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REVIEW ARTICLE

Omega-3 long-chain polyunsaturated fatty acids and fish oil supplementation during pregnancy: which evidence?

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Abstract

Objective: The aim of this study was to provide evidence-based recommendations for omega-3 supplementation during pregnancy through a systematic review of level-1 data published on this topic.

Methods: We reviewed all randomized-controlled trials (RCTs) including women who were randomized to treatment with either omega-3 supplementation or control (placebo or no treatment) during pregnancy and analyzed all the outcomes reported in the trials, separately. We planned to evaluate the effect of omega-3 on: preterm birth (PTB); pre-eclampsia (PE) and intrauterine growth restriction (IUGR); gestational diabetes; perinatal mortality; small for gestational age (SGA) and birth weight; infant eye and brain development; and postpartum depression.

Results: We identified 34 RCTs including 14 106 singletons and 2578 twins. These level-1 data showed that omega-3 was not associated with prevention of PTB, PE, IUGR, gestational diabetes, SGA, post-partum depression or better children development. Data about birth weight, perinatal mortality and childhood cognitive outcome were limited. Women with gestational diabetes who received omega-3 had significantly lower serum C-reactive protein concentrations, low incidence of hyperbilirubinemia in newborns and decreased newborns' hospitalization rate.

Conclusions: There was not enough evidence to support the routine use of omega-3 supplementation during pregnancy. Given the 73% significant decrease in perinatal death in the singleton gestations who started omega-3 supplementation $\leq$ 20 weeks, further research is needed. Large RCTs in multiple gestations and longer follow-up are also required.

Keywords

Meta-analysis, nutrition, perinatal death, pre-eclampsia, preterm birth, supplement, systematic review

History

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Introduction

Omega-3 fatty acids (*n*–3), such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are long-chain polyunsaturated fatty acids (LCPUFAs). These are essential polyunsaturated fatty acids (PUFAs) because the body cannot produce them, and therefore must be obtained through the diet or synthesized from their precursor alfa-linolenic acid. The pregnancy is a time of increased risk for omega-3 deficiency as they are used for the developing fetus [1–3] For this reason, omega-3 supplementation is often recommended during pregnancy [4,5].

The evidence of a positive association between omega-3 supplementation during pregnancy and maternal and neonatal outcomes came originally from observational studies [6–8]. Olsen et al. in 1986 first suggested that omega-3 supplementation during pregnancy may lead to better pregnancy outcomes by prolonging gestation [6]. Randomized-controlled trials (RCTs) have been performed to assess if omega-3 supplementation affects pregnancy outcomes, with contradicting results [9–42]. The aim of this study was to provide evidence-based recommendations for omega-3 supplementation during pregnancy through a review of all level-1 data published on this topic.

Methods

The search strategy included the use of key words related to ''fish oil,'' ''long chain polyunsaturated fatty acids,'' ''pregnancy,'' ''trial,'' ''randomized,'' ''docosahexaenoic,'' ''eicosapentaenoic,'' ''prostaglandins,'' ''DHA,'' ''EPA'' and ''omega-3'' in MEDLINE, Scopus, Sciencedirect, 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 March 2015. No restrictions for language or

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geographic location were applied. All published RCTs on omega-3 supplementation during pregnancy were carefully reviewed. Two reviewers (G. S. and V. B.) independently performed the search and reviewed citations for potentially eligible studies.

We reviewed all RCTs of women who were randomized to either omega-3 supplementation or control (i.e. placebo or no treatment) during pregnancy and analyzed all the outcomes reported in the trials both in singleton and in multiple gestations, separately. Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were excluded. We planned separate analyses to evaluate the effect of omega-3 supplementation on: spontaneous preterm birth (PTB) (i.e. PTB < 37 weeks); pre-eclampsia (PE) and intrauterine growth restriction (IUGR) (i.e. ultrasound estimated fetal weight <10th percentile); gestational diabetes; perinatal mortality (i.e. either stillbirth or neonatal death); small for gestational age (SGA) (i.e. birth weight <10th percentile for gestational age) and birth weight; infant eye and brain development; and postpartum depression.

Two review authors (G. S. and V. B.) independently assessed inclusion criteria, risk of bias and data extraction. Disagreements were resolved by consensus. The overall risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [43]. The overall review authors' judgments were categorized as ''low risk'', ''high risk'' or ''unclear risk'' of bias [43]. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms.

The data analysis was completed independently by two authors (G. S., V. B.) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistics [43]. In case of statistically significant heterogeneity ($I^2 \geq 50\%$), the random effect model of DerSimonian and Laird was used to obtain the pooled risk estimate, otherwise a fixed-effect model was planned [43]. The summary measures were reported as relative risk (RR) or as mean difference with 95% confidence interval (CI), with an RR < 1 indicating treatment benefit. p values < 0.05 was considered statistically significant.

The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42015017264). This systematic review was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [44].

Results

We identified 34 RCTs on omega-3 supplementation during pregnancy (Table 1) [9–42]. Most of them came from Northern Europe. The vast majority of women randomized were singleton gestations (14 106 women), making analyses possible for this population, while data were limited for multiple gestations (2,578 women). Most of them had a low overall risk of bias according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [43].

Figure 1 shows the flow diagram of information through the different phases of the review. No quasi-randomized trials were found during the search process.

Preterm birth (singleton gestations)

Nine RCTs including 3854 asymptomatic singleton gestations without prior PTB evaluated the prophylactic treatment with omega-3 supplementation in prevention of PTB [9–17]. A recent meta-analysis of these nine RCTs showed that omega-3 was not associated neither with significant prevention of PTB < 37 weeks (RR 0.90, 95% confidence interval (CI) 0.72–1.11; Figure 2) nor with improved neonatal outcomes [45]. However, in the planned subgroup analyses of omega-3 started ≤20 weeks and in the studies with low risk of bias, a significant decrease in perinatal death was found (RR 0.27, 95% CI 0.09–0.79; Figure 3).

Two large placebo-controlled and well-designed RCTs including 1080 women evaluated the efficacy of omega-3 in prevention of recurrent PTB in singleton gestations with prior PTB [27,28]. Pooled results of the two RCTs showed no statistically significant decrease in the incidence of recurrent PTB < 37 weeks (RR 0.81, 95% CI 0.59–1.12) and PTB < 34 weeks (RR 0.62, 95% CI 0.26–1.46), but showed longer latency (mean difference 2.10 d, 95% CI 1.98–2.2) and higher birth weight (mean difference 102 g, 95% CI 20.09–184.95) compared with omega-3 group with the placebo one in women with prior PTB [46]. We found no RCT assessed the efficacy of omega-3 in prevention of PTB in women with short cervical length.

Pre-eclampsia and intrauterine growth restriction (singleton gestations)

Seven RCTs, including 2869 singleton gestations, evaluated the efficacy of omega-3 supplementation during pregnancy in prevention of PE or IUGR [10,11,26,27,29,31,41]. Four trials enrolled high-risk singleton gestations (i.e. women with prior PE or IUGR) [10,11,27,31], while the other three had low-risk singleton gestations [26,29,41]. Three of these RCTs were well-designed trials [10,11,27], including the largest one with 1477 women enrolled [27]. However, only one trial showed a positive association between omega-3 and PE; it showed that daily oral DHA supplementation during pregnancy reduced the incidence of PE significantly in women with chronic hypertension (RR 0.25, 95% CI 0.09–0.69) [31].

A Cochrane review, including six trials on high-risk and on low-risk pregnancies [10,11,26,27,29,41], showed a small but significant increase in the mean length of gestation (mean difference 2.55 d, 95% CI 1.03–4.07), but no significant effect in prevention of PE (RR 0.86, 95% CI 0.59–1.27) or IUGR (RR 1.13, 95% CI 0.96–1.34) [47].

Another well-designed trial, including 533 healthy low-risk singleton gestations, showed that omega-3 supplementation during pregnancy had no statistically significant effect on blood pressure comparing to no treatment (RR 0.48, 95% CI 0.22–1.06) [25].

Table 1. Characteristics of the included trials.

	Study location	Participants	Inclusion criteria	Intervention daily	Primary outcome	Overall risk of bias
Olsen 1990 [33]	United Kingdom	1999 twin gestations	N/A	DHA 100 mg	Incidence of PE	Low
Olsen 1992 [9]	Denmark	397 singleton gestations	Singleton gestations without prior PTB	DHA 920 mg + EPA 1280 mg	Birth weight	Low
D'Almedia 1992 [29]	Angola	100 singleton gestations	Singleton gestations without prior PE	DHA 80 mg + EPA 140 mg	Incidence of PE	Low
Laivuori 1993 [34]	Finland	11 singleton gestations	Singleton gestations with PE	DHA 360 mg + EPA 540 mg	Biochemical outcomes	High
Sorensen 1993 [40]	Denmark	533 singleton gestations	Singleton gestations without prior PE	DHA 920 mg + EPA 1280 mg	Incidence of PE	Moderate
Bulstra-Ramakers 1994 [10]	Netherlands	63 singleton gestations	Singleton gestations with prior SGA	EPA 3000 mg	Incidence of SGA	Low
Onwude 1995 [11]	United Kingdom	232 singleton gestations	Singleton gestations without prior SGA	DHA 1080 mg + EPA 1620 mg	Incidence of SGA	Low
Van Houwelingen 1995 [23]	Netherlands	23 singleton gestations	N/A	DHA 920 mg + EPA 1280 mg	Biochemical outcomes	High
Salving 1996 [25]	Denmark	533 singleton gestations	Singleton gestations without prior PE	DHA 920 mg + EPA 1280 mg	Blood pressure	Unclear
Herrera 1998 [31]	Denmark	86 singleton gestations	Singleton gestations with chronic hypertension	DHA 450 mg	Incidence of PE	High
Borod 1999 [22]	Denmark	53 singleton gestations	N/A	DHA 230 mg	Biochemical outcomes	High
Olsen 2000 [27]	Northern Europe	898 singleton gestations and 579 twin gestations	Four harms: Singleton gestations with prior PTB, singleton gestations with prior SGA, singleton gestation with prior PE, twin gestations	DHA 900 mg + EPA 1300 mg	Incidence of PTB, incidence of SGA, incidence of PE, birth weight	Low
Helland 2001 [35]	Norway	590 singleton gestations	Nulliparous singleton gestations	DHA 500 mg + EPA 750 mg	Biochemical outcomes	Low
Malcolm 2003 [12]	United Kingdom	100 singleton gestations	Low-risk singleton gestations	DHA 100 mg	Infant visual function	Unclear
Montgomery 2003 [24]	United Kingdom	100 singleton gestations	N/A	DHA 400 mg	Biochemical outcomes	Unclear
Smuts 2003 [26]	USA	350 singleton gestations	Singleton gestation without prior PE or prior IUGR	DHA 220 mg	Incidence of IUGR	High
Smuts 2003 [39]	USA	53 singleton gestations	Singleton gestation without prior PE or prior IUGR	DHA 220 mg	Birth weight	High
Helland 2003 [41]	Norway	76 singleton gestations	Low-risk singleton gestations	DHA 803 mg + EPA 1183 mg	Children brain development	Low
Sanjuro 2004 [13]	Spain	16 singleton gestations	Singleton gestations without prior PTB	DHA 200 mg	Birth weight	Low
Colombo 2004 [20]	Spain	69 singleton gestations	N/A	DHA 220 mg	Infant attention in toddlerhood	Low
Boris 2004 [21]	Denmark	36 singleton gestations	N/A	DHA 900 mg + EPA 1300 mg	Biochemical outcomes	Low
de Groot 2004 [30]	Netherlands	58 singleton gestations	N/A	N/A	Biochemical outcomes	High
Decsi 2005 [14]	Multicenter	157 singleton gestations	Singleton gestations without prior PTB	DHA 500 mg	Incidence of PTB	Low
Tofail 2006 [15]	Bangladesh	400 singleton gestations	Singleton gestations without prior PTB or prior IUGR	DHA 1200 mg + EPA 1800 mg	Psychomotor development of infants	Low
Knudsen 2006 [36]	Denmark	3098 singleton gestations	N/A	DHA 2800 mg	GA at delivery	Low

(*continued*)

Table 1. Continued

	Study location	Participants	Inclusion criteria	Intervention daily	Primary outcome	Overall risk of bias
Makrides 2010 [16]	Denmark	3098 singleton gestations	Low-risk singleton gestations	DHA 800 mg + EPA 100 mg	Post-partum depression	Low
Ranajrusgbab 2010 [18]	Mexico	1094 singleton gestations	Low-risk singleton gestations	DHA 55 mg	Birth weight	Low
Harper 2010 [28]	USA	852 singleton gestations	Singleton gestation with prior PTB	DHA 800 mg + EPA 1200 mg	Incidence of prior PTB	Low
Escolano-Margarit 2011 [17]	Multicenter	90 singleton gestations	Low-risk singleton gestations	DHA 800 mg + EPA 1200 mg	Incidence of prior PTB	Low
Colombo 2013 [32]	USA	81 singleton gestations	Low-risk singleton gestations	DHA 600 mg	Childhood cognitive outcomes	Low
Carlson 2013 [19]	USA	350 singleton gestations	Low-risk singleton gestations	DHA 600 mg	Birth weight	Low
Gould 2014 [37]	Australia	185 singleton gestations	Low-risk singleton gestations	DHA 800 mg	Childhood cognitive outcomes	Low
Mulder 2014 [38]	Canada	270 singleton gestations	Low-risk singleton gestations	DHA 400 mg	Childhood cognitive outcomes	Unclear
Mulder 2014 [38]	Iran	54 singleton gestations	Singleton gestations with gestational diabetes	DHA 1000 mg	Biochemical outcomes	High
Total	–	14 106 singletons and 2578 twins	–	–	–	–

Figure 1. Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]). RCTs, randomized controlled trials.

Gestational diabetes

Only one RCT evaluated the effect of omega-3 on gestational diabetes [42]. This study, including only 54 singleton gestations, showed that women with gestational diabetes who where randomized to DHA group had a significantly lower serum C-reactive protein concentrations (mean difference −1158.00 ng/mL, 95% CI −2217.45 to −98.55), low incidence of hyperbilirubinemia in newborns (RR 4.33, 95% CI 1.03–18.19) and decreased newborns' hospitalization rate (RR 4.33, 95% CI 1.03–18.19). However, no effect was noticed on the incidence of cesarean delivery (RR 1.44, 95% CI 0.88–2.37), macrosomia (RR 6.27, 95% CI 0.37–124.61) and polyhydramnios (RR 6.27, 95% CI 0.37–124.61) and on birth weight (mean difference −13.00 g, 95% CI −55.31–29.31). We found no RCT assessed the efficacy of omega-3 in prevention of gestational diabetes in women without gestational diabetes.

Perinatal mortality (singleton gestations)

Eight RCTs evaluated the efficacy of omega-3 supplementation during pregnancy in prevention of perinatal mortality with contradicting results [7–9,13,15,16]. The pooled risk estimate showed no significant difference in the incidence of perinatal mortality (RR 0.61, 95% CI 0.30–1.24).

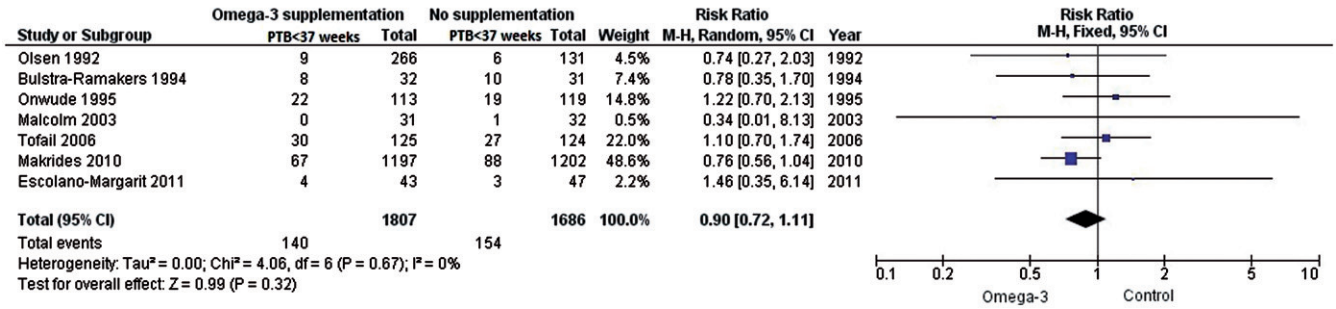

Figure 2. Forest plot for preterm birth less than 37 weeks in women without prior preterm birth. PTB, preterm birth; M–H, Mantel–Haenszel test; CI, confidence interval.

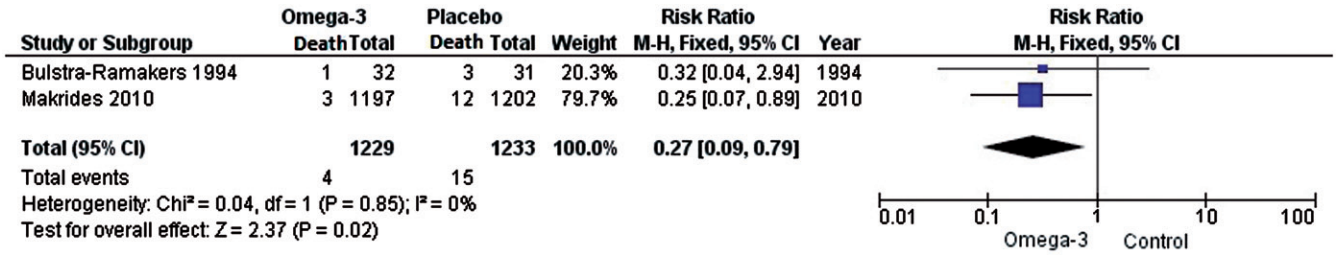

Figure 3. Forest plot for perinatal death in women who started omega-3 supplementation ≤ 20 weeks. Death, perinatal death; M–H, Mantel–Haenszel test; CI, confidence interval.

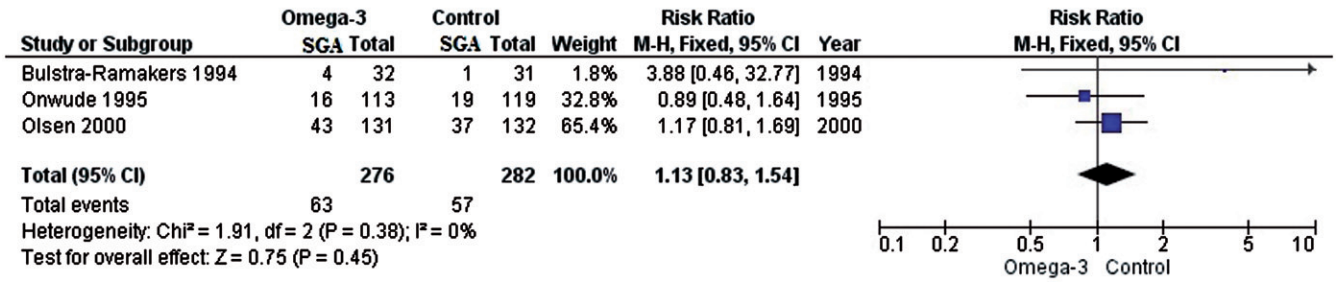

Figure 4. Forest plot for small for gestational age in women with small for gestational age. SGA, small for gestational age; M-H, Mantel–Haenszel test; CI, confidence interval.

Pooled results from trials in which supplementation started ≤ 20 weeks [10,16,17], including the largest and best-designed one [16], showed a 73% significant decrease in perinatal death, which was consistently defined as the sum of still birth and neonatal death (RR 0.27, 95% CI 0.09–0.79; Figure 3) [45].

Small for gestational age and birth weight (singleton gestations)

Omega-3 supplementation during pregnancy was not associated with prevention of SGA (RR 1.13, 95% CI 0.96–1.34) or low birth weight (RR 1.00, 95% CI 0.88–1.12), but was associated with statistically significantly higher birth weight (mean difference 47.24 g, 95% CI 1.05–93.44) [10,11,26,27,29,39,47]. Two trials showed that DHA supplementation during pregnancy could result in larger head circumferences (mean difference 0.5 cm, 95% CI 0.11–0.91) [18,19].

Pooled result from three RCTs, including 575 singleton gestation with prior birth weight <5th percentile for gestational age [10,11,27], showed that omega-3 did not prevent recurrent birth weight <5th percentile for gestational age (RR 1.13, 95% CI 0.83–1.54; Figure 4) [48].

Infant eye and brain development (singleton gestations)

Only two RCTs including 312 singleton gestations investigated the effect of maternal omega-3 supplementation on vision after birth [12,15]. A meta-analysis of the two RCTs showed no differences either in maturity of the retina at 1 week of age, or in visual function measured by visual evoked potentials to flash and pattern reversal stimuli at birth and at 10 and 26 weeks of age [49].

Data about neonatal development were derived mostly from observational studies. These studies generally demonstrated that DHA supplementation during pregnancy was

associated with improved neurodevelopmental outcomes in the child [49–52]. Level-1 data about brain development were controversial [16,17,20,37,41]. One trial showed that children born to the mothers supplemented with omega-3 had a 4% point advantage in scores on the Kaufman Assessment Battery for Children (K-ABC) [16], and in 2004 Colombo et al. reported that infants whose mothers had omega-3 supplementation during pregnancy showed less distractibility in the second year [20]. In 2011, Escolano-Margarit et al. concluded that a daily supplementation of DHA and EPA during pregnancy could lead in a better neurological outcome at 5.5 years of age [17]. Recent large and well-designed RCTs, that followed infants up to age 18 months, however, found no difference in cognitive and language scores and in attention and working memory between offspring of singleton gestations supplemented with DHA during pregnancy and those who received placebo [37,41].

Post-partum depression (singleton gestations)

Epidemiologic data showed that low seafood intake during pregnancy correlated with higher levels of depressive symptom during pregnancy [51,53]. However, the only RCT available (including 2399 singleton gestations) failed to demonstrate a clear and statistically significant benefit of omega-3 supplementation during pregnancy in preventing depressive post-partum symptoms (RR 0.85, 95% CI 0.70–1.02) [16].

Multiple gestations

One well-designed placebo-controlled multicenter trial reported data on multiple gestations, including 579 asymptomatic twins [27]. In this study, the authors found no benefits of omega-3 supplementations regarding PE, SGA, birth weight or PTB. Furthermore, twins randomized to omega-3 group delivered at the same gestational age of placebo group.

Another trial, including 1999 twins, showed no benefit of omega-3 supplementation in prevention of PE. However, this study had high-risk of bias and reported no information about the inclusion criteria [33]. No separate data about triplet gestations were available in the literature.

Discussion

We identified 34 RCTs on omega-3 supplementation during pregnancy [9–42]. These level 1-data showed that omega-3 supplementation during pregnancy was not associated with prevention of PTB, PE, IUGR, SGA or post-partum depression. Data about perinatal death, birth weight and neurological children development were still limited.

Our study has many strengths. One is the inclusion of only RCTs. To our knowledge, no prior systematic review on omega-3 during pregnancy is as large, up-to-date or comprehensive. We reviewed all the RCTs published on omega-3 supplementation during pregnancy and analyzed all the outcomes reported in these studies providing evidence-based recommendations for omega-3 supplementation during pregnancy. Prior meta-analyses [45,46,48] evaluated only few specific outcomes each (i.e. PTB, SGA, LBW, IUGR), while others were not analyzed at all (e.g. PE, gestational diabetes, brain development, maternal depression). Moreover, the prior meta-analyses included only singleton gestations while we included also multiple gestations in the current article.

There are several limitations to our review. Search strategies for retrieving RCTs and meta-analyses in electronic databases are limited and this could have influenced our findings. The included studies came from various regions of the world so the level of dietary intake of omega-3 could not be controlled for. Many of the trials reported only biochemical outcomes (Table 1). Data on multiple gestations were limited. We carried out a systematic review and not a meta-analysis and so publication bias and sensitivity analyses were not performed.

The use of omega-3 supplementation during pregnancy has been studied as a possible strategy to prevent PTB, PE, post-partum depression, as well as to increase birth weight; and so far, no potential adverse or toxic effects have been reported in the literature. The theories behind the studies were based on the observations of longer gestation in communities with high fish oil consumption [6,54]. A recent study showed that women who received low-dose fish intake during pregnancy had a higher risk of PTB [55]. The biological plausibility is that omega-3 fatty acids depress the synthesis of the prostaglandins (PGs) E_2 and may delay initiation of cervical ripening by switching the PGs synthetic pathways from PGE_2 to PGE_3, which have anti-inflammatory effects [56–58]. PGE_2 such as $PGE_{2\alpha}$, which derive enzymatically from n–6 PUFA (i.e. arachidonic acid), play a major role in the uterine contractions and biophysical changes associated with cervical ripening [59,60]. Figure 5 showed the prostaglandins synthetic pathways and the omega-3 mediated switching from PGE_2 to PGE_3 synthetic pathways. The different effects of PGs seem to be linked with the position of the last double bond (n–6 versus n–3): PGE_2 derived from arachidonic acid (n–6 PUFA), while PGE_3 from EPA acid (n–3 PUFA) (Figure 6) [56]. Moreover, omega-3 fatty acids given before the placentation increase placental labyrinthine antioxidant capacity [56,57]. This may explain the significant decreases in perinatal death in trials who started omega-3 ≤ 20 weeks [45]. For this reason, we might argue that effectiveness could be greater if supplementation was started in the first trimester.

According to the Food and Agriculture Organization of the United Nations (FAO), International Society for the Study of Fatty Acids and Lipids (ISSFAL), World Association of Perinatal Medicine, Australian & New Zealand Health Authorities and European Food Safety Authority, daily intake of omega-3 supplementation is recommended during pregnancy [4,61–65]. However, level-1 data from this systematic review indicated no enough evidence to support the routine use of omega-3 supplementation during pregnancy.

Given the 73% significant decrease in perinatal death in the singleton gestations who started omega-3 supplementation ≤ 20 weeks [45], further research is needed. Indeed, even with a summary estimate from 2462 women the ability to discern differences in perinatal death is impaired by type II error and until proper power trials are performed, this intervention should not be routinely available. We observed that with an α of 0.05 and 80% power, a sample size of 1850 patients in each group is required to detect a 73% reduction in

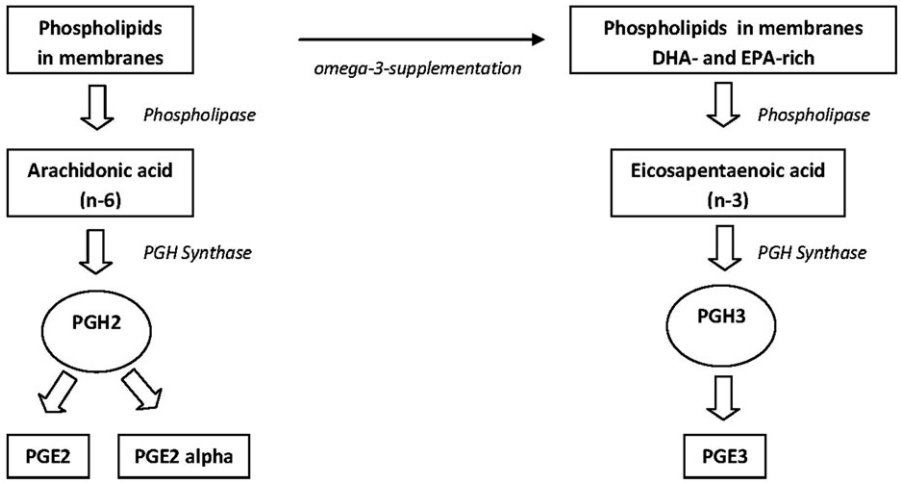

Figure 5. Omega-3 mediated switching from PGE2 to PGE3 synthetic pathways. PGH Synthase, prostaglandin-endoperoxide synthase also known as cyclooxygenase (COX); PGH2, prostaglandin H2; PGH3, prostaglandin H3; PGE2, prostaglandin E2; PGE3, prostaglandin E3; DHA, docosahexaenoic acids; EPA, eicosapentaenoic acids.

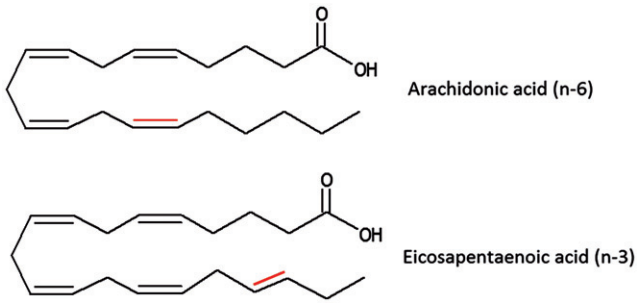

Figure 6. Structural formula of arachidonic (*n*–6) and eicosapentaenoic acid (*n*–3). Red double bond, last double bond.

perinatal death. Large RCTs in multiple gestations and longer follow-up are also required.

Declaration of interest

The authors report no conflict of interest. This study had no funding source.

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