OBSTETRICS

Omega-3 supplementation to prevent recurrent preterm birth: a systematic review and metaanalysis of randomized controlled trials

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The purpose of this study was to evaluate the efficacy of omega-3 supplementation for the prevention of recurrent preterm birth (PTB) in asymptomatic singleton gestations with previous PTB. We searched *fish oil*, *long chain polyunsaturated fatty acids*, *pregnancy*, and *omega-3* in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials from inception of each database to December 2014 with no limit for language. In addition the reference lists of all identified articles were examined to identify studies that were not captured by electronic searches. We performed a metaanalysis of randomized controlled trials of asymptomatic singleton gestations with previous PTB who were assigned randomly to prophylactic omega-3 supplementation vs control (either placebo or no treatment). The primary outcome was predefined as PTB at <37 weeks of gestation. The pooled results were reported as relative risk (RR) with 95% confidence interval (95% CI). The protocol of this review was registered with PROSPERO (registration number: CRD42015016371). Two randomized controlled trials that included 1080 women were analyzed. The mean gestational age at randomization was approximately 134 days in both groups (mean difference, 0.01 days; 95% CI, −0.13 to 0.14). Women who received omega-3 had similar rates of PTB at <37 weeks of gestation (34.5% vs 39.8%; RR, 0.81; 95% CI, 0.59−1.12) and PTB at <34 weeks of gestation (12.0% vs 15.4%; RR, 0.62; 95% CI, 0.26−1.46) compared with control subjects. The omega-3 groups had a statistically significantly longer latency (mean difference, 2.10 days; 95% CI, 1.98−2.22) and higher birthweight (mean difference, 102.52 g; 95% CI, 20.09−184.95) compared with control subjects; the other secondary outcomes (which included gestational age at delivery, spontaneous PTB at <37 and 34 weeks of gestation, admission to the intensive care unit, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and perinatal death) were similar. Omega-3 supplementation during pregnancy does not prevent recurrent PTB in asymptomatic singleton gestations with previous PTB. The benefits in longer latency and higher birth weight may deserve further study.

Key words: fish oil, omega-3, pregnancy, preterm birth

Preterm birth (PTB) remains the number 1 cause of perinatal death in many countries, including the United States.[1] Women with previous PTB are considered to be at high risk for recurrent PTB in a subsequent pregnancy.[2]

The exact mechanisms for the onset of term or preterm labor are not known exactly, but several biochemical changes have been reported. Prostaglandin concentrations are elevated in the maternal circulation before the beginning of spontaneous labor,[3] and exogenous administration of prostaglandins induces cervical dilation and uterine contractions.[4] Omega-3 fatty acids depress the synthesis of prostaglandins, but the role of omega-3 supplementation in the prevention of PTB is not yet clear.[5]

Randomized controlled trials (RCTs) performed to assess whether supplementation during pregnancy with polyunsaturated fatty acids (such as eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids) may prevent recurrence of PTB have shown contradictory results.[6,7]

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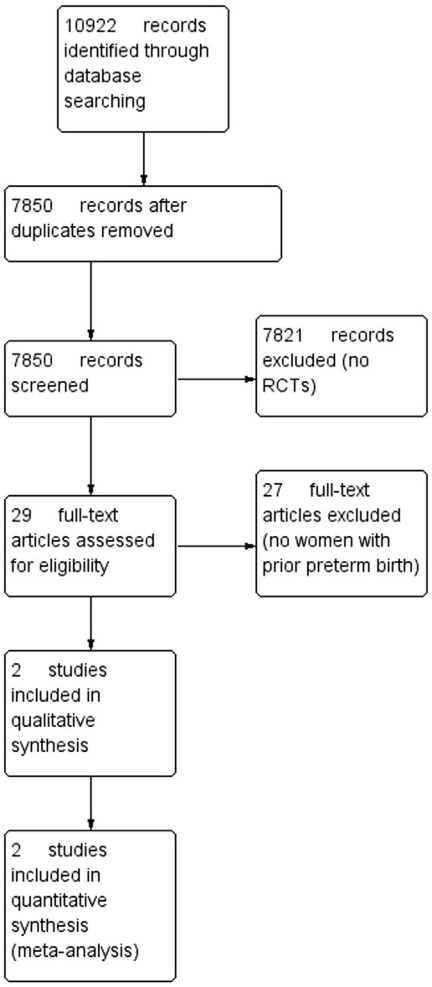
The aim of this metaanalysis was to evaluate the efficacy of omega-3 supplementation during pregnancy in the reduction of recurrence of PTB in asymptomatic singleton gestations with previous PTB.

Methods

Search strategy

We searched *fish oil*, *long chain polyunsaturated fatty acids*, *pregnancy*, and *omega-3* in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, Sciencedirect, and the Cochrane Central Register of Controlled Trials from inception of each database to December 2014 with no limit for language. In addition, the reference lists of all identified articles were examined to identify studies that were not captured by electronic searches.

FIGURE 1
Flow diagram



These are the studies that were identified in the systematic review.

RCTs, randomized controlled trials.

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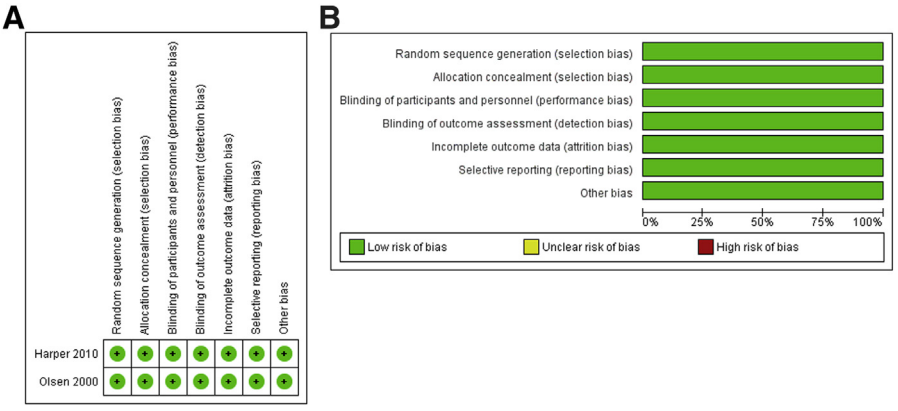
FIGURE 2
Assessment of risk of bias



A, Summary of risk of bias for each trial. The *plus sign* indicates a low risk of bias; the *minus sign* indicates a high risk of bias; the *question mark* indicates unclear risk of bias. **B,** Risk of bias graph about each risk of bias item presented as percentages across all included studies.

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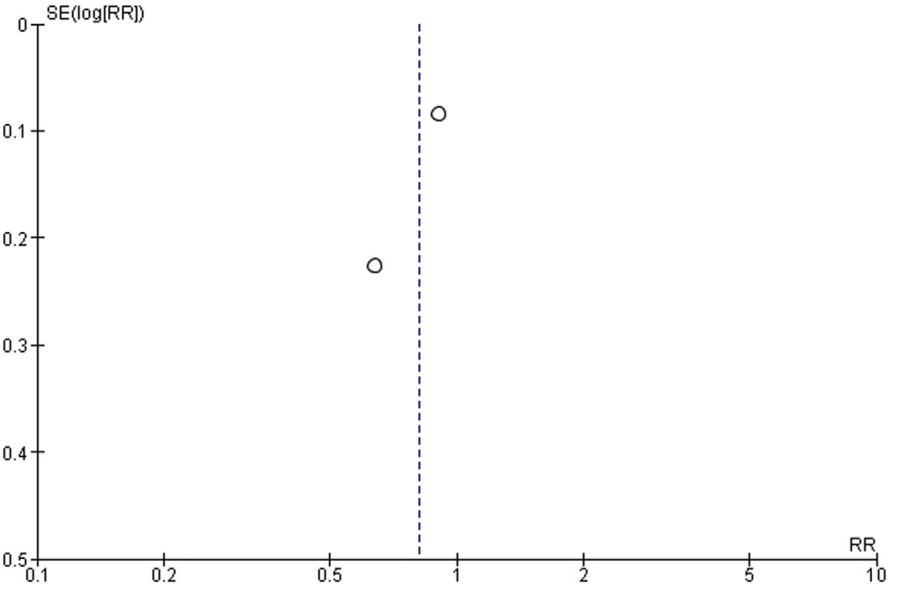
The electronic search and the eligibility of the studies were assessed independently by the authors. Differences were resolved by discussion.

Study selection, data extraction, and assessment of risk of bias

We included all RCTs of asymptomatic singleton gestations with previous PTB who were assigned randomly to prophylactic treatment with either omega-3 or control (either placebo or no treatment). All published RCTs on omega-3 during pregnancy were carefully reviewed. Exclusion criteria included quasirandomized trials (ie, trials in which allocation was done on the basis of a pseudorandom sequence [eg, odd/even hospital number or date of birth], alternation), trials in women with multiple gestations, and trials in women with intrauterine growth restriction or gestational hypertension/preeclampsia at the time of random assignment.

The primary outcome was PTB at <37 weeks of gestation. Secondary outcomes included gestational age at delivery, interval from random assignment to delivery (ie, latency), PTB at <34 weeks

FIGURE 3
Funnel plot for assessment of publication bias



Assessment of publication bias by funnel plot: no publication bias is evident.

RR, relative risk; *SE,* standard error.

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of gestation, spontaneous PTB (sPTB) at <37 and <34 weeks' gestation, and neonatal outcome that included birthweight, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, and perinatal death. All analyses were done with an intention-to-treat approach. All authors of the included trials were contacted for missing data.

The risk of bias in each included study was assessed by the use of the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[8]

Data synthesis

The data analysis was completed independently by the authors who used Review Manager (version 5.3, 2014; The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Discrepancies were resolved by discussion. Heterogeneity across studies was assessed with the use of the Higgins I^2 test.[8] In case of statistically significant heterogeneity, the random effects model of DerSimonian and Laird was used, otherwise a fixed effect model was managed.[8] The pooled results were reported as relative risk (RR) or as mean difference with 95% confidence interval (95% CI).

The protocol of this review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42015016371). The metaanalysis was performed according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[9]

Results

Study selection, study characteristics, and risk of bias of included studies

We identified 29 trials on omega-3 supplementation during pregnancy.[6,7,10-36] No similar systematic reviews were found during the search process. Two trials that met inclusion criteria for this metaanalysis were analyzed.[6,7] The flow of study identification is shown in Figure 1. From one of the studies, we obtained additional and unpublished data about PTB at <34 weeks of gestation, sPTB at <34 weeks of gestation, and birthweight.[7] The quality of RCTs that were included in our metaanalysis and assessed by the Cochrane Collaboration's tool revealed that both studies had a low risk of bias (Figure 2). Risk of publication bias was assessed by visual inspection of the funnel plot, and the symmetric plot suggested no publication bias (Figure 3).

The characteristics of the included trials are summarized in Table 1. A total of 1080 singleton gestations with at least 1 previous PTB were included. Both studies used daily oral docosahexaenoic and eicosapentaenoic acids supplementation as treatment and placebo as control. In one of the included studies, all participants (both intervention and control group) received weekly intramuscular 17-alpha-hydroxyprogesterone caproate 250 mg.[7] Of the 1080 singleton gestations included in the 2 trials, 544 gestations (50.4%) were assigned randomly to the omega-3 group and 540 gestations (49.6%) were assigned randomly to the control group. The mean of GA at randomization was approximately 134 days in both groups (mean difference, 0.01 days; 95% CI, −0.13 to 0.14).

TABLE 1
Descriptive data

Variable	Olsen et al 2000[6]	Harper et al 2010[7]
Study location	Northern Europe	United States
Patients, n (n/N)[a]	228 (108/120)	852 (434/418)
Intervention daily	Docosahexaenoic acid 900 mg and eicosapentaenoic acid 1300 mg	Docosahexaenoic acid 800 mg and eicosapentaenoic acid 1200 mg
Control	Placebo	Placebo
Follow up, %	98	100
Gestational age at random assignment, d	131.8 vs 130.5	137.2 vs 137.2
Mean age, y	29 vs 30	28 vs 27
Smoking, n/N[a]	50/110 vs 50/122	64/434 vs 72/418
Previous preterm birth, n/N[a]		
1	110/110 vs 122/122	274/434 vs 282/418
>1	0/100 vs 0/122	160/434 vs 136/418
Race, n/N		
African American	N/A	148/434 vs 145/418
White	N/A	245/434 vs 240/418
Other	N/A	41/434 vs 33/418
Primary outcome: preterm birth, wk	<37	<37

N/A, data not reported in the trial.

[a] Data are presented as the number of intervention vs the number of control subjects or as total number (intervention/control).

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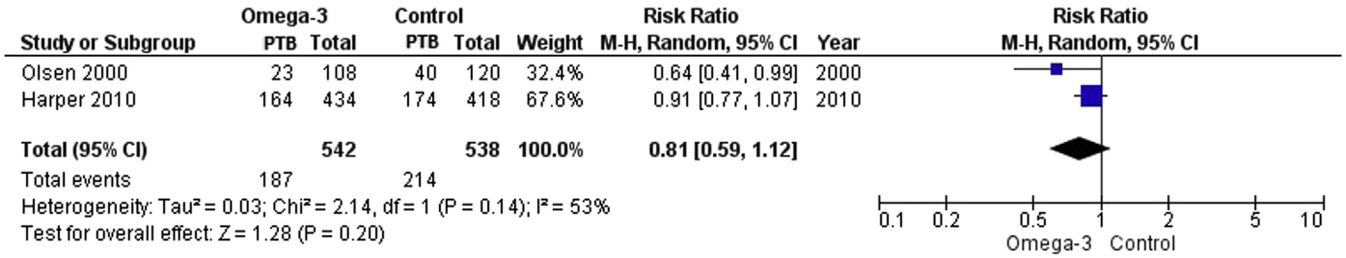
Synthesis of results

Women who received omega-3 supplementation had similar rates of PTB at <37 weeks' gestation (34.5% vs 39.8%; RR, 0.81; 95% CI, 0.59−1.12; Figure 4) and PTB<34 weeks (12.0% vs 15.4%;

FIGURE 4
Forest plot for preterm birth <37 weeks of gestation



The Forest plot gives values for preterm birth at <37 weeks of gestation. *Blue square*, risk ratio of the study with 95% confidence interval. *Small closed square*, Olsen risk ratio. *Large closed square*, Harper risk ratio. *Closed diamond*, pooled risk ratio.

Olsen 2000.[6] Harper 2010.[7]

CI, confidence interval; *M-H*, Mantel-Haenszel; *PTB*, preterm birth <37 weeks of gestation.

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RR, 0.62; 95% CI, 0.26–1.46) compared with controls. The omega-3 group had a significantly longer latency (mean difference, 2.10 days; 95% CI 1.98–2.22) and higher birthweight (mean difference, 102.52 g; 95% CI, 20.09–184.95) compared with control subjects; the other secondary outcomes were similar (Table 2).

No data about respiratory distress syndrome and bronchopulmonary dysplasia were reported.

Comment

Main findings

This metaanalysis of the 2 RCTs that evaluated the efficacy of daily oral omega-3 supplementation during pregnancy to reduce the incidence of

TABLE 2
Primary and secondary outcomes

Variable	Olsen et al, 2000[6]	Harper et al, 2010[7]	Total	Relative risk (95% confidence interval)
Gestational age at delivery mean, d	270/261	264/262	267/262	5.30[a] (−0.97 to 11.57)
Mean latency, d	137/130	127/125	132/128	2.10[a] (1.98–2.22)[b]
Preterm birth, n/N				
<37 wk	23/108 vs 40/120	164/434 vs 174/418	187/542 (34.5%) vs 214/538 (39.8%)	0.81 (0.59–1.12)
<34 wk	5/108 vs 16/120	60/434 vs 67/418	65/542 (12.0%) vs 83/538 (15.4%)	0.62 (0.26–1.46)
Spontaneous preterm birth, wk				
<37	N/A	143/434 vs 149/418	143/434 (32.9%) vs 149/418 (35.6%)	0.92 (0.77–1.11)
<34	N/A	51/434 vs 57/418	51/434 (11.8%) vs 57/418 (13.6%)	0.86 (0.61–1.23)
Birthweight, g	3169/2960	2858/2784	3013/2872	102.52[a] (20.09–184.95)[b]
Neonatal intensive care unit, n/N	N/A	110/427 vs 99/410	110/427 (25.8%) vs 99/410 (24.0%)	1.07 (0.84–1.35)
Intraventricular hemorrhage, n/N	N/A	10/427 vs 9/410	10/427 (2.3%) vs 9/410 (2.2%)	1.07 (0.44–2.60)
Necrotizing enterocolitis, n/N	N/A	3/427 vs 4/410	3/427 (0.7%) vs 4/410 (0.9%)	0.72 (0.16–3.20)
Sepsis, n/N	N/A	5/427 vs 3/410	5/427 (1.2%) vs 3/410 (0.7%)	1.60 (0.38–6.65)
Perinatal death, n/N	N/A	16/434 vs 17/418	16/434 (3.7%) vs 17/418 (4.1%)	0.91 (0.46–1.77)

Data are presented as the number of patients in the intervention vs the number of control subjects.

N/A, data not available.

[a] Mean difference; [b] Statistically significant.

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recurrence PTB shows that omega-3 supplementation does not prevent recurrent PTB compared with control. We found no statistically significant differences in the rate of PTB and in neonatal outcome; however, the women who received omega-3 supplementation during pregnancy had a longer latency and higher birthweight. Our results concur with previous level-1 data that showed that omega-3 supplementation is associated with some prolongation of pregnancy.[37] However, although statistically significant, a prolongation of gestation of 2.1 days is unlikely to be clinically meaningful.

Comparison with existing literature

Three other metaanalyses have evaluated the efficacy of omega-3 supplementation during pregnancy, but none of them analyzed women with previous PTB.[37-39] In 2006, Szajewska et al[38] showed that omega-3 supplementation could prolong the duration of low-risk pregnancies by approximately 1.5 days. The Cochrane Review also included RCTs with polyunsaturated fatty acids as control and RCTs with prostaglandin precursor as treatment; it showed that women who received fish oil supplementation had a mean gestation age of 2.6 days longer compared with control subjects but that no effects were found in the prevention of preeclampsia.[39] Another recent metaanalysis showed that omega-3 supplementation during pregnancy in singleton gestations without previous PTB, when evaluated in the best quality RCTs or started at <21 weeks gestation, is associated with 73% decrease in perinatal death but is not associated with any prolongation of gestation.[37] The biologic plausibility of the decrease in perinatal death is not clear and could be associated with the antiinflammatory effects of the omega-3 supplementation. [37]

Strengths and limitations

One of the strengths of our study is the inclusion of only RCT data on the prevention of PTB in a specific population (ie, singleton gestations with previous PTBs). This population represents one of the most at risk for PTB.[2,40] The 2 studies included had a low risk of bias and had the same primary outcome (ie, incidence of PTB at <37 weeks' gestation in women with previous PTB). Both of them were placebo-controlled, and well-designed trials. Furthermore, the total number of the included women was high. We obtained additional and unpublished data from one of the included studies.[7]

The most important limitation of our study is that we found only 2 studies that met the inclusion criteria; however, the number of included women was high. The level of dietary intake of omega-3 could not be controlled for. Indeed, there could be a difference in dietary intake of omega-3 in a population of Northern Europe[6] compared with a population in the US.[7]

Conclusions and implications

The biologic plausibility to explain the efficacy of omega-3 in the prevention of PTB is not completely clear. Omega-3 could down-regulate the production of prostaglandins E_2, and studies have showed that omega-3 fatty acids may have antiinflammatory effects.[41-43] Because prostaglandins E_2 plays a major role in uterine contractions and in the biophysical changes that are associated with cervical ripening, omega-3 may delay the initiation of cervical ripening.[41-43]

Based on these data, omega-3 supplementation during pregnancy currently cannot be recommended for the prevention of recurrent PTB. The benefits in longer latency and higher birthweight may deserve further study. ■

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