

Systematic Review

Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials

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It is hypothesized that the intake of long-chain PUFA (LC-PUFA) throughout pregnancy could protect against pre-eclampsia, pregnancy-induced hypertension or intra-uterine growth retardation, and is essential for optimal neural development. The objective of the present study was to systematically evaluate the effect of LC-PUFA supplementation of high-risk pregnant women's diets on pregnancy outcomes and growth measures at birth. We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library through March 2006 and references in reviewed articles for randomized controlled trials (RCT) comparing LC-PUFA supplementation with placebo or no supplementation in women with high-risk pregnancies. We found no evidence that supplementation influenced the duration of pregnancy or the percentage of preterm deliveries < 37 weeks of gestation. However, compared with controls, supplementation was associated with a significantly lower rate of early preterm delivery (< 34 weeks of gestation) (two RCT; *n* 291; relative risk 0.39 (95% CI 0.18, 0.84)). There was no significant difference in the infant birth weight, the rate of low birth weight (< 2500 g or < 10th percentile) and the recurrence of intra-uterine growth retardation. Other pregnancy outcomes (for example, the rate of pregnancy-induced hypertension, the rate of pre-eclampsia and the rate of Caesarean section) were also similar in both groups. In conclusion, the present data suggest that supplementation with *n*-3 LC-PUFA in women with high-risk pregnancies reduced the risk of early preterm delivery in the fatty acid-supplemented group compared with the placebo group, while no other effects on pregnancy outcomes were detected.

Polyunsaturated fatty acids: Fatty acids: High-risk pregnancy

Numerous studies reveal that long-chain PUFA (LC-PUFA) biological systems have the potential to influence maternal health during pregnancy as well as fetal and child health¹. Children delivered at term receive an important supply of *n*-3 fatty acids, especially in the third trimester of pregnancy. This supply is essential for optimal fetal growth and neurodevelopment^{2–4}. When the gestational period is shortened, a child delivered prematurely receives less exposure to fatty acids. It has been suggested that imbalance between *n*-3 and *n*-6 fatty acids may be associated with disturbances in the production of PG (prostaglandin and thromboxane) which are responsible for placental blood flow (indispensable for normal fetus growth and development) and participate in the initiation of labour⁵. Thus, LC-PUFA supplementation may decrease the risk of certain pregnancy complications, particularly pre-eclampsia, pregnancy-induced hypertension (PIH), intra-uterine growth retardation (IUGR) and preterm delivery (PD).

Recently, we published the results of a meta-analysis⁶ of six randomized controlled trials (RCT) showing that *n*-3 LC-PUFA supplementation during low-risk pregnancy may enhance the duration of pregnancy and head circumference, although the mean effect size was small. We found no additional benefits for a number of other maternal and child outcomes such as the percentage of PD, the rate of low birth weight, the risk of pre-eclampsia and the risk of eclampsia.

The present meta-analysis was undertaken to investigate the safety and efficacy of LC-PUFA in modulating various pregnancy outcomes and growth parameters at birth in high-risk pregnancies.

Material and methods

Criteria for inclusion of studies

Studies included in the present review had to be RCT or quasi-RCT comparing LC-PUFA supplementation with placebo or

Abbreviations: Earl, earlier pregnancy; IUGR, intra-uterine growth retardation; LC-PUFA, long-chain PUFA; PD, preterm delivery; PIH, pregnancy-induced hypertension; RCT, randomized controlled trial; RR, relative risk.

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no supplementation in high-risk pregnant women. After an initial assessment of the reviewed trials, we decided to focus on pregnancy complications and growth measures at birth. Additionally, we extracted all data related to adverse events. Trials with healthy pregnant women in twin pregnancies and/or with only biochemical outcomes were not included.

Search strategy to identify studies

The search strategy included the use of a validated filter for identifying RCT⁷, which was combined with a topic-specific strategy using PubMed's MeSH terms related to the exposure and its sources, for example, 'FA' or 'omega' or '*n*-6' or '*n*-3' or 'eicosapentaenoic acid' or 'EPA' or 'docosahexaenoic acid' or 'DHA' or 'arachidonic acid' or 'LC-PUFA' or 'long-chain FA' or 'essential FA' or 'fish oil', and relevant population terms, for example, 'high risk pregnancy' or 'gestational hypertension'. We performed a computerized literature search of MEDLINE (from 1966 to March 2006), EMBASE (from 1980 to March 2006), CINAHL (the Cumulative Index to Nursing and Allied Health) (from 1982 to March 2006) and the Cochrane Library (issue 2, 2005). We supplemented this search by examining published reviews and position papers. References in reviewed articles constituted additional sources. We imposed no limit with respect to the language of publications, but certain publication types (for example, letters to the editor, abstracts, proceedings from scientific meetings) were excluded.

Methods of the review

Trial selection. One reviewer (A. H.) initially screened the title, abstract and keywords of every record identified by the search strategy; this reviewer then retrieved the full text for potentially relevant studies and for trials where the relevance was unclear. Two reviewers (A. H. and H. S.) independently applied the inclusion criteria to each potentially relevant trial to determine its eligibility. When differences in opinion existed, they were resolved by discussion.

Quality assessment of trials. Two reviewers (A. H. and H. S.) independently, but without being blinded to the authors or journal, assessed the quality of the studies that met the inclusion criteria. The following strategies associated with good-quality studies were assessed: generation of allocation sequences and allocation concealment; blinding of investigators, participants, outcome assessors, and data analysis (yes, no, or not reported); intention-to-treat analysis (yes or no); comprehensive follow-up. The generation of allocation sequences was considered adequate if the resulting sequences were unpredictable (for example, computer-generated random numbers) and inadequate if the resulting sequences were predictable (for example, according to case record number). Allocation concealment was considered adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before enrolment of eligible participants in the study. The quality of the allocation concealment was considered unclear when randomization was used but no information about the method was available and considered inadequate when inappropriate methods of randomization were used. Methods for blinding were considered as double blind (neither patients

nor care providers or assessors knew which intervention was given), single blind (either patients or care providers or assessors were aware of intervention) and open (all parties were aware of intervention). In regard to the intention-to-treat analysis, a positive finding on the reviewers' part meant that the authors had specifically reported undertaking this type of analysis; a negative finding meant that authors did not report the use of intention-to-treat analysis, that we could not confirm its use on study assessment, or both. To evaluate the completeness of patient follow-up, we determined the percentage of participants excluded or lost to follow-up. Completeness of follow-up was considered to be adequate if $\geq 80\%$ of participants were included in the final analysis (or assumed to be adequate when there was no mention of losses to follow-up).

Data extraction. Two reviewers (A. H. and H. S.) independently performed data extraction by using standard data-extraction forms. When important data were not reported or were unclear, we contacted the corresponding authors of the primary studies for clarification. Discrepancies between reviewers were resolved by discussion. For dichotomous outcomes, we extracted the total number of participants and the number of participants who experienced the event. For continuous outcomes, we extracted the total number of participants and the means and standard deviations. We compared the extracted data to identify errors. One reviewer (H. S.) entered the data into REVIEW MANAGER for WINDOWS software (REVMAN version 4.2; The Cochrane Collaboration, Oxford, UK) for analysis.

Statistical methods for data analysis

We used the REVMAN for all statistical analyses. The weighted mean difference between the treatment and control groups was selected to represent the difference in continuous outcomes with 95% CI. The dichotomous outcomes for individual studies and pooled statistics are reported as the relative risk (RR) between the experimental and control groups (with 95% CI). To pool the data, we used either a fixed-effect or random-effects model approach, according to the heterogeneity in outcomes across studies. Heterogeneity was quantified by χ^2 and I^2 , which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. We took no formal steps to look for publication bias, such as by plotting effect sizes or by calculating test statistics. In most cases, there are few studies on any given effect, and any formal method would have had little power.

Description of studies

Initially we identified eight articles. Eventually, only four of them⁸⁻¹¹ with 1264 participants met our predefined inclusion criteria (Table 1). All included studies were fully peer-reviewed publications. A study by Olsen *et al.*¹¹ included six independent randomized clinical trials (four prophylactic and two therapeutic), and addressed various possible effects of fish oil supplementation in high-risk pregnancies. The inclusion criteria of the present review were met by only three prophylactic trials, which enrolled women after 16 weeks of gestation with an uncomplicated pregnancy but

Table 1. Characteristics of the included studies

Study	Generation of randomization	Allocation	Blinding	ITT	Follow-up (%)	Population	Intervention	Duration of intervention
Bulstra-Ramakers <i>et al.</i> (1995) ⁸	Adequate	Adequate	Yes	No	93	History of IUGR in earlier pregnancy (n 68)	EPA 3000 mg	From week 12–14
Moodley & Norman (1989) ⁹	Adequate	Adequate	Yes	Yes	100	Signs or symptoms of pre-eclampsia in the current pregnancy (n 47)	GLA + LA 4000 mg	Third trimester (minimum 2 weeks)
Olsen <i>et al.</i> (2000) ¹¹	Adequate	Adequate	Yes	Yes	98	History of: PD (n 232)	DHA 900 mg, EPA 1300 mg	From week 20
Earl-PD					94	IUGR (n 280)		
Earl-IUGR					90	PIH (n 386)		
Earl-PIH					99	Proteinuric or non-proteinuric PIH or asymmetrical growth retardation (n 233)	DHA 1080 mg, EPA 1620 mg	From week 19–26
Onwude <i>et al.</i> (1995) ¹⁰	Adequate	Adequate	Yes	Yes				

ITT, intention to treat analysis; IUGR, intra-uterine growth retardation; GLA, γ -linoleic acid; LA, linoleic acid; Earl, earlier pregnancy; PD, preterm delivery; PIH, pregnancy-induced hypertension.

with a history of PD (Earl-PD), IUGR (Earl-IUGR), or PIH (Earl-PIH) in an earlier pregnancy. The remaining three trials of the Olsen *et al.* study¹¹ were excluded: one prophylactic trial enrolled women with current twin pregnancies; two therapeutic trials did not report any useable data by outcomes of the present review. In addition, four RCT were also excluded (Table 2). In brief, the studies were excluded because the population in one trial was the same as reported in another study¹², the type of supplementation was combination LC-PUFA with another intervention¹³, and in one trial investigators included a mixed population of women in low- and high-risk pregnancies¹⁴. Further, one of the initially included studies¹⁵ was eliminated due to its poor methodological quality – completeness of follow up in this trial was inadequate (only 63% of participants were included in the final analysis).

Participants

Table 1 summarizes characteristics of women with high-risk pregnancies. In brief, two studies^{8,11} included women considered to be in high-risk pregnancies because (1) they had an earlier pregnancy PD (Olsen *et al.* Earl-PD trial¹¹), (2) had IUGR (Olsen *et al.* Earl-IUGR trial¹¹ and Bulstra-Ramakers *et al.*⁸), or (3) had PIH (Olsen *et al.* Earl-PIH¹¹). Two RCT^{9,10} included women with a complication in the current pregnancy.

Intervention

The sources as well as the doses and duration of LC-PUFA supplied varied among trials (Table 1). In one trial investigators used primrose oil alone⁹, in one RCT investigators reported supplementation with EPA alone⁸, and in the remaining two studies^{10,11} investigators used fish oil as a varied combination of EPA with DHA. In the included studies, the daily dose of DHA was about 900–1080 mg. The trials differed in the starting time of intervention, beginning as early as from week 12 of gestation⁸ to as late as week 30 of gestation^{9,11}.

Methodological quality of the included studies

All four trials used an adequate randomization method and an adequate method to conceal allocation. All trials were described as ‘double blinded’. An adequate description of the intention-to-treat analysis was provided only in three RCT^{8,10,11}. Withdrawals and dropouts were described adequately in all studies. All trials included an adequate number of participants in the final analysis (Table 1).

Results

Duration of pregnancy

Based on the results of two RCT^{8,10}, involving 295 participants, we found no evidence that supplementation influences the duration of pregnancy > 37 weeks of gestation (RR 0.99 (95% CI 0.9, 1.1)) (Fig. 1). One study reported data on the duration of pregnancy in days. The results of this trial showed a significant difference between the supplemented and non-supplemented group (269.2 (SD 19.7) v. 260.7

Table 2. Characteristics of the excluded studies

Study	Study design, purpose, and/or reason(s) for exclusion
D'Almeida <i>et al.</i> (1992) ¹⁴	Mixed population of healthy pregnant women (79%) and women with high-risk pregnancies (21%)
Herrera <i>et al.</i> (1998) ¹³	As a supplementation investigators used a low-dose linoleic acid with a combination of Ca
Laivouri <i>et al.</i> (1993) ¹⁵	Poor methodological quality; only 63% of participants included in final analysis
Pavlowich <i>et al.</i> (1999) ¹²	The population was the same as reported in the Olsen study ¹¹
Olsen <i>et al.</i> (2000) ¹¹	Women with current twin pregnancies Two therapeutic trials did not report any useable data by outcomes of the present review

(SD 29.5) d, mean difference 8.5 (SD 1.9) d, $P=0.01$; Olsen *et al.* Earl-PD¹¹).

In addition, the results of the analysis demonstrated no association of maternal fatty acid intake with risk of PD < 37 weeks of gestation (three RCT^{8,10,11} involving 523 participants; RR 0.82 (95% CI 0.6, 1.12)). However, when the effects of supplementation were examined on the rate of early PD (< 34 weeks of gestation), the RR was found to be reduced in the supplemented group (two RCT^{8,11} involving 291 participants; RR 0.39 (95% CI 0.18, 0.84)) (Fig. 1).

Birth weight

In the two RCT involving 494 infants, we found no significant difference in mean birth weight between supplemented and non-supplemented control subjects (pooled weighted mean difference -21.7 (95% CI -129.4 , 85.9) g; Fig. 2) (Olsen *et al.* Earl-PD and Olsen *et al.* Earl-IUGR¹¹). Data from the Moodley & Norman study⁹ were not included in the meta-analysis. That study presented only the mean, without the standard deviations of outcomes. However, these data showed no significant difference in birth weight for those supplemented compared with control (2.62 (range 1.00–3.05) v. 2.66 (range 1.90–3.25) kg).

There was also no significant difference in the rate of infants born with low birth weight, defined as birth weight below the 10th percentile (two RCT^{8,10} involving 295 infants; RR 1.03 (95% CI 0.73, 1.47)), as well as birth weight below 2500 g (two RCT (Olsen *et al.* Earl-PD and Olsen *et al.* Earl-IUGR¹¹); 494 infants; RR 1.03 (95% CI 0.71, 1.51)) (Fig. 1).

Only one RCT¹¹ reported data on the recurrence of IUGR. There was no significant difference between supplemented and non-supplemented subjects (RR 1.17 (95% CI 0.81, 1.69)).

Other pregnancy outcomes

We found no evidence that supplementation with any LC-PUFA influences PIH (three RCT^{8,10,11} involving 645 women; RR 1.06 (95% CI 0.87, 1.29)). Similarly, there was no significant difference between groups, when we assessed proteinuric PIH (two RCT^{8,10} involving 295 women; RR 0.99 (95% CI 0.56, 1.74)) and non-proteinuric PIH (two RCT^{8,10} involving 295 women; RR 1.20 (95% CI 0.33, 1.47)). In addition, two RCT^{8,10} involving 449 women recorded use of anti-hypertensive therapy. These data did not differ significantly between supplemented and non-supplemented subjects (RR 0.73 (95% CI 0.46, 1.15)). Based on one study (Olsen *et al.* Earl-PIH), no difference in the rate of pre-eclampsia was found (one RCT¹¹ involving 321 women; RR 0.72 (95% CI 0.35, 1.49)). In two RCT^{8,10}

involving 295 participants, no significant difference between supplemented and non-supplemented women was observed in the rate of Caesarean delivery (RR 1.30 (95% CI 0.89, 1.90)). The rate of fetal and/or neonatal death was similar in both groups (two RCT^{8,10} involving 295 participants; RR 0.6 (95% CI 0.15, 2.42)) (Fig. 1).

Heterogeneity

Significant heterogeneity was found for birth weight < 2500 g (χ^2 5.15; $P=0.02$; I^2 80.6%). For other outcomes, there was no heterogeneity.

Adverse events

A narrative synthesis of these data on adverse events was undertaken. Among four trials included in the review, adverse effects were reported only in two of them^{10,11}. In the study by Onwude *et al.*¹⁰ the response rate for the adverse events questionnaire was only 32%. The reported side effects between fish oil and placebo were belching (2.4 v. 0%), unpleasant taste (17 v. 5.9%), nausea (9.7 v. 2.9%) and stomach pains (4.8 v. 0%). With regard to the condition of the child after delivery, 27% respondents in the supplemented group and 35% in the control group reported that the children had suffered minor illness. In addition, there was one case in the supplemented group of staphylococcal septicaemia.

Olsen *et al.*¹¹ combined all six independent trials into a single study. They compared the incidence of adverse effects between supplemented and non-supplemented subjects; separate data for the individual trials were not reported. These extracted data showed that the population of women who reported belching and unpleasant taste was significantly greater in the fish oil group than in the control group (29.2 v. 8.1%, and 17.0 v. 2.3%, respectively). Other complaints such as nausea, vomiting, diarrhoea, constipation, nose bleeding and vaginal bleeding were equally distributed between the two groups. There was a possible trend regarding infant intracranial haemorrhage which was greater in the fish oil than the olive oil group (RR 2.4 (95% CI 0.6, 11.6); $P=0.22$). However, no differences were observed between both groups in any of the examined variables, which could reflect other bleeding complications (such as nose bleeding and vaginal bleeding leading to hospital admittance).

Discussion

The results of the present analysis indicate that *n*-3 LC-PUFA fish oil supplementation during high-risk pregnancy reduced the risk of early PD (< 34 weeks of gestation). However,

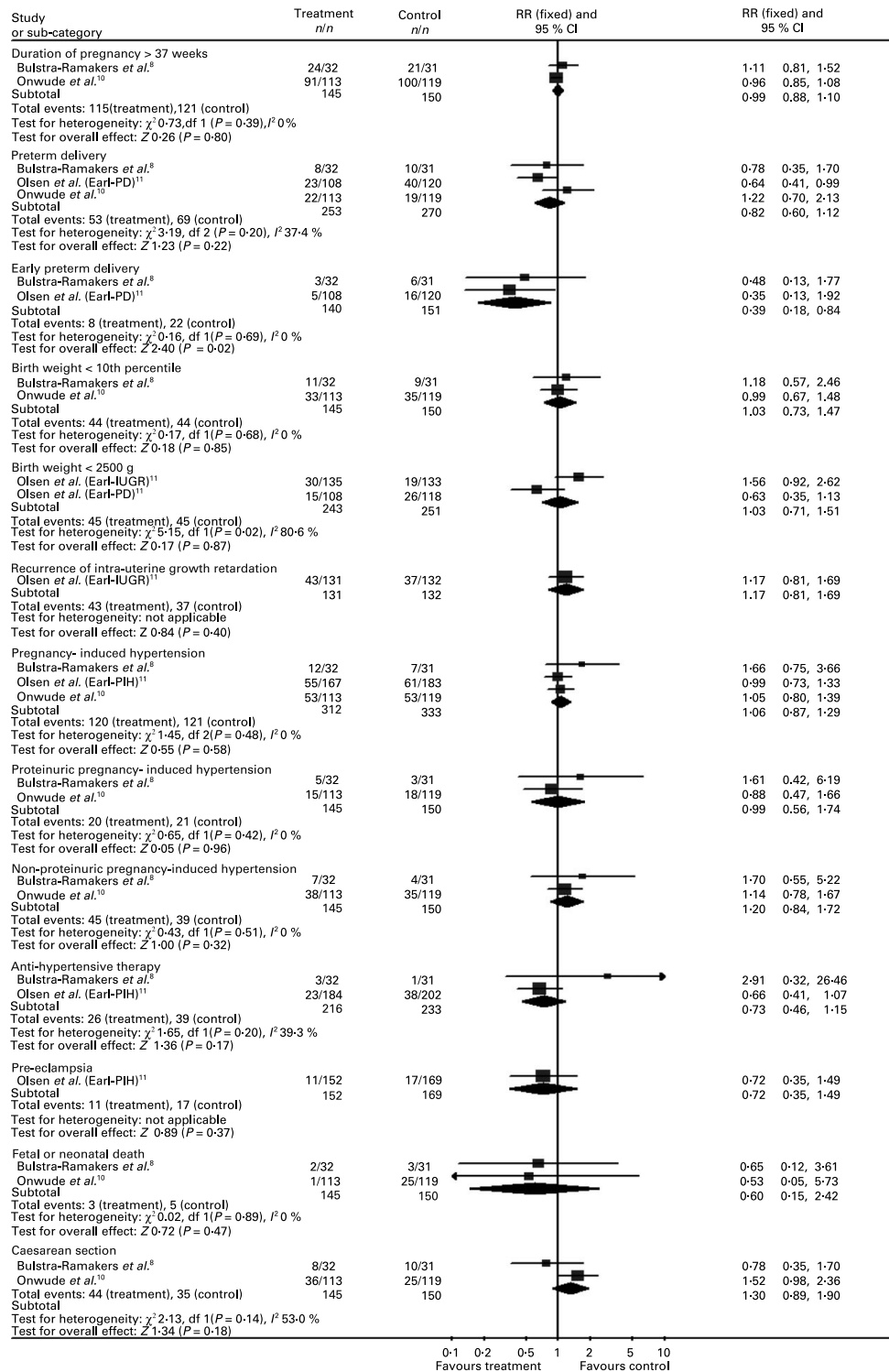


Fig. 1. Relative risk (RR) and 95% CI of the pregnancy outcomes in women supplemented with n-3 long-chain PUFA as compared with women who received no supplementation or placebo. Values for individual trials and pooled data (fixed-effect model) are shown. Earl-PD, preterm delivery in an earlier pregnancy; Earl-IUGR, intra-uterine growth retardation in an earlier pregnancy; Earl-PIH, pregnancy-induced hypertension in an earlier pregnancy.

since there was a significant heterogeneity for birth weight < 2500 g and since usually weight correlated with gestational week, the significant result of a lower incidence of early PD should be viewed with caution.

The conclusions from the present review apply only to women whose pregnancies are high-risk pregnancies. As we demonstrated earlier⁶, available results from RCT involving women at low risk of preterm birth indicate that maternal

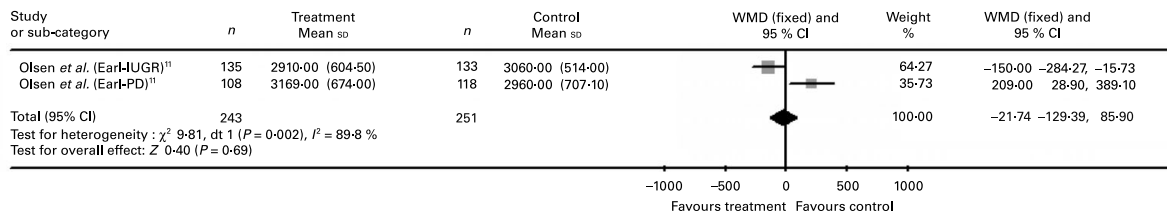


Fig. 2. Weighted mean difference (WMD) and 95% CI of the birth weight (g) of infants born to women who during pregnancy were supplemented with *n*-3 long-chain PUFA as compared with the infants born to women who received no supplementation or placebo. Values for individual trials and pooled data (fixed-effect model) are shown. Ear-IUGR, intra-uterine growth retardation in an earlier pregnancy; Ear-PD, preterm delivery in an earlier pregnancy.

LC-PUFA supplementation is associated with a small increment in the duration of pregnancy; however, the implications of this finding for later growth and development are not clear.

The results of the present review, as well as our previous review,⁶ are in line with the conclusions of the recent Cochrane Review¹⁶ that concluded there is not enough evidence to support the routine use of marine oil, or other PG precursor, supplements during pregnancy to reduce the risk of pre-eclampsia, preterm birth, low birth weight or small for gestational age.

The present review focused on the effect of LC-PUFA supplementation during high-risk pregnancy on pregnancy outcomes and infant growth measures. Although it has been proposed that accretion of *n*-3 fatty acids has the potential to improve infants' neurocognitive development and visual function,^{17,18} we did not find any studies which examined this issue in the population of high-risk pregnancies.

Limitations

We acknowledge several limitations to the present review. The trials differed considerably in the definition of what constituted high-risk pregnancy, which may be an argument against combining the results. Unfortunately, sufficient details to extract data about separate participant types were not available in the original trials. Thus, the delineation of more defined populations was not feasible. A further limitation is that intervention studies used various supplementations (i.e. primrose oil, EPA, EPA and DHA). This variability may have introduced a bias in the cumulative data. Nevertheless, we decided to pool the results together to estimate the extent to which LC-PUFA supplementation, achieved by a variety of means, generally has an impact on pregnancy outcomes and growth measures at birth. Due to a limited number of studies available, we abstained from subgroup analysis based on the type of intervention. The sample sizes in some trials, as well as the number of trials for some comparisons (for example, IUGR, or pre-eclampsia), were very small. The pooled sample sizes were also small, and, thus, there was little statistical power; consequently, we cannot exclude chance as an explanation for the results of many comparisons.

In our meta-analysis, the statistical tests of the homogeneity (total consistency) of the results, with one exception, were non-significant. However, it is important to stress that the power of the statistical methods that investigate heterogeneity is limited, particularly for meta-analyses based on a small number of studies, as in this case. Consequently, the results

of our meta-analysis, particularly those regarding pregnancy outcomes, should be viewed with caution.

Our meta-analysis is based on a limited number of studies and indicated that more studies are needed to address this topic. Nevertheless, we believe that our demonstration of clinical uncertainty about this issue is an important finding. As pointed out by Alderson & Roberts,¹⁹ clinical uncertainty is a prerequisite for the large-scale RCT needed to evaluate the influence of such interventions; it also helps to clarify available treatment options and stimulate new and better research.

Conclusions

Some evidence exists that maternal LC-PUFA supplementation is associated with a small reduction in risk of early PD. However, there was no convincing indication of any prophylactic effects of LC-PUFA supplementation on IUGR, PIH or other pregnancy complications. There is not enough evidence to recommend the routine use of LC-PUFA supplementation in high-risk pregnancy. Further studies that have larger sample sizes and that take confounding factors into account are needed to examine the effects of such supplementation in high-risk pregnancies.

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