Ultrasound Obstet Gynecol 2015; **46**: 659–664
Published online 4 November 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14910

Omega-3 supplementation during pregnancy to prevent recurrent intrauterine growth restriction: systematic review and meta-analysis of randomized controlled trials

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KEYWORDS: birth weight; intrauterine growth restriction; meta-analysis; omega-3; small-for-gestational age

ABSTRACT

Objective *To evaluate the efficacy of omega-3 supplementation during pregnancy in preventing intrauterine growth restriction (IUGR) in women with apparently uncomplicated singleton pregnancy and previous IUGR pregnancy.*

Methods *For this systematic review, the research protocol was designed* a priori. *Searches were performed in electronic databases for studies published from inception of each database to December 2014. A combination of search terms was used including 'fish oil', 'long chain polyunsaturated fatty acids', 'intrauterine growth restriction', 'small for gestational age' and 'omega-3'. We included all randomized controlled trials (RCTs) of women with an uncomplicated singleton pregnancy and a prior IUGR pregnancy who were randomized to receive prophylactic treatment with omega-3 supplementation or either placebo or no treatment (control). Trials that included women with multiple gestations and those with only biochemical outcomes available were excluded. Pooled estimates were based on relative risk (RR) with 95% CI. Primary outcome was incidence of IUGR as defined in the RCTs.*

Results *Three RCTs including 575 women with uncomplicated singleton pregnancy with prior IUGR were analyzed. Women who received omega-3 supplementation during pregnancy had the same incidence of IUGR, defined as estimated fetal weight < 5th or < 3rd centiles, as had controls (22.8%* vs *20.2%, respectively; RR, 1.13 (95% CI, 0.83–1.54)). Compared to controls, women who received omega-3 supplementation delivered later (mean difference, 1.4 (95% CI, 1.28–1.63) weeks), had a longer latency (mean difference, 2 (95% CI, 1.73–2.08) weeks), had a similar incidence of perinatal death (2.1%* vs *3.3%, respectively; RR, 0.60 (95% CI, 0.15–2.42)) and similar birth weight (mean difference, 50 g (95% CI, −26 to 246 g)).*

Conclusions *Omega-3 supplementation during pregnancy does not prevent recurrence of IUGR in women with uncomplicated singleton pregnancy and a previous IUGR pregnancy.*

INTRODUCTION

Intrauterine growth restriction (IUGR) is a complication of pregnancy associated with increased risk of neonatal mortality and morbidity[1]. According to the American College of Obstetricians and Gynecologists (ACOG), IUGR is 'one of the most common and complex problems in modern obstetrics'[1]. IUGR is defined differently in different studies; the definition used by ACOG is an estimated fetal weight (EFW) < 10th centile for gestational age[1]. Some studies use EFW < 5th centile[2]. Women with prior pregnancies complicated by IUGR have an increased risk of approximately 20% for recurrence of IUGR in a subsequent pregnancy[3].

All pregnant women should eat a well-balanced diet incorporating a variety of food, including fish[4]. Consumption of fish and fish oil is protective against cardiovascular disease, especially in those at risk of coronary artery disease[5]. The beneficial effects of fish oil seem to be associated with its omega-3 long chain polyunsaturated fatty acids, such as eicosapentaenoic (EPA), docosapentaenoic (DPA) and docosahexaenoic (DHA) acids[4,5].

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Accepted: 22 May 2015

In 1986, Olsen *et al.* suggested that intake of omega-3 during pregnancy may increase fetal and birth weights[6]. Randomized controlled trials (RCTs) have been performed to assess the benefits of omega-3 supplementation during pregnancy to prevent recurrence of IUGR and other adverse neonatal outcomes, with contradictory results[7–37].

The aim of this meta-analysis was to evaluate the efficacy of omega-3 supplementation during pregnancy in reducing the incidence of IUGR in women with an apparently uncomplicated singleton pregnancy who had a previous IUGR pregnancy.

METHODS

The research protocol was designed *a priori*, defining methods for search strategy, study selection, data collection and analysis. Searches were performed in EMBASE, OVID, MEDLINE, ClinicalTrials.gov, Scopus, PROSPERO International Prospective Register of Systematic Reviews and The Cochrane Central Register of Controlled Trials, with a combination of search terms related to 'fish oil', 'long chain polyunsaturated fatty acids', 'intrauterine growth restriction', 'small for gestational age' and 'omega-3' for studies published from inception of each database to December 2014. No restrictions for language or geographical location were applied. The electronic search and review of eligibility of the studies identified were performed independently by two authors (G.S. and V.B.). Differences that arose during the selection process were resolved by discussion.

We included all RCTs of women with uncomplicated singleton pregnancy and previous pregnancy complicated by IUGR (as defined in the studies) who were randomized to receive prophylactic treatment with omega-3 supplementation or either placebo or no treatment (control). All published RCT studies on omega-3 supplementation during pregnancy were reviewed carefully. Exclusion criteria were quasirandomized trials (i.e. trials in which allocation was on the basis of a pseudorandom sequence, such as odd/even hospital number or date of birth, alternation), trials that included women with multiple gestations, trials with either only biochemical outcomes or no informative outcomes and trials in pregnant women with IUGR or gestational hypertension at the time of randomization.

Risk of bias in each included trial was assessed using the criteria outlined in The Cochrane Handbook for Systematic Reviews of Interventions. Seven domains related to risk of bias were assessed in each included study as there is evidence that these are associated with biased estimates of treatment effect: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding to outcome assessment, 5) incomplete outcome data, 6) selective reporting, 7) other bias. Review authors' judgments were categorized as having low, high or unclear risk of bias[38].

Data extraction was completed by two independent investigators (G.S. and L.S.). Each investigator independently extracted data from each study and analyzed the data separately. Differences were reviewed and resolved by common review of all data. Composite data were extracted from studies that did not stratify data. All authors were contacted for missing data. All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. Primary outcome included the rate of IUGR (as defined in the studies). Secondary outcomes were gestational age at delivery in weeks, latency (time from randomization to delivery) in weeks, occurrence of preterm birth (PTB) < 37 weeks and < 34 weeks, occurrence of spontaneous PTB (sPTB) < 37 weeks and < 34 weeks, birth weight in grams, admission to neonatal intensive care unit (NICU), incidence of neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), neonatal sepsis and perinatal death. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42015016232). We assessed primary outcome in subgroup analysis according to the definition of IUGR used in the original trials.

Statistical analysis

Data analyses were completed independently by two authors (G.S. and L.S.) using Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). Completed analyses were compared and differences were resolved by review of all data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic[38]. In the case of statistically significant heterogeneity, a random-effects model of DerSimonian and Laird was applied to obtain the pooled relative risk (RR) estimate; otherwise, a fixed-effect model was used[38]. Pooled results were reported as RR or as mean difference with 95% CI. The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement[39].

RESULTS

Initially, 29 RCTs reporting on omega-3 supplementation during pregnancy were identified[9–37]. No similar systematic reviews were found during the search process. Twenty-six studies were excluded as they did not include women with a previous pregnancy complicated by IUGR[10,11,14–37]. Three trials met the inclusion criteria and were included in the meta-analysis[9,12,13]. A flowchart summarizing study identification and selection is given in Figure 1. All included studies had a low or unclear risk of bias according to the Cochrane risk of bias tool (Figure 2). Publication bias was assessed and a funnel plot is shown in Figure 3; the symmetrical plot suggested no publication bias. Statistical heterogeneity among studies was low, with no inconsistency in RR estimates ($I^2 = 0\%$).

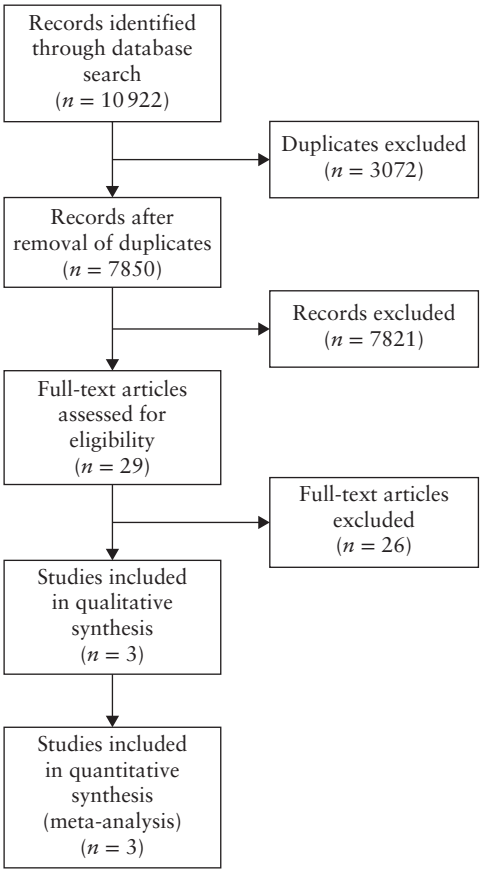

Figure 1 Flowchart summarizing identification and selection of studies in this systematic review.

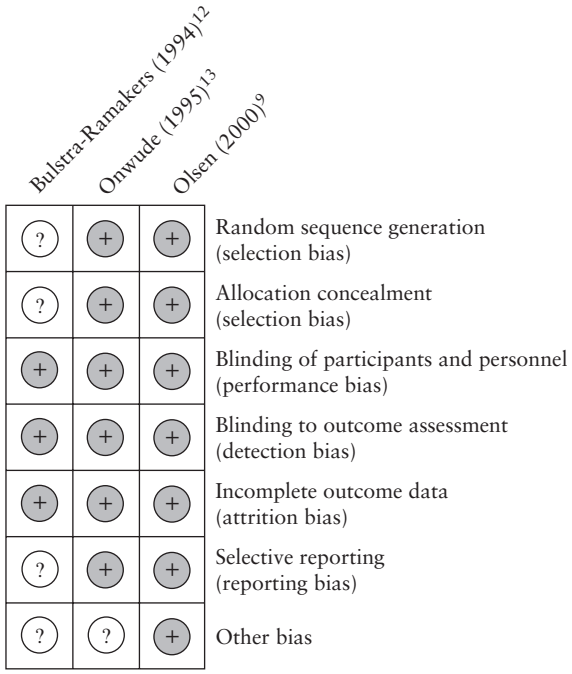

Figure 2 Quality assessment of risk of bias in randomized controlled trials included in the meta-analysis. ⊕, low risk of bias; ?, unclear risk of bias.

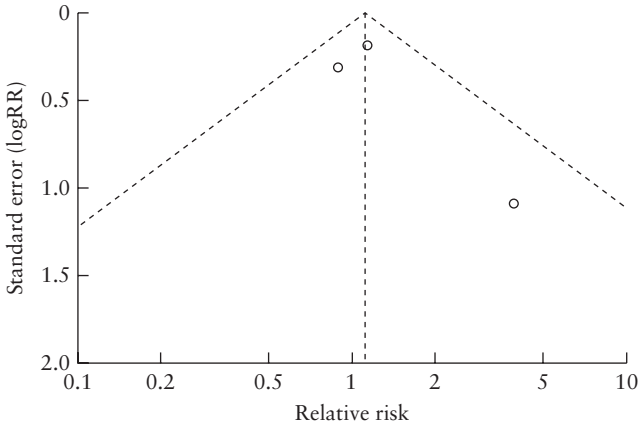

Figure 3 Funnel plot for assessment of publication bias of randomized controlled trials in the meta-analysis. RR, relative risk.

Of the 575 women analyzed, 286 were randomized to the omega-3 supplementation group and 289 to the control group. All studies used placebo as the control treatment (Table 1). All women had a history of pregnancy complicated by IUGR. The definition of IUGR differed among the trials: two used EFW < 3rd centile[12,13] and one used EFW < 5th centile[9]. No differences were found for gestational age at randomization (mean difference, 0.5 (95% CI, 0.48–1.48) weeks). Compared to women who received a placebo during pregnancy, women who received omega-3 supplementation during pregnancy had a similar rate of recurrence of IUGR (22.8% *vs* 20.2%, respectively; RR, 1.13 (95% CI, 0.83–1.54); Figure 4), delivered at a later gestational age (mean difference, 1.4 (95% CI, 1.28–1.63) weeks) and had a longer latency (mean difference, 2 (95% CI, 1.73–2.08) weeks; Table 2).

Women who received omega-3 supplementation had rates of perinatal death (2.1% *vs* 3.3%, respectively; RR, 0.60 (95% CI, 0.15–2.42)) and birth weights (mean difference 50 g (95% CI, −26 to 246 g)) that were similar to those who received a placebo (Table 2). No trials reported data on PTB, sPTB, submission to NICU or incidence of RDS, BPD, IVH, NEC or sepsis.

Women randomized to the omega-3 group had a similar incidence of IUGR compared to controls when subgroup analyses were performed for trials that defined IUGR as EFW < 5th centile (30.1% *vs* 25.2%, respectively; RR, 1.20 (95% CI, 0.84–1.70)) and those that defined IUGR as EFW < 3rd centile (13.8% *vs* 13.3%, respectively; RR, 1.04 (95% CI, 0.59–1.86; Table 2).

DISCUSSION

This meta-analysis of RCTs evaluating the efficacy of omega-3 supplementation during pregnancy in women with a singleton pregnancy and a prior pregnancy complicated by IUGR shows that omega-3 supplementation is not associated with prevention of IUGR recurrence or better neonatal outcomes. Women who received omega-3 supplementation delivered later in gestation and had a longer latency. Although non-significant, there were five perinatal deaths in the placebo group and three in the

Table 1 Characteristics of included randomized controlled trials that allocated women with a singleton pregnancy and history of intrauterine growth restriction (IUGR) to receive omega-3 supplementation or placebo

	Study		
Characteristic	*Olsen (2000)*[9]	*Onwude (1995)*[13]	*Bulstra-Ramakers (1994)*[12]
Study location	Northern Europe	UK	The Netherlands
Study population (*n*)	280 (141 *vs* 139)	232 (113 *vs* 119)	63 (32 *vs* 31)
Daily intervention	DHA 900 mg and EPA 1300 mg	DHA 1080 mg and EPA 1620 mg	EPA 3000 mg
Control type	Placebo	Placebo	Placebo
Mean maternal age (years)	29 *vs* 30	27 *vs* 26	NA
Smoking (*n*/*N* (%))	72/141 (51.1) *vs* 72/139 (51.8)	42/113 (37.2) *vs* 32/119 (26.9)	NA
GA at randomization (weeks)	18 *vs* 19	24 *vs* 24	NA
Definition of IUGR	EFW < 5th centile	EFW < 3rd centile	EFW < 3rd and < 5th centiles

Data are presented for women who received omega-3 supplementation *vs* women in the corresponding control group. Only the first author of each study is given. All studies were published in the English language and included women with a previous pregnancy complicated by IUGR. In all studies, the primary outcome was recurrence of IUGR. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GA, gestational age; NA, not available.

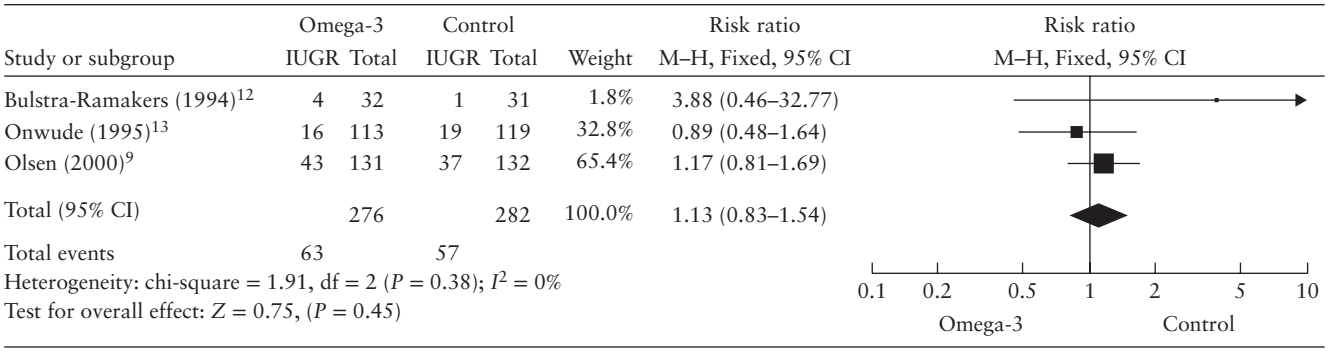

Figure 4 Forest plot of recurrence of intrauterine growth restriction (IUGR) in women with singleton pregnancy and history of pregnancy complicated by IUGR who received omega-3 supplementation or placebo. M–H, Mantel–Haenszel test.

Table 2 Primary and secondary outcomes in randomized controlled trials that allocated women with singleton pregnancy and history of intrauterine growth restriction (IUGR) to receive omega-3 supplementation or placebo

	Study					
Outcome	*Olsen (2000)*[9]	*Onwude (1995)*[13]	*Bulstra-Ramakers (1994)*[12]	*Total*	I^2 (%)	*RR or mean difference (95% CI)*
n	280 (141 *vs* 139)	232 (113 *vs* 119)	63 (32 *vs* 31)	575 (286 *vs* 289)	—	—
IUGR (*n*/*N* (%))	43/131 (32.8) *vs* 37/132 (28.0)*†	16/113 (14.2) *vs* 19/119 (15.7)‡	4/32 (12.5) *vs* 1/31 (3.2)‡	63/276 (22.8) *vs* 57/282 (20.2)	0	1.13 (0.83 to 1.54)
EFW < 5th centile (*n*)	43/131 (32.8) *vs* 37/132 (28.0)*	—	6/32 (18.8) *vs* 4/31 (12.9)	49/163 (30.1) *vs* 41/163 (25.2)	0	1.20 (0.84 to 1.70)
EFW < 3rd centile (*n*)	—	16/113 (14.2) *vs* 19/119 (15.7)	4/32 (12.5) *vs* 1/31 (3.2)	20/145 (13.8) *vs* 20/150 (13.3)	42	1.04 (0.59 to 1.86)
Mean latency (weeks)	21 *vs* 18	14 *vs* 13	NA	—	0	2 weeks (1.73 to 2.08)§
Birth weight (g)	2910 *vs* 3060	3033 *vs* 2983	NA	—	0	50 g (−26 to 246)
Perinatal death (*n*)	NA	1/113 (0.9) *vs* 2/119 (1.7)	2/32 (6.3) *vs* 3/31 (9.7)	3/145 (2.1) *vs* 5/150 (3.3)	0	0.60 (0.15 to 2.42)

Data are presented as pertinent to the omega-3-receiving group *vs* the corresponding control group. Only the first author of each study is given. *Data missing for some women in original trial. Estimated fetal weight (EFW): †< 5th centile; ‡< 3rd centile. §Statistically significant. NA, not available; RR, relative risk.

supplementation group (non-significant 40% reduction). Our results compare with prior Level 1 data that showed omega-3 supplementation to be associated with some prolongation of pregnancy[7,40–42].

Four other meta-analyses have evaluated the efficacy of omega-3 supplementation during pregnancy[7,40–42]. The first showed that omega-3 supplementation may increase pregnancy duration and head circumference in low-risk singleton pregnancies, but the mean effect size was small[40]. A Cochrane Review included RCTs that allocated women to receive polyunsaturated fatty acids as a control and RCTs that allocated women to receive a prostaglandin precursor as treatment; the review showed that women who received fish oil supplementation had a mean gestational age at delivery of 2.6 days longer compared to that of controls[7]. Another recent meta-analysis showed that omega-3 supplementation during pregnancy in women with a singleton pregnancy and no previous PTB is associated with lower rates of perinatal death when evaluated in high-quality RCTs, or in women who received omega-3 supplementation before 21 weeks' gestation[41]. Finally, a fourth meta-analysis showed that omega-3 did not prevent recurrence of PTB in women with a prior PTB[42].

A strength of our study is the inclusion of RCT data on omega-3 supplementation during pregnancy in a specific population, i.e. women with a singleton pregnancy and a prior IUGR pregnancy. Other strong points are that all included studies had a low risk of bias according to the Cochrane risk of bias tools and all reported the recurrence of IUGR as the primary study outcome. Furthermore, no prior similar meta-analyses were found during the search process and heterogeneity among studies was very low. The rate of recurrence of IUGR in each study and in the overall results was consistent with that in the literature[3].

Limitations of our study were inherent to those of the RCTs included. Two studies had as primary outcome incidence of EFW < 3rd centile, while the other used EFW < 5th centile. These lower cut-offs (< 5th compared to < 10th centile) allow identification of more fetuses that have truly failed to meet their growth potential. The RCTs included were performed in various regions of the world; thus, the level of dietary intake of omega-3 could not be controlled for. Two studies used DHA and EPA while the third administered only EPA. Olsen *et al.* reported some occurrence of perinatal death; however, they did not stratify data according to primary outcome and, consequently, it was not possible to determine how many deaths were observed in fetuses with recurrent IUGR. None of the included studies reported the common indications for delivery.

The use of omega-3 supplementation during pregnancy has been studied as a possible strategy to prevent several conditions, e.g. PTB, pre-eclampsia and IUGR, as well as to increase birth weight. The theories behind the studies were based on observations of longer gestation in communities with a high consumption of fish oil[6,7,43,44], but the biological plausibility is not completely clear. Long chain polyunsaturated fatty acids may delay initiation of cervical ripening by inhibition of the production of prostaglandins (PGs)[45,46]. They decrease the synthesis of $PGE_{2,}$ by switching the PGs synthetic pathway from PGE_2 to PGE_3, which has anti-inflammatory effects[46–48]. Indeed, PGE_2, such as $PGE_{2\alpha}$, derived enzymatically from n-6 polyunsaturated fatty acid (i.e. arachidonic acid), plays a major role in inflammation[47]. Moreover, omega-3 fatty acids increase placental labyrinthine antioxidant capacity[49]. It has been hypothesized that omega-3 increases fetal growth rate by improving placental blood flow due to a lowered thromboxane/prostacyclin ratio and blood viscosity by correcting the imbalance in vasoactive PG[50,51]. For this reason, a possible explanation of the fact that our data show no association between omega-3 supplementation and prevention of recurrence of IUGR may be that omega-3 supplementation was implemented too late in pregnancy, after placentation.

Based on these Level 1 data, omega-3 supplementation during pregnancy cannot be recommended currently for prevention of IUGR in women with singleton pregnancies and a history of pregnancy complicated by IUGR. The non-significant reduction in perinatal death requires further research. Indeed, with a summary estimate based on 295 women, the ability to discern differences in perinatal death is impaired by Type II error and, consequently, large well-designed and properly powered trials are needed. We observed that with an α of 0.05 and 80% power, a sample size of 650 women in each group is required to detect a 40% decrease in perinatal death.

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