European Journal of Obstetrics & Gynecology and Reproductive Biology 198 (2016) 40–46

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies

Sumit Kar [a,*], Min Wong [b], Ewelina Rogozinska [c], Shakila Thangaratinam [a,c,d]

[a] Women's Health Unit, Royal London Hospital, Bart's Health NHS Trust, London, UK
[b] Department of Obstetrics & Gynaecology, Whipps Cross University Hospital, Bart's Health, London, UK
[c] Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[d] Multidisciplinary Evidence Synthesis Hub (MESH), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

ARTICLE INFO

Article history:
Received 12 July 2015
Received in revised form 12 November 2015
Accepted 23 November 2015

Keywords:
Pregnancy
Omega-3 fatty acid
Preterm birth

ABSTRACT

Objective: Preterm birth continues to be the one of the leading causes of infant deaths worldwide. There is a need for effective, easily available, safe and acceptable interventions to prevent preterm delivery, especially before 34 weeks of gestation. Omega-3 fatty acids such as EPA (eicosapentanoic acid) and DHA (docosahexanoic acid) are available as over the counter nutritional supplements, and are taken by women to improve pregnancy outcomes, without any clear recommendations. We undertook a systematic review to assess the effects of omega-3 fatty acids on early (<34 weeks) and any (<37 weeks) preterm delivery.
Methods: We searched MEDLINE, EMBASE and Cochrane Library from inception to 2014 without any language restrictions. Study selection, quality assessment and data extraction were done by two independent reviewers. Results were summarized as relative risks and 95% confidence intervals for dichotomous outcomes and mean differences for continuous outcomes.
Results: Of the nine included trials (5980 women), six (4193 women) evaluated the effects of omega-3 fatty acids on early preterm delivery. The risk of early preterm delivery was reduced by 58% (RR 0.42; 95% CI 0.27–0.66; $I^2 = 0\%$; $p = 0.0002$) and any preterm delivery by 17% (RR 0.83; 95% CI 0.70–0.98; $I^2 = 0\%$; $p = 0.03$) with the intervention. There was a significant increase in the mean gestational age by 1.95 weeks (95% CI 0.42–3.48 weeks; $I^2 = 0.47$; $p = 0.01$) and mean birth weight by 122.1 g (95% CI 47.4–196.8; $I^2 = 0.84$; $p = 0.001$) in the intervention group compared to the controls. Subgroup analysis showed no significant differences in the effects between the groups according to the risk status, dose and timing of the intervention.
Conclusion: Omega-3 fatty acids are effective in preventing early and any preterm delivery. The intervention is simple and easily available and has the potential to influence population based strategies in the prevention of preterm birth.

Introduction

Gestational age at delivery is the single most important determinant in the survival and long term neurodevelopment of the new born [1,2]. Early preterm infants often need prolonged intensive care for prematurity related morbidity, and long term support for neurodevelopmental problems. A baby born before 34 weeks of gestation costs around £60 K to the UK National Health Service (NHS), and $150 K to the US healthcare system [3]. Delaying premature births by a week could potentially save £260 million a year in UK [3].

Current management strategies focus on the prevention of all preterm births, including late preterm births between 34 and 37 weeks of gestation, and less on the clinically important outcome of early preterm delivery. Furthermore, interventions to prevent preterm births such as progesterone and cervical cerclage have limitations such as cost, availability and safety [2]. There is a need for a population based strategy that focusses on primary prevention of preterm birth, especially before 34 weeks gestation. Such an intervention needs to be easily accessible, cheap, and acceptable to women with minimal side effects.

Omega-3 fatty acids such as DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) are available as over the counter supplements for pregnant women. There are no clear recommendations on their intake in pregnancy. The long chain polyunsaturated fatty acids (LC-PUFA) have been evaluated for their potential role in preventing preterm delivery. However, systematic reviews

* Corresponding author at: Obstetrics & Gynaecology, East Surrey Hospital, Surrey & Sussex Healthcare NHS Trust, Redhill, Surrey RH1 5RH, UK.
Tel.: +44 7860109386; fax: +44 1737231707.
E-mail address: drsumitk33@gmail.com (S. Kar).

http://dx.doi.org/10.1016/j.ejogrb.2015.11.033
0301-2115/

to date including the Cochrane review [4] have provided conflicting conclusions regarding the effect of omega-3 fatty acids in preventing preterm delivery [5,6]. It is necessary to update the evidence in view of emerging evidence in this area, particularly for clinically important outcomes [4].

We undertook a systematic review to evaluate the effect of omega-3 fatty acids in pregnancy, on early preterm delivery before 34 gestational weeks, any preterm delivery, and other maternal and neonatal outcomes.

Methods

Literature search

We searched the electronic databases EMBASE, MEDLINE, and Cochrane from inception till 2014 to find relevant citations. Reference lists of the primary articles were searched for additional studies. Our search terms included both key words and text words that combined the intervention terms related to unsaturated fatty acid, omega 3 fatty acids, marine oil, fish oil, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) with outcome terms such as preterm birth, preterm labor and preterm delivery. The searches were undertaken with input from a clinical librarian.

Study selection

The studies were selected in a two stage process. In the first step, the electronic citations were reviewed for potential eligible studies. In the second step, full copies of the identified studies were obtained for detailed evaluation. We included randomized controlled studies that assessed the effects of omega-3 fatty acids on early and any preterm delivery. We excluded studies on women with multiple pregnancies and those that included women on any other treatment that could prevent preterm delivery. Two independent reviewers (SK and MW) undertook study selection. A third reviewer (ST) was involved when there was any disagreement.

Data extraction

Data were extracted in duplicate by two independent reviewers using predesigned forms. Any disagreements were resolved by discussion, and if needed by involving a third reviewer. We extracted data on study author, year, inclusion and exclusion criteria, risk status of the population, type, dose, and frequency of intervention, gestational age at commencement of intervention, and neonatal outcomes. Dichotomous data were entered in 2×2 tables, and continuous data in 2×1 tables to evaluate the effect of omega-3 fatty acids on the relevant outcomes.

Study quality assessment

We assessed the quality of the included studies according to standard recommendations [7]. We designed a checklist to assess the risk of bias for each study. These included assessment for selection bias (methods of randomization, allocation concealment), performance bias (blinding) and attrition bias (follow up, missing data). Quality assessment was done by two researchers and any disagreements were resolved by involving a reviewer.

Statistical analysis

We summarized the results as relative risks and 95% CI for dichotomous outcomes and mean differences for continuous outcomes. Heterogeneity was explored with I^2 statistic. Subgroup analysis was planned a priori to assess the differential effect of the intervention based on risk factors, timing and dose of the intervention. We undertook a sensitivity analysis by excluding non-spontaneous preterm deliveries. The risk of publication bias was estimated by Harbord's modified test for small-study effect

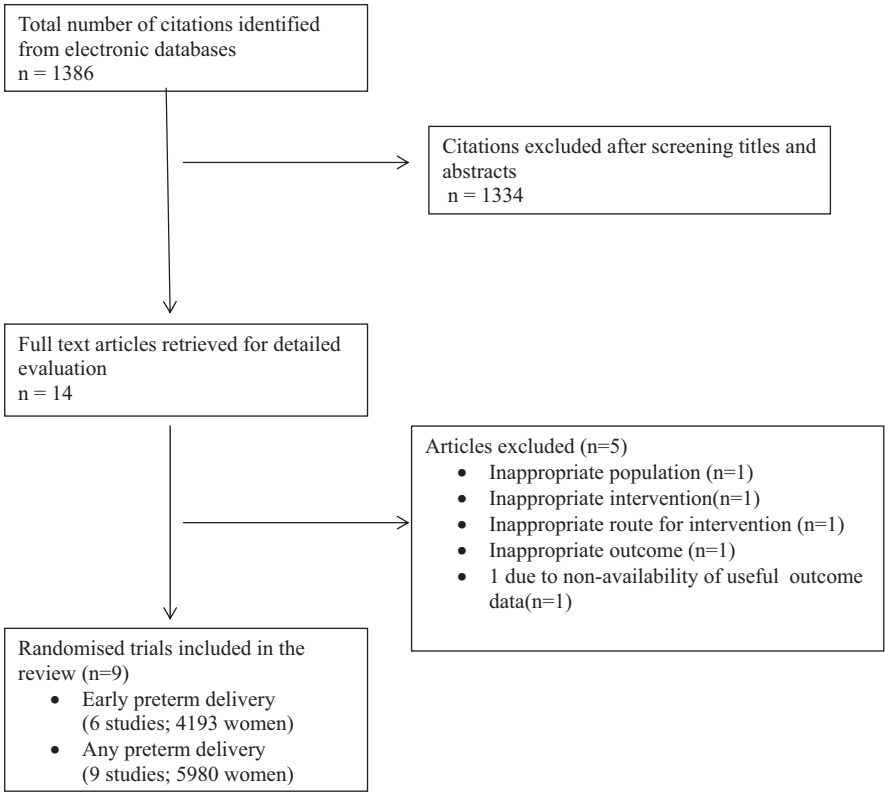


Fig. 1. Study identification process in the systematic review of omega-3 fatty acids in the prevention of early and any preterm delivery.

[8]. All analyzes were done using Revman software (RevMan 5.2, Cochrane Collaboration, Oxford, UK).

Results

Fig. 1 summarizes the process of study identification and study selection. From 1386 citations, we identified 14 relevant studies. 5 studies were excluded various reasons.

Characteristics of included studies

Six randomized trials (4193 women) studied the effect of omega-3 fatty acids on early preterm delivery [5,9–13] and nine (5980 women) on any preterm births [5,9–16]. The interventions included EHA, DHA or both EHA and DHA. The dose of the omega-3 fatty acids ranged from 133 mg to 3000 mg per day. The intervention was commenced at various gestations, with 78% of studies (7/9) starting before 24 weeks. A third of the studies included low risk women [5,14,15], a third studied high risk women [11–13] and a third evaluated the effect of intervention in women of any risk status [9,10,16]. Women with pre-eclampsia, pregnancy induced hypertension, and abnormal uterine artery Doppler, small for gestational age baby, unexplained still birth or preterm birth in previous pregnancies were considered to be at high risk of preterm delivery.

Quality of the included studies

The randomization was adequate in all studies. Six of the nine studies (67%) had adequate concealment and blinding. The analysis was by intentions to treat in 78% (7/9) of the included studies. There was more than 80% follow up in all the studies. More than 80% of studies reporting early preterm delivery as an outcome had adequate blinding and concealment (5/6), and the analysis was by intention to treat in 83% of the studies (5/6) (Fig. 2).

Effect of omega-3 fatty acids on preterm birth

Early preterm delivery before 34 weeks of gestation

Omega-3 fatty acids reduced the risk of early preterm delivery by 58% (RR 0.42, 95% CI 0.27–0.66, $p = 0.0002$) (Fig. 3). There was no heterogeneity between the studies ($I^2 = 0\%$). Sensitivity analysis by excluding women without spontaneous preterm birth showed that the beneficial effect of the intervention persisted (RR 0.44, 95% CI 0.25–0.78, $p = 0.005$) with no significant heterogeneity ($I^2 = 11\%$). Subgroup analysis according to the risk status of the individuals (any risk vs. high risk) revealed no significant difference in the effect between the groups ($p = 0.52$) (Table 1).

Any preterm delivery before 37 weeks of gestation

The risk of any preterm birth was significantly reduced by 17% (RR 0.83, 95% CI 0.70–0.98, $p = 0.03$) with no heterogeneity ($I^2 = 0\%$) (Fig. 3). There was no significant difference in the effect between the subgroups according to the dose (<400 mg/day vs. >400 mg/day) ($p = 0.91$) or timing (<24 weeks vs. >24 weeks gestational age) ($p = 0.66$) of the intervention, or the risk status of the population (any risk vs. high risk) ($p = 0.96$) (Table 1).

Effect of omega-3 fatty acids on neonatal outcomes

The gestational age at delivery was reported in six studies [5,10,12,14–16]. There was a significant increase in the gestational age at delivery in the intervention group compared to the control group (MD 2.43 weeks; 95% CI 0.93–3.93 weeks; $I^2 = 0.58\%$; $p = 0.002$) (Table 2). The beneficial effect on gestational age continued, after excluding the study on high risk women (MD 1.35 weeks, 95% CI 0.39, 2.31) with no heterogeneity ($I^2 = 0\%$).

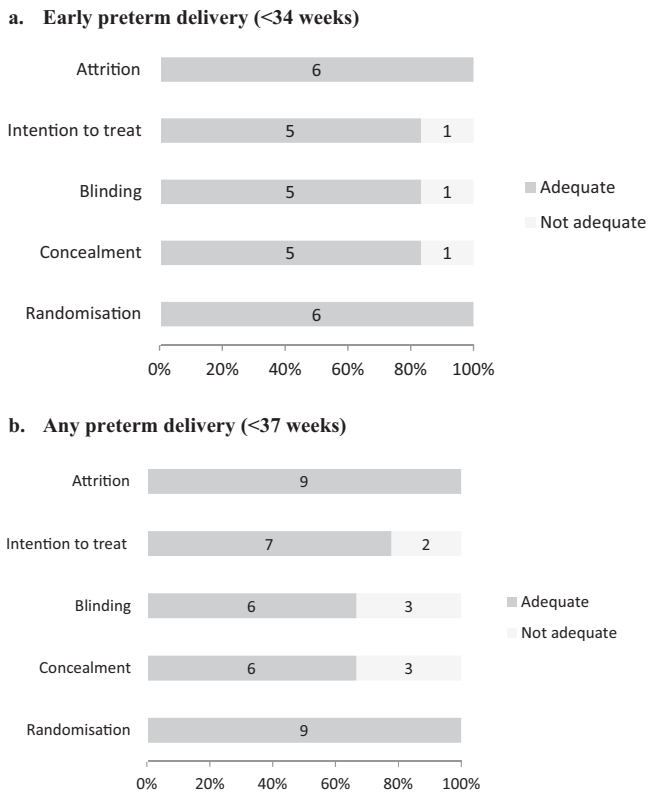


Fig. 2. Quality of the included studies in the systematic review on omega-3 fatty acids in the prevention of early and any preterm delivery.

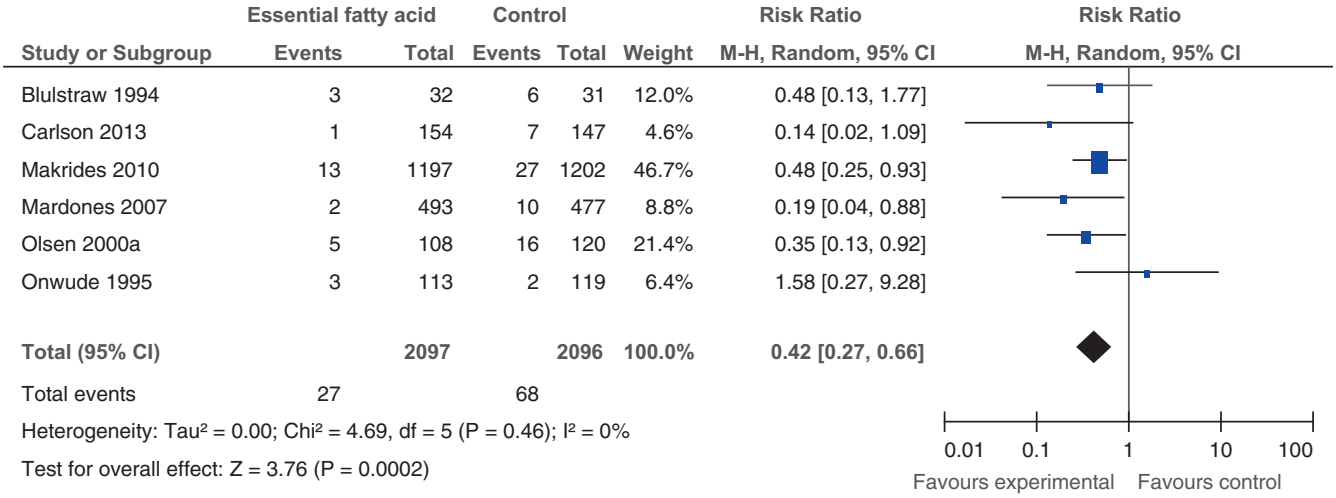
Supplementation with omega-3 fatty acids significantly increased the birth weight of the new born by 122.1 g (95% CI 47.4–196.8 g, $p = 0.001$, $I^2 = 84\%$) (Table 2). This increase in weight was observed in all studies with varied precision. Eight studies [5,9–13,15,16] reported the risks for fetal growth restriction. There was an 18% reduction in the intervention group (RR 0.82; 95% CI 0.66–1.03; $I^2 = 41\%$; $p = 0.09$) compared to the controls.

Admission to the neonatal unit was evaluated in four studies [5,9,12,16]. There was no significant difference between the groups in the risk of admission (RR 0.89, 95% 0.75–1.06; $I^2 = 9\%$; $p = 0.2$). The risk of neonatal death was reported in five studies and two studies reported on still birth [5,9,11–15]. There was an overall reduction in perinatal death by 49% (RR 0.51; 95% CI 0.26–1.01; $I^2 = 0\%$; $p = 0.05$). There were no differences in the proportion of neonates with an Apgar score less than 7 at 1′ (RR 0.94; 95% CI 0.61–1.43) and 5′ (1.43; 95% CI 0.55–3.72) in the two

Table 1
Subgroup analysis in the meta-analysis of the effects of omega-3 fatty acids on preterm delivery.

Subgroup	No. of studies	No. of women	RR (95% CI)	*p* value for interaction
Early preterm delivery (<34 weeks)				
High risk	3	3670	0.36 (0.18–0.71)	0.52
Any risk	3	523	0.50 (0.24–1.06)	
Any preterm delivery (<37 weeks)				
High risk	4	814	0.83 (0.61–1.11)	0.96
Any risk	5	5166	0.83 (0.66–1.05)	
Dose >400 mg	8	5689	0.83 (0.69–1.00)	0.91
Dose <400 mg	1	291	0.86 (0.44–1.69)	
Intervention < 24 w	7	5156	0.84 (0.69–1.03)	0.66
Intervention > 24 w	2	824	0.75 (0.45–1.25)	

a. Early preterm birth (< 34 weeks)



b. Any preterm birth (< 37 weeks)

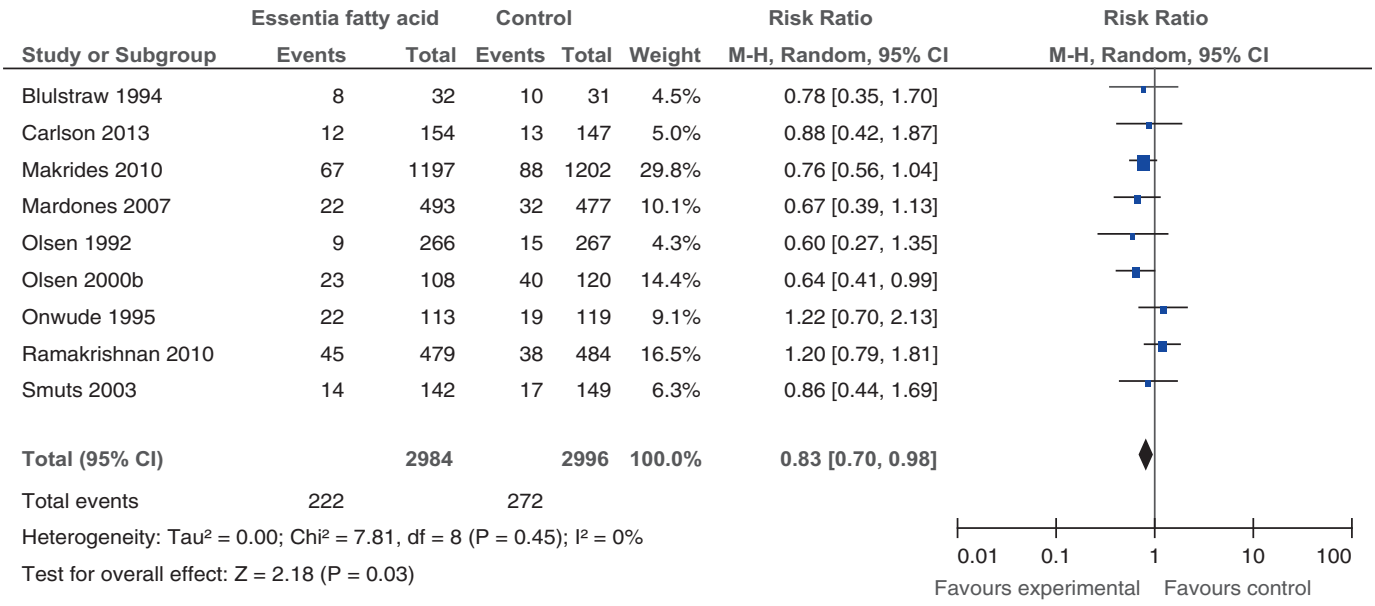


Fig. 3. Pooled estimates of the effects of omega-3 fatty acid on preterm birth.

Table 2
Effects of omega-3 fatty acids on neonatal outcomes in the systematic review on omega-3 fatty acids in the prevention of preterm delivery.

Outcome	No. of studies	No. of women	RR	MD	95% CI	*p* value	I^2%
Gestational age at delivery	6	3335		2.43 w	0.93–3.93	0.002	58
Birth weight	7	5734		122.1 g	47.37–196.82	0.001	84
Neonatal death	7	6751	0.51		0.26–1.01	0.05	0
Admission to the neonatal unit	4	5129	0.89		0.75–1.06	0.20	9
Small for gestational age	8	5469	0.82		0.66–1.03	0.09	41
Apgar score at 1′ < 7	2	1503	0.94		0.61–1.43	0.77	0
Apgar score at 5′ < 7	2	1506	1.43		0.55–3.72	0.47	0

groups. We found no evidence of small group effects for preterm birth before 37 weeks (Harbord's modified test $p = 0.872$) and for births before 34 weeks' gestation (Harbord's modified test, $p = 1.00$).

Adverse effects

Individual studies varied in the reporting of side effects. The most commonly reported side effects were gastrointestinal and

included belching, heartburn, nausea and vomiting, unpleasant taste, abdominal pain and diarrhea and constipation. Studies did not report any significant difference between the groups in vomiting or nausea [11,12,15]. Belching (29% vs. 8%) and unpleasant taste (17% vs. 2%) were observed more often in the intervention group by Olsen et al.

Discussion

Summary

Omega-3 fatty acids are effective in reducing the risk of early and any preterm delivery. The effect does not differ according to the risk status of women, dose or timing of intervention. Supplementation with omega-3 fatty acids prolonged the gestational age at delivery and the birth weight of the newborns. The effect of the intervention on neonatal outcomes is less well known.

Strengths and limitations

Our review has systematically assessed the effects of omega-3 fatty acid supplementation on the clinically relevant outcome of early preterm delivery. Our search was comprehensive without language restrictions and we assessed the quality of the included studies. We explored the effects of various factors such as characteristics of the population and intervention on the effects of the supplements. We took every effort to meta-analyze studies that were clinically homogeneous.

The included studies varied in the inclusion criteria, type of omega-3 fatty acid, dose and timing of administration. There is also limited information of the compliance with the intervention. Furthermore, despite contacting the authors, we were unable to obtain the data for early preterm birth in studies that had reported preterm birth as an outcome measure. Although the studies had access to newborn data, this was reported in very few studies. Given the small number of studies in each subgroup we were unable to perform meta regression analysis.

Mechanism of action

Omega-3 fatty acids were first evaluated for their potential role in preventing preterm delivery based on the observation that women who ingested significant portions of seafood in pregnancy had longer gestations and larger babies. LCPUFA are present in abundance in seafood and play a key role in modulation of immune function and inflammation [17]. LCPUFA increases B-oxidation of fatty acids in peroxisome and reduce hepatic fatty acid production [21]. They reduce long term adverse cardiovascular outcomes.

Both maternal and fetal levels of omega-3 fatty acids are correlated to maternal intake, due to significant trans placental transportation [18,19]. Increased intake of omega-3 fatty acids reduces the hepatic synthesis of omega-6 fatty acids which are precursors of PGE2 and PGF2 alpha [22] that cause myometrial contractility and cervical ripening. Their beneficial effect could also be attributed to their influence on the eicosanoids environment in favor of PGI2, that causes uterine relaxation [20,22].

Current strategies for preventing preterm birth

Existing policies to prevent preterm birth focus on identification of women at risk of preterm delivery. This includes symptomatic women, previous history of preterm delivery and women with shortened cervix measured by ultrasound. Interventions such as progesterone and cervical cerclage have been shown to be beneficial in preventing any and early preterm delivery [23]. Although these interventions are beneficial and may also be cost effective, they rely on the stratification of women by risk status prior to commencing the intervention. The above strategies have two limitations. Firstly, half of women who suffer early preterm delivery do not have any risk factors, and hence may not receive the intervention [24]. Secondly, a risk assessment technique such as cervical length measurement has restrictions such as access to ultrasound and training, operator skill and inter and intra observer variability. These problems are increased manifold in a low income country setting.

Existing evidence on omega-3 fatty acids and preterm births

Since the publication of the first review on marine oil and preterm delivery by Cochrane in 2006, large randomized studies have added relevant data to the evidence base. Subsequent reviews that included either only low risk or high risk women, consistently demonstrated an increase in gestational age with intervention [25,26]. However, they did not identify a beneficial effect on preterm delivery before 37 weeks and were unable to provide conclusions on early preterm delivery due to the small number of studies. Our meta-analysis is the largest to-date in this area and has collated data from over 4000 women that have been published since the previous reviews. Based on emerging evidence, omega-3 fatty acids have shown a beneficial role in preventing preterm births, especially less than 34 weeks of gestation.

Recommendations for clinical practice

The daily intake of omega-3 fatty acids in pregnancy is often less than 300 mg/day as recommended by the World Health Organisation. Western diets have intakes as low as 15 mg/day. Dietary advice to pregnant women will need to incorporate advice to increase the intake of food rich in omega-3 fatty acid such as oily fish at least twice a week. The beneficial effect was observed for early preterm delivery in unselected population with no significant side effects. Hence there is a role for omega-3 supplements in pregnancy, and pregnant women and clinicians will be able to make informed decisions regarding the intake of supplements. It is possible that the supplements could increase the risk of postdates pregnancy as seen in the study by Makrides et al. Furthermore, women need to be informed that the optimal type and dose of omega-3 fatty acids, and the duration and commencement of the supplement that provides the maximal benefit is not known.

Recommendations for future research

Current evidence is focussed more on preterm delivery as an event and less on other clinically important neonatal and long term outcomes. Long term follow up of newborns who have been recruited into the trials will provide information on the effects of the intervention on neurodevelopment of the child. ORIS is a large randomized trial that aims to assess the effects of omega-3 fatty acid on early preterm delivery. An Individual Patient Data meta-analysis of current trials can identify the differential effects of the intervention based on the dose and duration of the intervention.

Funding

The authors have no support or funding to report.

Competing interests

The authors have declared that no competing interests exist.

Appendix A. Characteristics of included studies in the systematic review of omega-3 fatty acids in the prevention of early and any preterm delivery

Study	Year	Population			Quality of studies					Intervention				Outcome
		No of women	Inclusion criteria	Exclusion criteria	Randomization	Concealment	Blinding	ITT	Attrition	Supplement	Commenced	Duration	Frequency	
Ramakrishnan	2010	1094	18–35 y, 18–22/40, plan to deliver in specified hospital, breastfeed >3/12, live in area >2 y post-del	High-risk pregnancy (h/o complications inc abruption, PET/PIH, serious bleeding in current pregnancy, physician ref), lipid metabolism/ absorption disorders, regular fish oil/DHA, chronic meds e.g. epilepsy	A	A	A	A	A	DHA	18–22 wks	Up to delivery	OD	<37 wks Any live birth before 37 wks GA. BW.
Olsen	1992	533	30/40 midwife appt	h/o abruption, serious bleeding in current preg, regular use of PG inhibitors, multiple preg, fish allergy, regular fish oil	A	NA	NA	A	A	EPA + DHA	30 wks	Up to delivery	OD	<37 wks Any live birth before 37 wks GA. BW.
Olsen	2000	228	Previous preterm delivery, no h/o IUGR, PIH	Twins, DM, severe fetal malformations, placental abruption, drugs, alcohol, NSAID. Allergy to fish, regular intake of fish	A	A	A	NA	A	EPA + DHA	16 wks	Up to delivery	OD	Delivery <37 wks & <34 wks GA. BW. NICU.
Smuts	2003	347	16–36 yrs, 24–28 wks pregnancy, singleton, planned to deliver at Truman Medical Centre	<16 or >36 yrs, weight >240 lb, serious illness (cancer, lupus, hepatitis, infectious disease), DM, GDM, chronic hypertension	A	NA	NA	NA	A	DHA	24–28 wks	Up to delivery	OD	Delivery < 37 wks GA. BW. NICU.
Mardones	2007	970	>18 yrs, Para 0–5, up to 20 wks, no drugs/ alcohol abuse, BMI ≤21.2	Multiple pregnancies, chronic disease that can affect fetal growth, smokers.	A	NA	NA	A	A	Omega 3 fatty acid	20 wks	up to 36 wks	OD	Delivery < 34 wks & <37 wks. GA. BW
Makrides	2010	2399	Singleton, <21 wks,	Prenatal supplements with DHA, major fetal anomaly, bleeding disorders, on anticoagulants, drug or alcohol abuse, another fatty acid trial, English was not main language	A	A	A	A	A	DHA + EPA	20 wks	Up to delivery	OD	Delivery <34 wks & <37 wks. BW

Appendix A (*Continued*)

Study	Year	Population			Quality of studies					Intervention				Outcome
		No of women	Inclusion criteria	Exclusion criteria	Randomization	Concealment	Blinding	ITT	Attrition	Supplement	Commenced	Duration	Frequency	
Bulstraw	1994	63	h/o IUGR with or without PIH in previous pregnancy	Diabetes, SLE, other connective tissue disease, already on aspirin for other obstetric reason.	A	A	A	A	A	EPA	12–14 wks	?? up to delivery	TDS	Delivery <34 wks & <37 wks. NND
Onwude	1995	232	h/o one or more babies <3rd centile, PIH/PET, unexplained still birth, primi with	Diabetes, chronic hypertension, on anticoagulation, multiple pregnancy	A	A	A	A	A	EPA + DHA	19–26 wks	Up to 38 wks	BD-QDS	Delivery <32 wks & <37 wks. NND
Carlson	2013	301	8–20 wks, 16–36 yrs, planned hospital delivery at Kansas City Metropolitan Area	Multiple pregnancy, pre existing DM, hypertension, serious health condition (cancer, lupus, hepatitis, HIV, AIDS, alcohol & chemical dependency).	A	A	A	A	A	DHA	20 wks	Up to delivery	OD	Delivery <37 wks. GA. BW.

EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid, IUGR – intrauterine growth restriction, PIH – pregnancy induced hypertension, quality of studies: ITT – intention to treat, A – adequate, NA – not adequate.
Outcomes: PTD – preterm delivery; GA – gestational age; BW – birth weight; NND – neonatal death; NICU – neonatal intensive care unit.
Population: Primi – primigravida; PG – prostaglandin; GDM – gestational diabetes mellitus; DM – diabetes mellitus; HIV – human immune deficiency virus; AIDS – acquired immune deficiency syndrome.

References

[1] Harper M, Thom E, Klebanoff MA, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol 2010;115(2 Pt 1):234–42.

[2] RCOG. Tocolysis for women in preterm labour Royal College of Obstetricians and Gynaecologists – Greentop guideline no 1b. London; 2011.

[3] Mangham L. The cost of Preterm Birth throughout childhood in England and Wales. J Am Acad Pediatr 2009.

[4] Makrides M, Dudley L, Olsen S. Marine oil, and other prostaglandin precursor supplementation of pregnancy uncomplicated by pre-eclampsia or intra uterine growth restriction. Cochrane Collab 2012.

[5] Carlson S. DHA supplementation and pregnancy outcome. Am J Clin Nutr 2013;80(97):8–815.

[6] Helland IB, Saugstad OD, Smith L, et al. Similar effects on infants of $n-3$ and $n-6$ fatty acids supplementation to pregnant and lactating women. Pediatrics 2001;108(5):E82.

[7] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[8] RMH. A modified test for small-study effects in meta analysis of controlled trials with binary end points. Stat Med 2006;25(20):3443–57.

[9] Makrides M. Effects of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children; 2010.

[10] Mardones F, Urrutia MT, Villarroel L, et al. Effects of a dairy product fortified with multiple micronutrients and omega-3 fatty acids on birth weight and gestation duration in pregnant Chilean women. Public Health Nutr 2008;11(1):30–40.

[11] Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol 1995;102(2):95–100.

[12] Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies Fish Oil Trials In Pregnancy (FOTIP) Team. Br J Obstet Gynaecol 2000;107(3):382–95.

[13] Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. Br J Obstet Gynaecol 1995;102(2):123–6.

[14] Olsen SF, Sørensen JD, Secher NJ, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet 1992;339(8800):1003–7.

[15] Ramakrishnan U, Stein AD, Parra-Cabrera S, et al. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico. Food Nutr Bull 2010;31(2 Suppl.):S108–16.

[16] Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol 2003;101(3):469–79.

[17] Calder PC. Immunomodulation by omega-3 fatty acids. Prostaglandins Leukot Essent Fatty Acids 2007;77(5-6):327–35.

[18] van Houwelingen AC, Sørensen JD, Hornstra G, et al. Omega-3 fatty acid status in neonates after fish-oil supplementation during late pregnancy. Br J Nutr 1995;74(5):723–31.

[19] Velzing-Aarts FV, van der Klis FR, van der Dijs FP, et al. Effect of three low-dose fish oil supplements, administered during pregnancy, on neonatal long-chain polyunsaturated fatty acid status at birth. Prostaglandins Leukot Essent Fatty Acids 2001;65(1):51–7.

[20] Olsen SF, Hansen HS, Sørensen TI, et al. Intake of marine fat, rich in $(n-3)$-polyunsaturated fatty acids, may increase birthweight by prolonging gestation. Lancet 1986;2(8503):367–9.

[21] Hansen HS, Olsen SF. Dietary $(n-3)$-fatty acids, prostaglandins, and prolonged gestation in humans. Prog Clin Biol Res 1988;282:305–17.

[22] Giorlandino C, Brizzi C, Gioriandino M, Taramanni C. Effects of vaginally administered DHA fatty acids on pregnancy outcome in high risk pregnancies for preterm delivery: a double blinded randomised controlled trial. J Perinat Med 2013;7(3):42–6.

[23] Conde-Agudelo A, Romero R, Nicolaides K, et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. Am J Obstet Gynecol 2013;208(January (1)):42.e1–42.e18. http://dx.doi.org/10.1016/j.ajog.2012.10.877 [Epub 15.11.12].

[24] Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. Br J Obstet Gynaecol 2006;113:17–42.

[25] Szajewska H, Horvath A, Koletzko B. 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. Am J Clin Nutr 2006;83(6):1337–44.

[26] Horvath A, Koletzko B, Szajewska H. Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a metaanalysis of randomized controlled trials. Br J Nutr 2007;98(2):253–9.