity: N (%)					<0.001
Non-Hispanic White	419 (49.2)	243 (60.3)	89 (42.8)	87 (36.3)	
Non-Hispanic Black	287 (33.7)	95 (23.6)	78 (37.5)	114 (47.5)	
Hispanic	121 (14.2)	51 (12.7)	36 (17.3)	34 (14.2)	
Other	24 (2.8)	14 (3.5)	5 (2.4)	5 (2.1)	
Gestational age at randomization (weeks) median(IQR)	19.6 (18.21)	19.6 (18,21)	19.7 (17,9, 21.6)	19.4 (18,20.9)	0.86
Parity (median, IQR)	2 (1,2)	1 (1,2)	2 (1,2.5)	2 (1,3)	0.002
Education <12 years n (%)	164 (19.3)	63 (15.7)	48 (23.1)	53 (22.1)	0.04
Married n(%)	628 (73.7)	306 (75.7)	152 (73.1)	170 (70.8)	0.38
Smoking n(%)	136 (160)	61 (15.1)	30 (14.4)	45 (18.8)	0.37
Drug use n(%)	18 (2.1)	8 (2.0)	5 (2.4)	5 (2.1)	0.94
Pre-gestational diabetes n(%)	16 (1.9)	6 (1.5)	3 (1.4)	7 (2.9)	0.38
Gestational diabetes n(%)	55 (6.5)	15 (3.7)	10 (4.8)	30 (12.5)	<0.001
Prior delivery characteristics					
≥ one prior preterm birth n(%)	247 (29.0)	111 (27.5)	68 (32.7)	68 (28.3)	0.39
Gestational age of earliest prior preterm birth (weeks), median IQR	32 (26, 34)	32 (28, 35)	31 (25, 34)	30 (25, 34)	0.0002
Fish intake in early pregnancy (<22 weeks)					
Any fish at randomization n(%)	599 (70.3)	272 (67.3)	144 (69.2)	183 (76.3)	0.05
≥1 serving of fish/wk at baseline n(%)	423 (49.7)	189 (46.8)	98 (47.1)	136 (56.7)	0.04
Type of fish (grams/week) (mean±standard deviation) [*]					
Tuna	0.15 (±0.29)	0.15 (±0.31)	0.12 (±0.24)	0.18 (±0.32)	0.16
Dark meat fish (salmon, mackerel, sardines, bluefish, swordfish)	0.24 (± 0.68)	0.26 (± 0.73)	0.26 (± 0.26)	0.19 (± 0.53)	0.36
Other fish	0.14 (± 0.32)	0.12 (± 0.27)	0.15 (± 0.36)	0.19 (±0.35) [**]	0.02
Shellfish	0.10 (± 0.19)	0.10 (± 0.20)	0.09 (±0.19)	0.09 (±0.16)	0.87

[*] Variables not normally distributed. The majority of women ate 0–1 servings/wk, median, IQR is 0 (0,0) for all groups. Mean and standard deviation are presented.

[**] Obese compared to lean women p=0.01

[#] P value for comparison of all three BMI categories

Table 2:

Fish intake and preterm birth (PTB) among lean, overweight and obese women in the Maternal Fetal Medicine Unit Omega-3 Trial (n=852)

				Maternal pre-pregnancy body mass index								
	Total (n=852)			Lean (n=404)			Overweight (n=208)			Obese (n=240)		
	Fish intake (serving/wk)			Fish intake (serving/wk)			Fish intake (serving/wk)			Fish intake (serving/wk)		
	<1/wk	≥1/wk	P*	<1/wk	≥1/wk	P*	<1/wk	≥1/wk	P*	<1/wk	≥1/wk	P*
Preterm birth												
< 37 weeks	192 (44.8)	146 (34.5)	0.002	106 (49.3)	63 (33.3)	0.001	47 (42.7)	32 (32.7)	0.14	39 (37.5)	51 (37.5)	1.00
Spontaneous preterm birth												
< 37 weeks	171 (39.9)	121 (28.6)	0.001	97 (45.1)	52 (27.5)	0.001	40 (36.4)	25 (25.5)	0.09	34 (32.7)	44 (32.4)	0.96
< 35 weeks	80 (18.6)	63 (14.9)	0.14	46 (21.4)	22 (11.6)	0.01	18 (16.4)	13 (13.3)	0.53	16 (15.4)	28 (20.6)	0.30

* p-value denotes chi-square test.