Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that there is some evidence that n-3 long-chain polyunsaturated fatty acid supplementation is associated with a small increase in the duration of pregnancy and in infant head circumference, but the clinical importance of this is unclear and further studies are required. This was a well-conducted review and the authors' cautious conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of long-chain polyunsaturated fatty acid (LC-PUFA) supplementation on pregnancy and foetal growth outcomes in women with low-risk pregnancies.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched from inception to August 2005; the search terms were reported. In addition, published reviews and position papers were examined and reference lists of included studies were screened. No language restrictions were applied. Abstracts and proceedings from scientific meetings were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared LC-PUFA supplementation with placebo or no supplementation were eligible for inclusion. Studies that evaluated precursors of essential fatty acids were excluded. All of the included studies evaluated supplements containing n-3 LC-PUFA; none evaluated n-6 LC-PUFA. The evaluated supplements varied with respect to dose and source of n-3 LC-PUFA, docosahexaenoic acid (DHA) and eicosapentaenoic acid. The review grouped studies as higher dose (approximately 1,000 mg/day DHA) and lower dose (approximately 200 mg/day DHA). Sources of supplements included fish oil, fat and eggs. Controls included corn oil, sunflower oil, olive oil, placebo, ordinary eggs and low intake of eggs. Interventions were commenced from week 15 to week 30 of gestation.

Participants included in the review
Studies in healthy pregnant women were eligible for inclusion. Studies in women with high-risk pregnancies (in which the mother and/or developing foetus were at higher than normal risk for complications during or after pregnancy and birth) were excluded.

Outcomes assessed in the review
Studies that only assessed biochemical outcomes were excluded. After examining the included studies, the reviewers decided to focus on pregnancy outcomes and growth measures at birth. The review assessed pregnancy outcomes, infant growth outcomes and adverse events. Pregnancy outcomes included the duration of pregnancy, percentage of pre-term deliveries, rates of low birth weight, pre-eclampsia, eclampsia, Caesarean section, gestational diabetes and placental weight. Infant growth outcomes included head circumference, birth weight and length at birth.

How were decisions on the relevance of primary studies made?
One reviewer screened titles and abstracts and identified potentially relevant studies and studies of unclear relevance. Two reviewers independently selected studies from those previously identified. Any disagreements were resolved by
Assessment of study quality
Two reviewers independently assessed validity using the following criteria: generation of allocation sequence; allocation concealment; blinding of the investigators, participants, outcome assessors and data analysts; intention-to-treat (ITT) analysis; and comprehensiveness of follow-up (80% or more follow-up was considered adequate). Studies were classified according to the risk of bias: low risk (one or fewer criterion not met), medium risk (three or fewer criteria not met), or high risk (more than three criteria not met).

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. Authors of primary studies were contacted to clarify data, if required. The numbers of events of interest and total number of participants were extracted for dichotomous data, while means and standard deviations were extracted for continuous data. Mean differences were calculated for continuous outcomes and risk ratios were calculated for dichotomous outcomes.

Methods of synthesis
How were the studies combined?
Pooled weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for continuous data, while pooled risk ratios with 95% CIs were calculated for dichotomous data. Fixed-effect models were used in the absence of significant heterogeneity and random-effects models used in its presence. Studies reporting adverse events were combined in narrative. Publication bias was assessed using the test for asymmetry of the funnel plot (described by Egger et al.).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic (p<0.05 indicated significant heterogeneity) and the I-squared statistic. A sensitivity analysis was performed by repeating the analysis after excluding studies classified as having a high risk of bias.

Results of the review
Six RCTs (n=1,278) were included.

Only one study was considered to have a low risk of bias. Two studies reported adequate allocation concealment, five studies reported double-blinding, one study reported adequate ITT analysis, three studies reported adequate follow-up rates, and all studies adequately reported withdrawals and drop-outs.

Pregnancy outcomes. Supplementation with n-3 LC-PUFA was associated with a significantly longer duration of pregnancy (WMD 1.57 days, 95% CI: 0.35, 2.78; based on 6 RCTs, n=1,278). No statistically significant heterogeneity was detected (p=0.35, I-squared 10.8%). There were no significant differences between n-3 LC-PUFA and control in the percentage of pre-term deliveries, or rates of low birth weight, pre-eclampsia, eclampsia, Caesarean section, gestational diabetes, or placental weight. No statistically significant heterogeneity was detected for any of these analyses.

Growth measures in infants. Supplementation with n-3 LC-PUFA was associated with significantly greater head circumference than control (WMD 0.26 cm, 95% CI: 0.02, 0.49; based on 4 RCTs, n=729). No statistically significant heterogeneity was detected (p=0.20, I-squared 34.8%). After excluding studies classified as having a high risk of bias, there was no significant difference between supplementation and control (WMD 0.26 cm, 95% CI: -0.02, 0.53). There were no significant differences between n-3 LC-PUFA and control in birth weight or length at birth. No statistically significant heterogeneity was detected for any of these analyses.

Adverse effects (reported in 3 RCTs).

One study reported similar rates of withdrawal between cod liver oil and corn oil (43.1% versus 38.7%). One study
stated that significantly more women reported belching and unpleasant taste with fish oil compared with olive oil (70% versus 20% and 42% versus 7.4%, respectively, p<0.001) and significantly greater blood loss with fish oil compared with olive oil (p=0.04). One study reported that significantly more women consuming DHA from eggs reported one or more adverse events compared with women eating regular eggs (38% versus 25%, p<0.01), but serious adverse event rates were similar between treatment groups.

Authors' conclusions
There is some evidence that n-3 LC-PUFA supplementation given to low-risk pregnant women is associated with a small increase in the duration of pregnancy and in infant head circumference, but the clinical importance of this is unclear and further studies are required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, and study design; the primary review outcomes were not determined in advance. Several relevant sources were searched and attempts were made to minimise language bias. However, no attempts were made to minimise publication bias; the reviewers examined the potential for publication bias and found none, although they acknowledged the limited value of a negative finding based on a small number of studies. Validity was assessed and the results reported. Methods were used to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. The studies were appropriately combined using meta-analysis, statistical heterogeneity was assessed, and sensitivity analyses were performed. Differences between the studies were discussed and study quality was taken into account when summarising the evidence. This was a well-conducted review and the authors’ cautious conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice. Research: The authors stated the need for larger studies that take confounding factors into account to evaluate the effects of LC-PUFA supplements on rates of low birth weight, other growth measures, and infant visual function and cognitive development. There is also a need for a systematic review of the effects of fish-oil supplementation in women at high-risk of pre-term delivery.

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