The Fish Oil to Reduce Tobacco Use iN Expectant mothers (FORTUNE) feasibility trial

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BACKGROUND: Three small clinical trials have suggested that supplementation with n-3 long-chain polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid) found in fish oils may reduce nicotine cravings and at higher doses reduce cigarette consumption. Pregnant women who smoke have fewer pharmacologic options to aid them with smoking cessation. Although n-3 long-chain polyunsaturated fatty acid supplementation has been studied in pregnancy, few studies have evaluated doses of ≥4 g per day, and no previous studies have selectively enrolled pregnant women who smoke. High-dose n-3 long-chain polyunsaturated fatty acids may aid cessation but could be poorly tolerated in pregnant women who smoke because of gastrointestinal side effects.

OBJECTIVE: We conducted a feasibility trial to determine the tolerability of high-dose n-3 long-chain polyunsaturated fatty acid supplementation in pregnant women who smoked. We hypothesized that n-3 long-chain polyunsaturated fatty acid doses of 4.2 g a day would be well-tolerated relative to an olive oil placebo. We assessed red blood cell phospholipid membrane concentrations at baseline and end of therapy (4 weeks) and piloted outcomes for a future efficacy trial of n-3 long-chain polyunsaturated fatty acid supplementation for smoking cessation in pregnancy.

STUDY DESIGN: We recruited 28 pregnant women between the gestational ages of 6 and 36 weeks who reported daily cigarette smoking and were motivated to quit to participate in a double-blind placebo-controlled randomized feasibility trial of 4.2 g per day of n-3 long-chain polyunsaturated fatty acid supplementation. Participants reported cigarettes per day, completed the Fagerström Test for Cigarette Dependence, and provided blood, urine, and exhaled CO samples. We used repeated-measures analysis of variance to pilot analyses of changes in cigarettes per day and Fagerström Test for Cigarette Dependence scores.

RESULTS: At baseline, red blood cell membrane eicosapentaenoic acid concentrations were negatively correlated with cigarettes per day (r=−0.44; P=.04). By 4 weeks, circulating n-3 long-chain polyunsaturated fatty acid levels increased by 18% in the n-3 long-chain polyunsaturated fatty acid supplementation arm vs a decrease of 3% in the placebo arm. Occurrence of gastrointestinal side effects such as burping, heartburn, diarrhea, abdominal pain, or nausea did not differ statistically between study arms. At 4 weeks, participants allocated to the n-3 long-chain polyunsaturated fatty acids arm reported a median of 3 cigarettes per day (interquartile range, 1−8) vs 7 cigarettes per day (interquartile range, 1−14) in the placebo arm, which was not statistically significant (P=.99). Participants allocated to the n-3 long-chain polyunsaturated fatty acids arm had a decrease of 1 (interquartile range, 0−1) on the Fagerström Test for Cigarette Dependence score vs 0 (interquartile range, 0−0) for placebo (P=.46).

CONCLUSION: High-dose n-3 long-chain polyunsaturated fatty acids may be tolerated in pregnant women who smoke; however, there was a high level of participant dropout, with more participants allocated to the fish oil arm becoming lost to follow-up. These results will inform the design of a future large-scale randomized controlled trial to test the impact of fish oil supplements on smoking cessation in pregnancy.

Key words: n-3 long-chain polyunsaturated fatty acids, nicotine metabolites, pregnancy, red blood cell phospholipids, smoking, tobacco dependence

Introduction

Smoking is the most important modifiable risk factor for adverse pregnancy outcomes and is associated with preterm delivery, growth restriction of infants, preterm-related deaths, and sudden infant death syndrome.[1−4] Almost 11% of US women report smoking during pregnancy, with higher tobacco use observed in younger women and those with lower educational levels.[5,6] Quit rates during pregnancy reported between 2000 and 2010 ranged from 35% to 75%, with risk factors for persistent smoking including lower educational status, smoking ≥10 cigarettes per day, multiparity, and coexisting psychiatric problems.[5−7] For these particularly high-risk individuals, promoting smoking cessation can be challenging because the United States Food and Drug Administration −approved smoking cessation medications such as varenicline and bupropion are contraindicated given the lack of evidence to support their safety in pregnant women, and nicotine replacement therapy is used on a limited basis.[8−10] The identification of safe and effective adjuvant pharmacotherapies to promote smoking cessation in pregnant women would have a powerful clinical impact on maternal−fetal health outcomes.

EDITOR'S CHOICE

N−3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs), which are found in fish oils, may have beneficial effects in pregnancy; however, at present, data are insufficient to recommend omega-3 fatty acid supplementation for the sole purpose of reducing the risk of preterm birth or preventing perinatal depression.[11,12] However, it is possible that certain subgroups of women, such as those who smoke cigarettes, may be more likely to benefit from supplementation than others.[12,13] We and others have found that red blood cell (RBC) phospholipid

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AJOG MFM at a Glance

Why was this study conducted?

Smoking in pregnancy is associated with significant adverse pregnancy outcomes. Three small clinical studies in nonpregnant smokers have suggested that supplemental n-3 long-chain polyunsaturated fatty acids (LCPUFAs) may reduce nicotine cravings and cigarettes smoked per day, with higher doses of n-3 LCPUFA being more effective. Whether higher doses of n-3 LCPUFA are tolerated in pregnant women is unclear.

Key findings

Supplemental n-3 LCPUFA of 4.2 grams a day may be well-tolerated without an increase in gastrointestinal side effects over a 4-week period.

What does this add to what is known?

These results will inform the design of a future large-scale randomized clinical trial to determine if high-dose supplemental n-3 LCPUFAs affect smoking behavior in pregnancy.

membrane concentrations of the n-3 LCPUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are significantly lower in smokers than in nonsmokers.[14–18] This smoking-induced n-3 LCPUFA relative deficiency could have significant implications for smoking cessation efforts given that n-3 LCPUFAs play an important role in behavior. For example, in rodent models, n-3 LCPUFA deficiencies result in structural changes in nervous tissue that affect dopaminergic and serotonergic systems, resulting in hypofunctioning of the dopaminergic mesocorticolimbic pathways that are related to reward and dependence.[19,20] Importantly, correction of these deficiencies through dietary n-3 LCPUFA supplementation can reverse these changes.[21–24] During ad libitum smoking, the nicotine in cigarette smoke causes elevation of dopamine in the nucleus accumbens,[25,26] which may partially restore reward system deficits, but at the cost of exposure to myriad toxins in cigarette smoke. During abstinence from smoking, when nicotine is removed, pregnant women may be particularly vulnerable to reward hypofunctioning. It has been hypothesized that correcting the hypofunctioning dopaminergic system through n-3 LCPUFA supplementation might reduce the symptoms of withdrawal associated with smoking cessation and reduce nicotine cravings.[27] Further support for this idea stems from evidence that in humans, n-3 LCPUFA supplementation reduces anxiety symptoms, and may thus promote abstinence from smoking by mitigating negative affect associated with nicotine withdrawal.[28]

Three recent, small clinical trials lend support to the use of n-3 LCPUFAs for smoking cessation. Zaparoli et al[29] evaluated the effect of 1 gram of n-3 LCPUFA on smokers and found no change in cigarettes per day (CPD) but a statistically significant reduction in self-reported nicotine cravings. Rabinovitz[30] and Sadeghi-Ardekani et al[31] used a higher dose of n-3 LCPUFA (4750 mg and 1500 mg, respectively) and found a statistically significant reduction in nicotine cravings and a reduction in CPD. All 3 studies were small, and the findings would require validation in a larger sample. Evaluating the effect of n-3 LCPUFAs in pregnant women who smoke could be valuable, and if effective, this could be an immediate therapeutic option. N-3 LCPUFAs have been extensively studied in pregnant women and are considered safe with only mild side effects, such as nausea or "fish burps."[32] However, a Cochrane review of 70 randomized control studies found only 2 previous studies that used dosages of ≥4 g daily, and no previous studies that specifically recruited pregnant women who smoke.[32]

The purpose of this feasibility study was to collect data on tolerability of high-dose n-3 LCPUFAs (4.2 g per day) in pregnant women who smoke, and to develop, test, and refine procedures for a larger efficacy trial. Finally, we planned to gather preliminary effect size data on outcomes including self-reported craving and withdrawal, reduction in smoking, and biochemically verified abstinence. We hypothesized that pregnant women who smoke would tolerate high-dose n-3 LCPUFAs.

Material and Methods

Study population

We recruited pregnant women who were actively smoking from March through September 2017. Potential participants reporting ≥1 cigarettes daily were considered active smokers. Study inclusion criteria included age of 18 to 45 years, currently self-reported cigarette use of ≥1 CPD, and between 6- and 36-weeks' gestation as determined by medical record review. Exclusion criteria included: self-reported allergy to fish or seafood, self-reported current use of fish oil supplements, unstable psychiatric disease requiring hospitalization or active medication changes within the preceding 3 months determined by medical record review (excluding admissions to convert oral opioids to buprenorphine therapy), and unstable pregnancy-related medical problems as determined by medical record review. Participants were identified through electronic medical record reviews of upcoming visits to Vanderbilt University Medical Center Obstetrics and Gynecology Clinics. Potential participants who were identified through medical record review were sent a letter inviting them to participate in the study and were called by study staff. Participants who met the inclusion criteria as determined by phone interview were scheduled for a baseline visit at the Clinical Research Center at the Vanderbilt University Medical Center.

Eligible participants were randomized to either n-3 LCPUFA capsules (Lovaza GlaxoSmithKline, Research Triangle Park, NC) or olive oil capsules. Participants allocated to n-3 LCPUFA supplementation were instructed to take 5 capsules daily, providing a total

daily dose of 2325 mg of EPA and 1875 mg of DHA. Participants allocated to the placebo (olive oil) arm were also instructed to take 5 capsules daily. Placebo capsules were similar in size and color. We chose this dose on the basis of previous trials that reported that higher n-3 LCPUFA doses (4750 mg per day) were associated with a reduction in CPD, whereas the study using the lower dose (1000 mg per day) did not report such reduction.[29,30]

At the baseline visit, after eligibility was confirmed and consent was obtained, participants were randomized on the basis of a 1:1 permuted block randomization design stratified by current tobacco use (≤10 CPD or >10 CPD). The randomization schema was created by the study statistician and maintained by the Vanderbilt Investigational Drug Services. Both study participants and study staff were blinded to the assignments.

The trial included 3 in-person visits: at baseline, 2 weeks, and 4 weeks. A detailed smoking history was obtained at each visit. In addition, participants completed the Fagerström Test for Cigarette Dependence (FTCD) and a questionnaire regarding gastrointestinal symptoms to assess potential side effects of the oils. Blood, urine, and exhaled CO measurements were collected. At the end of the baseline visit, participants were dispensed a 4-week supply of medication and a pill diary. At the baseline visits participants were given a booklet and a digital video disk detailing the Smoking Cessation and Reduction in Pregnancy Treatment (SCRIPT) program.[33] Participants were briefly oriented to the program before completing the baseline visit. At the 4-week visit, unused pills were collected for pill counts, and participants were asked to speculate which study arm they had been assigned to. Participants were paid a total of $120 ($40 per visit) for participation and completion of the survey instruments.

Biological measurements

We used the piCO Smokerlyzer (Bedfont Scientific Ltd, Harrietsham, United Kingdom) to assess end-expired CO. Participants were advised to hold their breath for 15 seconds before blowing in the device. A CO of <10 ppm was the cutoff used to verify quitting. Nicotine metabolites in blood were measured using an isotope dilution high-performance liquid chromatography−atmospheric pressure chemical ionization −tandem mass spectrometry in a commercially available testing center. Nicotine metabolites in urine were measured using a quantitative liquid chromatography−tandem mass spectrometry. RBC membrane phospholipids were extracted using the method of Folch −Lees (133). Fatty acid methyl esters were identified by comparing the retention times with those of known standards. Inclusion of the internal standard, dipentadecanoyl phosphatidylcholine (C15:0), permitted quantitation of phospholipid amount in the sample. Results of the fatty acid analyses were presented as percentage of fatty acid over total membrane fatty acids. All laboratory staff were blinded to study allocation arm.

Outcomes

As part of this feasibility trial, safety and tolerability outcomes included: (1) reported adverse events, and (2) rate of discontinuation of study medication owing to side effects. We also included pilot primary efficacy outcomes including reduction in total number of CPD from baseline to 4 weeks. The pilot secondary efficacy outcomes included: (1) reduction in the FTCD questionnaire (range of 0−10, with higher scores indicating greater cigarette dependence), and (2) point prevalence abstinence at 4 weeks, biochemically confirmed by end-expired CO.

Statistical analysis

Baseline characteristics stratified by treatment allocation were compared using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. We calculated Spearman partial correlation coefficients between RBC membrane n-3 LCPUFAs and baseline measures. Changes at 2 weeks and 4 weeks compared with baseline were determined for the primary and secondary outcomes. We estimated differences in the change at baseline using a Wilcoxon (Mann−Whitney) rank-sum test evaluated at a 5% significance level. We compared the rates of gastrointestinal side effects between the 2 study arms using repeated-measures analysis of variance (ANOVA). We also compared the change outcome over the course of the trial between arms using repeated-measures ANOVA. Because these variables were skewed, we log-transformed the variables to be compliant with the assumption of normality. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

The Fish Oil to Reduce Tobacco Use iN Expectant Mothers (FORTUNE) study was approved by the Vanderbilt University Medical Center Institutional Review Board and registered at ClinicalTrials.gov (NCT03077724).

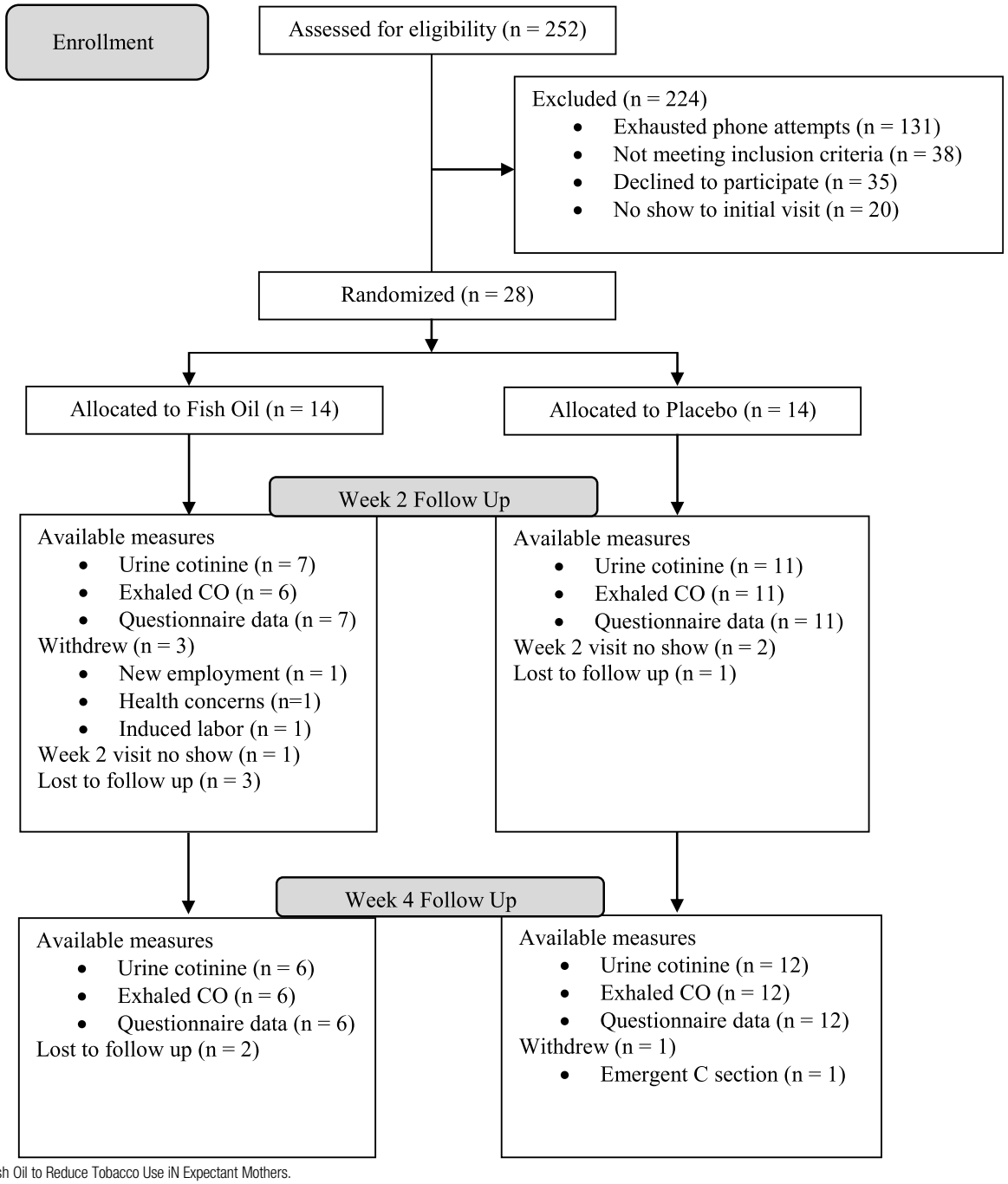
Results

A total of 28 participants were randomized to either n-3 LCPUFA or olive oil supplementation (Figure). There was substantial participant dropout over the course of the study, resulting in 43% (6/14) of participants completing all 3 visits in the n-3 LCPUFA arm and 86% (12/14) in the olive oil arm. The mean age of the study participants was 31 years (interquartile range [IQR], 27−35), with a baseline median number of CPD of 9.3 (IQR, 2.3−18.8) and a baseline score on the FTCD of 8 (IQR, 7−9) (Table 1).

At baseline, total RBC membrane n-3 LCPUFA levels were inversely correlated with urine hydroxycotinine (r=−0.43; P=.05) and end-expiratory CO (r=−0.53; P=.01). (Table 2). RBC membrane EPA levels were inversely correlated with CPD (r=−0.44; P=.04) and urine cotinine (r=−0.48; P=.03).

Regarding compliance with study medication, 17 participants returned unused pills or empty bottles, 82% of whom (14/17) reported >80% compliance. As an additional marker of compliance, we measured RBC membrane n-3 LCPUA levels. Circulating n-3 LCPUFA levels in participants randomized to fish oil increased by 27% at 2

FIGURE
Consort diagram of the FORTUNE study



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weeks vs a decrease of 8% in the placebo group, and by 18% at 4 weeks vs a decrease of 3% with placebo.The absolute difference between study arms in RBC membrane n-3 LCPUFA levels was 2.65% at 2 weeks (*P*=.29) and 1.58% at 4 weeks (*P*=.23), indicating that participants were taking the supplements.

There were no statistically significant differences in gastrointestinal side effects between the study arms (Table 3). In all participants regardless of study arm, a transient increase in reported symptoms appeared at 2 weeks, and seemed to resolve by 4 weeks. There was no marked increase in reported gastrointestinal side effects at 4 weeks in

TABLE 1
Baseline characteristics and biomarker measurements by treatment allocation

Characteristics and measurements	Fish oil N=14	Placebo N=14
Sociodemographic		
Age (y), median (IQR)	32 (25–35)	31 (28–34)
Race, n (%)		
White	12 (85.7)	9 (64.3)
African American	1 (7.1)	4 (28.6)
Other	1 (7.1)	1 (7.1)
Marital status, n (%)		
Never married, not living with a partner	3 (21.4)	4 (28.6)
Not married and living with a partner	3 (21.4)	7 (50.0)
Married	5 (35.7)	2 (14.3)
Separated, divorced, widowed	3 (21.4)	1 (7.1)
Education, n (%)		
No or some high school	2 (14.3)	1 (7.1)
High school graduate, GED, or trade school	4 (28.6)	5 (35.7)
Some college	4 (28.6)	8 (57.1)
College graduate, graduate/professional	4 (28.6)	0 (0)
Income, n (%)		
<$25,000	7 (50)	8 (57.1)
>$10,000 and <$25,000	3 (21.4)	4 (28.6)
>$75,000	1 (7.1)	0 (0)
Patient declined to answer	3 (21.4)	2 (14.3)
Cigarettes per day, median (IQR)	9.9 (2.8–17.9)	9.3 (1.0–20)
Fagerström Test for Cigarette Dependence, median (IQR)	8.5 (7.0–9.0)	8.0 (6.0–9.0)
Biological markers		
Blood markers		
Eicosapentaenoic acid, % total fatty acids	0.27 (0.19–0.36)	0.31 (0.24–0.48)
Docosahexaenoic acid, % total fatty acids	5.35 (4.71–6.65)	5.22 (4.92–5.93)
Total n-3, % total fatty acids	7.87 (7.12–9.06)	7.95 (7.49–8.68)
Cotinine, ng/mL	88 (36–131)	83 (12–132)
OH-cotinine, ng/mL	36.5 (20–62)	42 (3–85)
Nicotine metabolic ratio	0.68 (0.32–1.0)	0.57 (0.51–0.72)
Urine markers		
Cotinine, ng/mL	764 (396–1000)	688 (109–1289)
OH-cotinine, ng/mL	4892 (3125–5000)	4200 (760–5000)
End-expired CO		
Parts per million	20.5 (13–22)	22.5 (4–34)

IQR, interquartile range.

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neither arm. No participants withdrew because of issues related to medication tolerability, and there were no reported adverse events related to study participation. A single serious adverse event was recorded in the n-3 LCPUFA group related to an unexpected hospitalization secondary to a lapse in prescribed (ie, nonstudy) medication.

At the end of the 4-week intervention, the participants allocated to the n-3 LCPUFA arm reported a median of 3 CPD (IQR, 1–8) vs 7 CPD (IQR, 1–14) in the olive oil arm. A median reduction of 1 point on the FTCD was observed in the n-3 LCPUFA arm at 2 and 4 weeks, with no change in scores in the placebo group. After adjusting for repeated measures, there was no statistically significant difference between change from baseline in CPD or FTCD scores at 2 or 4 weeks (Table 4). At 4 weeks, participants allocated to the n-3 LCPUFA had a greater reduction of urine cotinine (P=.04) and of end-expiratory CO (P=.02).

Only 2 participants achieved biochemically confirmed abstinence at 4 weeks. Both participants were allocated to the placebo arm, and both had a low number of CPD at baseline (1 and 3). No participants with a baseline exhaled CO >10 ppm achieved complete abstinence.

At the end of the study, participants (n=18) were asked to identify what study product they had received. In the n-3 LCPUFA arm, 50% (3/6) of participants believed they were taking fish oil, 33% (2/6) believed they were taking olive oil, and 17% (1/6) were unsure of their treatment allocation. For the olive oil arm, 17% (2/12) reported they were taking fish oil, 33% (4/12) reported they were taking olive oil, and 58% (7/12) were unsure of their treatment allocation.

Discussion

Principal findings

In this randomized controlled feasibility study, we found that pregnant women who smoke may tolerate n-3 LCPUFA supplementation at >4 g per day; however, our sample was very small, which could limit the generalizability of these

TABLE 2
Correlations between baseline red blood cell membrane n-3 long-chain polyunsaturated fatty acid concentrations and study measurements (n=28)

Study measurements	Eicosapentaenoic acid		Docosahexaenoic acid		Total n-3 LCPUFA	
	R	*P* value[a]	R	*P* value	R	*P* value
Eicosapentaenoic acid			0.43	.04		
Cigarettes per day	−0.44	.04	−0.29	.21	−0.41	.07
Fagerström Test for Cigarette Dependence	−0.41	.06	−0.09	.68	−0.25	.26
Blood cotinine	−0.41	.07	−0.18	.45	−0.36	.11
Blood hydroxycotinine	−0.39	.08	−0.30	.19	−0.42	.06
Urine cotinine	−0.48	.03	−0.13	.57	−0.37	.10
Urine hydroxycotinine	−0.34	.14	−0.34	.14	−0.43	.05
End-expiratory CO	−0.47	.03	−0.43	.04	−0.53	.01

LCPUFA, long-chain polyunsaturated fatty acid.

[a] *P* values determined using Spearman partial correlation coefficients.

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findings. We found no statistically significant evidence of a reduction in our pilot efficacy outcomes of CPD or FTCD scores over the 4-week study, although the study was limited by a small sample size and dropouts. These null results could be secondary to the small sample size. However, a larger, adequately powered clinical trial is warranted given the safety profile of fish oil supplements in pregnancy, the findings in previous trials of nonpregnant smokers, and the likely n-3 LCPUFA deficiency observed in pregnant women who smoke.

Results

Our results extend previous work in nonpregnant samples to a sample of pregnant women who smoke daily. Rabinovitz[30] randomized 50 healthy nonpregnant smokers who were not interested in quitting to either 4750 mg of EPA+DHA per day for 30 days or placebo. The study reported only 1 participant lost to follow-up and found a statistically significant reduction in self-reported tobacco craving and CPD in the n-3 LCPUFA group compared with the placebo group. Of interest, even 30 days after stopping the intervention, individuals allocated to the n-3 LCPUFA group reported lower levels of tobacco cravings compared with the placebo group. Sadeghi-Ardekani et al[31] found a statistically significant reduction in CPD and nicotine cravings (FTND) at the end of the 3-month study period. This study had a follow-up of 81% and randomized 54 participants who were exclusively male and very heavy smokers (31−35 CPD).

In a third trial of n-3 LCPUFAs for treatment of smoking in nonpregnant adults, Zaparoli et al[29] randomized 63 healthy smokers to either 1023 mg per day of EPA+DHA or placebo for 90 days. Loss to follow-up was considerable in this study, with only 62% of the participants completing the study (38% dropped out). The study was analyzed using an intention-to-treat design. A statistically significant difference was observed in nicotine dependence between the n-3 LCPUFA and the placebo group, with a 23% reduction in dependence score for smokers allocated to n-3 LCPUFA. There was no difference between the groups in CPD.

The current study was significantly smaller than previous studies and uniquely featured pregnant women who smoke, which may account for the discrepancy in findings. Thus, the current study adds to nascent literature on n-3 LCPUFAs by lending support to the feasibility of high-dose n-3 LCPUFAs in pregnant women who smoke.

TABLE 3
Self-reported gastrointestinal side effects

Side effects		Percentage reporting symptoms >3 times a wk[a]			*P* value[b]
		Baseline	2 wk	4 wk	
Burping	Fish oil	17%	40%	17%	.34
	Olive oil	17%	30%	17%	
Diarrhea	Fish oil	0	0	0	.73
	Olive oil	0	10%	8%	
Heartburn	Fish oil	33%	40%	0%	.71
	Olive oil	9%	40%	8%	
Abdominal pain	Fish oil	17%	40%	0	.20
	Olive oil	17%	20%	0	
Change in taste	Fish oil	17%	0	0	.29
	Olive oil	8%	0	8%	

[a] Includes individuals with all 2 or more questionnaires complete (n=18; fish oil N=6; olive oil N=12).; [b] *P* value determined using logistic regression and repeated-measures analysis of variance with log-transformed dependent variables.

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Clinical and research implications

N-3 LCPUFAs have the potential to favorably affect several health metrics for pregnant women who smoke. Beyond the potential applications of n-3 LCPUFAs to reduce tobacco use (eg, by correcting deficiencies in dopamine

TABLE 4
Change in cigarettes per day and cigarette dependence at 2 weeks and 4 weeks[a]

Outcome variable		Change at 2 wk	*P* value[b]	Change at 4 wk	*P* value[b]	*P* value[c]
Cigarettes per day	FO	−1.12 (−2.5 to 0)	.71	−0.94 (−1.6 to 0.5)	.51	.75
	OO	−0.25 (−2.12 to 1.0)		−0.69 (−5.5 to −0.3)		
Fagerström Test for Cigarette Dependence	FO	−1.0 (−1.0 to 0)	.35	−1.0 (−2.0 to 0)	.01	.38
	OO	0 (−1.0 to 0)		0 (0−0)		

FO, Fish Oil; *OO*, Olive Oil.

[a] Total N=18 (n=6 in the fish oil group and n=12 in the olive oil group). Changes at 2 weeks and at 4 weeks are both compared with the baseline value; [b] *P* values for differences between arms determined using Wilcoxon rank-sum test;; [c] *P* value for overall change determined using logistic regression and repeated-measures analysis of variance with log-transformed dependent variables.

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reward pathways), the critical role of DHA in fetal neural development has led to significant interest in the study of fish oil supplements in pregnancy. As pregnancy progresses, the baseline deficiency of DHA in pregnant women who smoke may become exacerbated during periods of intense neural tube and retinal development. In addition, n-3 LCPUFAs have been studied for a potential role in promoting other key outcomes of a healthy pregnancy. Randomized controlled trials (RCTs) of n-3 LCPUFA supplementation in pregnant women have had mixed results on preeclampsia risk and intrauterine growth restriction; however, recent meta-analyses have suggested a beneficial effect of supplemental n-3 LCPUFAs on preterm labor risk.[34,35] However, to date, no RCT of n-3 LCPUFA supplementation for adverse pregnancy outcomes has prospectively stratified by smoking status, and only 1 RCT has done so post hoc.[36] Among 136 smokers, supplemental n-3 LCPUFAs (2 g per day) produced a lower risk of spontaneous preterm delivery (relative risk [RR], 0.56; 95% confidence interval [CI], 0.36−0.87), whereas no effect was observed among 715 nonsmokers (RR, 1.04; 95% CI, 0.84−1.29; *P*=.013).[37] This intriguing finding suggests that n-3 LCPUFA supplementation may be most beneficial in smokers, a group with known deficiencies of n-3 LCPUFAs, for preventing adverse pregnancy outcomes.

Our study in a unique population of pregnant women who smoke confirms and extends previous studies of n-3 LCPUFA supplementation in which smoking status of participants typically was not reported. These studies also showed that n-3 LCPUFA supplementation was well-tolerated, with the most common side effect reported being "fishy burps," with no differences in bleeding complications, nausea, emesis, diarrhea, or abdominal pain.[35] Although several expert panels recommend pregnant and lactating women to consume at least 200 to 300 mg per day of DHA on average, no formal guidelines exist advocating the use of supplements.[38,39] Thus, future clinical trials are required to determine whether supplemental n-3 LCPUFAs may reduce smoking-related neonatal complications and affect smoking rates in pregnant women.

Strengths and limitations

A strength of our study included the specific enrollment of pregnant women who smoke, collection of biological markers of tobacco use and n-3 LCPUFA exposure, and the use of high doses of n-3 LCPUFAs. Several limitations warrant discussion. This was a feasibility study, not designed to produce definitive findings. Nausea and vomiting were important outcomes; however, participants were recruited across a very wide range of gestational age, and subsequently this could have introduced confounding into the study results. The participant dropout was high, which was likely related to the inconvenience of having all study-related visits at a location that was geographically separate from the participants' clinical care (ie, the subjects had to travel specifically to the Vanderbilt University Medical Center Clinical Research Center). Given the low socioeconomic status of the participants, this may have represented an undue burden, and it serves as an important design consideration to inform a future larger study. It is possible that participants who were lost to follow-up did experience gastrointestinal side effects that were just not reported, which would affect our overall findings of tolerability. There were more participants who were lost to follow-up in the fish oil arm, which could suggest that high-dose n-3 LCPUFA supplementation was poorly tolerated; however, given the overall small sample size of the clinical trial, the imbalance of participants lost to follow-up could be owing to chance. Given the overall small sample size, it is not surprising that baseline demographic factors were not completely balanced between the groups, which could have introduced confounding into our results. We did not perform an intention-to-treat analysis given the overall small size of the study population, the lack of even distribution of confounders at baseline, and the high rate of missing data. Although all participants were given materials and were oriented to the SCRIPT program, an additional weakness was the lack of a substantial behavioral counseling component to support smoking cessation. This likely contributed to the lack of any heavy smokers achieving abstinence. Guidelines for smoking cessation in pregnancy support the need for behavioral interventions.[40] In addition, we did not account for potential

stressors in pregnancy that might serve as barriers toward smoking cessation. Finally, the study intervention was of limited duration (4 weeks), which is shorter than typical smoking cessation interventions and could have underpowered our results. In addition, we found that RBC phospholipid membrane concentrations of n-3 LCPUFAs seemed to be lower at 4 weeks than at 2 weeks, which might indicate a decrease in medication compliance.

Conclusions

In summary, in this feasibility study we found that high-dose n-3 LCPUFA supplements may be well-tolerated in pregnant women who smoke. By design, the study was not powered to detect differences in smoking behavior, and as expected we did not see a statistically significant reduction in CPD or the FTCD score. Given the recent evidence that n-3 LCPUFAs may reduce the risk of preterm birth specifically in smokers, and the known n-3 LCPUFA deficiencies observed in smokers, additional clinical trial work is needed to test the efficacy of n-3 LCPUFAs for smoking cessation and preterm birth in pregnant women who smoke. ■

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