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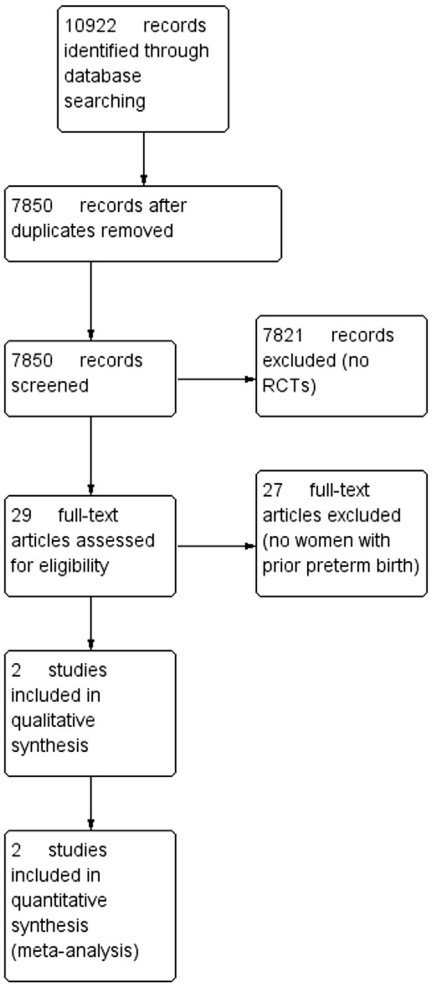
The aim of this metaanalysis was to evaluate the efficacy of omega-3 supplementation during pregnancy in the reduction of recurrence of PTB in asymptomatic singleton gestations with previous PTB.

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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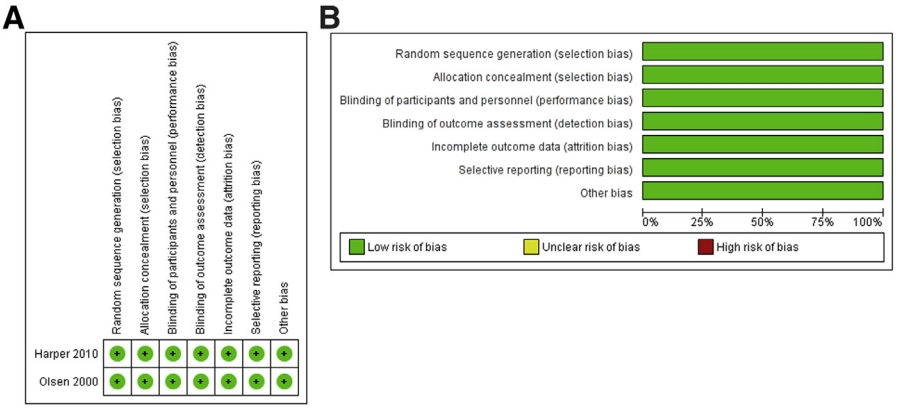
FIGURE 2
Assessment of risk of bias



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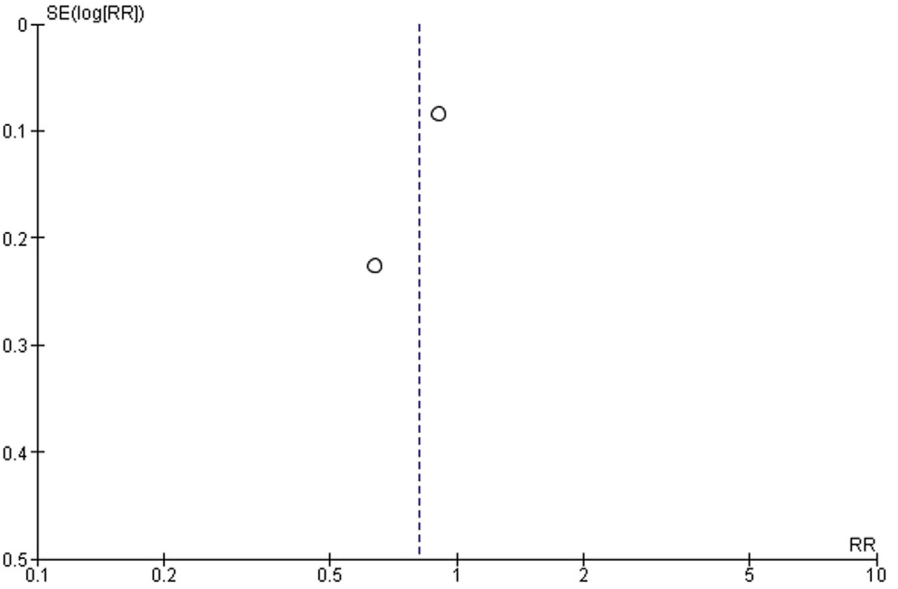
The electronic search and the eligibility of the studies were assessed independently by the authors. Differences were resolved by discussion.

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.

Saccone. Omega-3 and recurrent preterm birth. Am J Obstet Gynecol 2015.