Prostaglandins, Leukotrienes and Essential Fatty Acids 186 (2022) 102495

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

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

ISSFAL statement number 7 – Omega-3 fatty acids during pregnancy to reduce preterm birth

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ARTICLE INFO

Keywords:
Omega-3 fatty acids
DHA
Pregnancy
Prematurity

ABSTRACT

Globally, preterm birth is the leading cause of death in children under the age of 5 years and survivors may suffer life-long consequences. Following many years of investigation, there is strong evidence that a proportion of preterm births can be prevented by increasing maternal dietary omega-3 long chain polyunsaturated fatty acid (LCPUFA) intake during pregnancy. This Statement provides a synthesis of contemporary evidence on the role of omega-3 LCPUFA on prevention of preterm birth and is designed to provide fatty acid-specific knowledge and guidance for medical practitioners, midwives, health services, professional bodies and policy makers to consider for their contextual situations. The evidence synthesis, which underpins this statement, is based on the 2018 Cochrane systematic review with supplemental evidence from RCTs completed since that time as well as other systematic reviews. Heterogeneity between studies was explored to understand how the effect of omega-3 supplementation may vary in different population groups and by dose and type of omega-3 supplementation. Most trials were conducted in upper-middle or high-income countries and the evidence are most applicable in those settings. The evidence synthesis confirmed that omega-3 LCPUFA, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have an important role to play in determining gestational length in singleton pregnancies. Adequate intake of omega-3 LCPUFA in early pregnancy, consistent with existing nutritional guidelines, is associated with a lower risk of preterm and early preterm births for women with singleton pregnancies. Therefore, women with adequate omega-3 intakes in early pregnancy should maintain these intakes. Women who are low in omega-3 fatty acids will benefit most from omega-3 LCPUFA supplementation to reduce their risk of early birth. In such cases supplementation with a total of about 1000 mg of DHA plus EPA is effective at reducing risk of early birth, preferably with supplementation commencing before 20 weeks' gestation.

Abbreviations

LCPUFA,	Omega-3 long chain polyunsaturated fatty acid
RCTs,	randomized controlled trials
DHA,	docosahexaenoic acid
EPA,	eicosapentaenoic acid
RR,	risk ratio
CI,	confidence interval
ORIP,	Omega-3 fats to Reduce the Incidence of Prematurity
ADORE,	Assessment of DHA On Reducing Early Preterm Birth

1. Introduction

Preterm birth, especially early preterm birth, accounts for more than 85% of all perinatal complications and neonatal deaths and can have life-long consequences [1,2]. Children born preterm may suffer a myriad of physical and neurodevelopmental sequelae. From early childhood, neurocognitive complications may arise, manifesting as developmental delay, cerebral palsy, hearing and visual impairments, learning difficulties and psychiatric disorders [3]. Prematurity represents a significant psychological and financial toll on parents and a substantial societal economic burden, estimated to cost $1.6 – $2.6 billion annually,

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https://doi.org/10.1016/j.plefa.2022.102495
Received 27 September 2022; Accepted 28 September 2022
Available online 30 September 2022

depending on the country, size of population and prematurity rate [4–6]. Although a disproportionate share of these costs is incurred in neonatal intensive care for those born very preterm, there are substantial incremental costs associated with preterm birth that extend beyond initial hospitalization and among infants born even just a few weeks preterm. Despite this high burden, about two thirds of preterm births occur without known biological causes and strategies for prevention are a clear priority [7,8]. The most promising preventive intervention to emerge, that safely reduces preterm (<37 week's gestation) and early preterm (<34 weeks' gestation) birth, is maternal supplementation with omega-3 long chain polyunsaturated fatty acids (LCPUFA) [9–11]. This has necessitated an appraisal of the omega-3 LCPUFA requirements during pregnancy and their specific role for prematurity risk reduction.

To date, most advisories and nutritional guidance recommending intake of omega-3 LCPUFA during pregnancy, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been linked with sustaining omega-3 LCPUFA supply to the fetus to support brain growth and subsequent neurodevelopmental outcomes of infants and children [12–14]. There is consistency between these advisories suggesting that pregnant women should consume approximately 200 mg of DHA/day. This amount can be achieved from a varied omnivorous diet including fish, seafood, lean red meat, and eggs; 1–2 portions of fish per week alone could ensure an intake of 200 mg DHA/day. Many of these advisories, including the ISSFAL supported consensus statement of the Perinatal Lipid Working Group, are more than 10 years old and did not focus specifically on the effects of omega-3 LCPUFA on prematurity [12]. At that time, the best evidence available was a 2006 Cochrane review of marine oil supplementation in pregnancy, which included six randomized controlled trials (RCTs), most with highly specific at-risk populations [15]. These data demonstrated prolongation of gestational length and increased infant birth weight, however, were not considered robust enough to make specific recommendations regarding omega-3 supplementation in pregnancy to reduce prematurity [15].

In recent years, increasing attention has focused on the effect of maternal dietary intake of omega-3 LCPUFA on perinatal outcomes resulting in more than 70 RCTs completed. Collectively, trials summarized in the recently published 2018 Cochrane review, show improvements in several outcomes including a longer duration of gestation, higher birth weight and reduced risks of preterm birth and early preterm birth [11]. These findings have necessitated a specific evaluation of the role of omega-3 LCPUFA on preterm birth in relation to dose, timing of supplementation, baseline omega-3 status and an appraisal of the relative balance of DHA and EPA. It is postulated that the mechanisms of preterm birth involve both fatty acids; EPA is a precursor of the 3-series prostaglandins that are homologues and significantly less potent than the 2-series prostaglandins E2 and F2α (derived from arachidonic acid) known to be involved in uterine contractions and cervical ripening. Moreover, both EPA and DHA may relax the myometrium averting the early onset of labor and may inhibit activation of trophoblastic inflammatory pathways which in turn, may reduce the inflammation implicated in some preterm birth [16,17].

The aims of this ISSFAL statement are to summarize the available evidence pertaining to the effect of dietary omega-3 LCPUFA during pregnancy on preterm birth. This statement focuses on nutritional needs during pregnancy with specific exploration of omega-3 dose, balance of DHA and EPA, timing of supplementation and effect of maternal omega-3 status on efficacy of omega-3 supplementation. The statement is designed to provide current nutritional fatty acid knowledge that can be used and adapted by medical practitioners, midwives, health services, professional bodies and policy makers to inform practice and policy guidance in their specific contexts or situations. As with most clinical approaches, policy and practice is driven at the local level to account for regional or country specific health risk factors, disease prevalence as well as the capacity of local health services. To further support local implementation of omega-3 policies and practices to reduce the risk of prematurity we identify priority research questions.

2. Methods

Professors Maria Makrides, Robert Gibson and Dr Karen Best proposed to the ISSFAL executive board a statement on the relationship between omega-3 fatty acids and perinatal outcomes. After receiving support from the ISSFAL board, the procedure for writing ISSFAL statements, as described on the ISSFAL website (https://www.issfal.org/procedures-for-statements), was followed. In brief, this required a recent published systematic review specific to the subject area. The prepared statement, guided by a synthesis of the evidence, was available to the ISSFAL membership for comment for a period of 4 weeks. The authors considered the commentary and updated the statement accordingly (Supplementary material, Appendix). The final statement was approved by at least a 75% majority of the ISSFAL Board.

This statement contains evidence from the Cochrane Review of 'Omega-3 Addition in Pregnancy' published in 2018 [11]. In addition, supplemental evidence from RCTs completed since this time as well as other systematic reviews of relevant investigations have been incorporated. We focused our attention on the results of RCTs with omega-3 LCPUFA intervention/s vs control in conjunction with a grading of quality, because this most often leads to "trusted" guidance [18]. RCTs published to August 2021 are included.

3. Description of RCTS included in the evidence synthesis

The 2018 Cochrane review includes all trials of omega-3 LCPUFA up to August 2018 in any form or dose during pregnancy (including as supplements, food, or dietary advice). The review included 70 RCTs, involving 19,927 women at low, mixed, or high risk of poor pregnancy outcomes. Nearly half of the trials included women at increased/higher risk for factors which might increase the risk of adverse maternal and birth outcomes. Most of the trials were conducted in upper-middle or high-income countries (e.g., Australia, China, Denmark, England, The Netherlands, USA) and most included women who were carrying singleton pregnancies. The intervention dose ranged between 200 mg and 2700 mg omega-3 LCPUFA per day as DHA and EPA, chiefly as triglycerides, and was administered mainly throughout the second half of pregnancy. The majority of RCTs in the review were conducted before the contemporary widespread use of prenatal supplements containing low-dose (~200 mg/day) omega-3 LCPUFA (DHA and EPA) [11].

Since the 2018 Cochrane review, three key trials of omega-3 LCPUFA in pregnancy have been published, all with a focus on length of gestation and/or preterm birth. Populations studied include Australia [10], China [19] and the USA [9]. Makrides et al. randomized 5544 women (<20 weeks' gestation) to receive 900 mg/day of omega-3 LCPUFA (800 mg DHA + 100 mg EPA) or control (20 mg DHA+EPA) from before 20 weeks' gestation until 34 weeks' gestation, to reduce the risk of early preterm birth [10]. A three-group parallel randomized controlled trial by Olsen et al. included 5531 women in China to examine the effect on gestation duration of two doses of supplemental omega-3 LCPUFA compared to control. Women were randomized to a high fish oil group (2000 mg omega-3 LCPUFA, including 700 mg DHA + 1100 mg EPA), a low fish oil group (500 mg omega-3 LCPUFA, including 185 mg DHA + 275 mg EPA), or olive oil (control group) from mid pregnancy to 259 days (37 weeks) of gestation [19]. The trial by Carlson et al. was a randomized superiority trial to test the effectiveness of two doses of the omega-3 LCPUFA as DHA on early preterm birth by dose and enrolment DHA status [9]. 1100 women were randomized to consume either 1000 mg DHA or 200 mg DHA from enrolment (12– 20 weeks' gestation) until delivery [9].

4. Results of the evidence synthesis

Here we provide an update to the 2018 Cochrane review with the addition of RCTs completed since its publication, herein referred to as the 2021 Cochrane update. We include the three key trials outlined

above as well as several smaller trials reporting pregnancy outcomes following omega-3 LCPUFA supplementation. The 2021 Cochrane update for this statement includes data from 80 trials and is summarized in **Table 1**.

4.1. Omega-3 LCPUFA supplementation: prematurity and length of gestation outcomes

Primary outcomes in the 2021 Cochrane update include preterm birth, early preterm birth, and prolonged pregnancy. Women treated with omega-3 LCPUFA had a 35% reduction in early preterm birth <34 weeks' gestation (RR 0.65; 95% confidence interval [CI] 0.46 – 0.92) and a 12% reduction in preterm birth <37 weeks' gestation (RR 0.88; 95% CI 0.81 – 0.95) compared with no or minimal omega-3 fatty acid supplementation (**Table 1**). Mean gestational length was modestly greater in women who received omega-3 LCPUFA (mean difference 1.36 days, 95% CI 0.77 – 1.96). Omega-3 LCPUFA possibly increased the incidence of pregnancies continuing beyond 42 weeks' gestation (RR 1.31; 95% CI 1.01 – 1.70), **Table 1**, although the incidence was low in the more recent trials due to changes in obstetric practice that limit prolongation of pregnancy beyond the middle of the 41st week of gestation [20]. There was insufficient evidence to determine the effects of omega-3 LCPUFA on induction of labor for post-term (RR 1.12; 95% CI 0.74 – 1.70).

Table 1
2018[1] and 2021 cochrane review perinatal outcomes – Omega-3 LCPUFA supplementation vs no or minimal omega-3 LCPUFA.

Outcome	Year	Trials	Participants	Risk ratio and 95% confidence intervals	Quality
Preterm birth (<37w)	2021	36	23,726	RR 0.88, 0.81 – 0.95	High-certainty evidence
	2018	26	10,304	RR 0.89, 0.81 – 0.97	High-certainty evidence
Early Preterm Birth (<34w)	2021	12	16,782	RR 0.65, 0.46 – 0.92	High-certainty evidence
	2018	9	5,204	RR 0.58, 0.44 – 0.77	High-certainty evidence
Length of gestation	2021	50	23,359	average MD 1.36 days, 0.77 – 1.96	Moderate-certainty evidence
	2018	41	12,517	average MD 1.67 days, 0.95 – 2.39	Moderate-certainty evidence
Prolonged gestation (>42w)	2021	9	16,079	RR 1.31, 1.01 – 1.70	Moderate-certainty evidence
	2018	6	5,141	RR 1.61, 1.11 – 2.33	Moderate-certainty evidence
Birth weight	2021	51	20,104	average MD 71 g, 39 – 102 g	High-certainty evidence
	2018	44	11,584	average MD 76 g, 38.05,113.43	High-certainty evidence
Large for gestational age	2021	9	10,310	RR 1.13, 1.01 – 1.28	Moderate-certainty evidence
	2018	6	3,722	RR 1.15, 0.97 – 1.36	Moderate-certainty evidence
Small for gestational age	2021	11	13,494	RR 1.02, 0.93 – 1.13	Moderate-certainty evidence
	2018	8	6907	RR 1.01, 0.90 – 1.13	Moderate-certainty evidence

CI, confidence interval; MD, Mean Difference; RR, Risk Ratio; W, weeks

[1] Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database Syst Rev. 2018;11(11):CD003402.

4.2. Omega-3 LCPUFA supplementation: other outcomes

Importantly, other outcomes associated with prematurity, such as infant birthweight was also influenced by omega-3 LCPUFA supplementation resulting in an average mean increase of 71 g (95% CI 39 – 102 g), **Table 1**. This may be commensurate with the modest 1-2 day increase in the duration of gestation, when all the available data are combined. There was no difference in small for gestational age (RR 1.02; 95% CI 0.93 – 1.13) but a possible small increase in large-for-gestational age (RR 1.13; 95% CI 1.01 – 1.28), **Table 1**. Importantly, there were no adverse effects on vaginal bleeding or other pregnancy outcomes [11].

4.3. Consistency with other systematic reviews

Consistency of results between relevant systematic reviews is extensively discussed in the 2018 Cochrane publication with most discrepancies being accounted for by fewer included trials in other reviews compared with the Cochrane review [11]. A more recently published systematic review of omega-3 LCPUFA supplementation in pregnancy and preterm birth (to June 2020) [21] included RCTs by Makrides 2019 [10] and Olsen 2019 [19]. The review by Serra et al. report similar overall findings for prematurity outcomes to the 2021 Cochrane Update (**Table 1**) but suggest that the effect of omega-3 LCPUFA supplementation on preterm and early preterm birth loses statistical significance in sensitivity analysis of high-quality trials, which surprisingly exclude Olsen 2000 [21]. Apart from such variation in trial inclusion, heterogeneity between studies also exists and requires investigation. This includes variations in populations, inclusion criteria, doses, and type of omega-3 LCPUFA between studies that may be addressed through a series of subgroup analyses or other secondary analyses, which are reported below. Thus, understanding the differences between trials and how this may influence the results of meta-analyses is important to the interpretation of how trial results may apply to different settings and contexts.

4.4. Dose of omega-3 LCPUFA supplementation

Subgroup analyses for studies intervening with <500 mg omega-3 LCPUFA, 500 – 1000 mg omega-3 LCPUFA or >1000 mg omega-3 LCPUFA in the 2021 Cochrane update, showed no significant interaction between subgroups. Although this indicates no clear or consistent differences for of omega-3 LCPUFA dose on prematurity outcomes and is consistent with the 2018 Cochrane review [11], the greater reductions for preterm birth <37 weeks' gestation were achieved for the 500 – 1000 mg dose, while the >1000 mg dose was associated with the better effect for reduction in early preterm birth <34 weeks' gestation.

4.5. Balance of DHA and EPA in supplementation

The 2021 Cochrane update is consistent with the 2018 Cochrane review [11] in showing no clear subgroup differences based on type of supplements (DHA/largely DHA vs mixed EPA/DHA) on prematurity outcomes. It is important to note that for the outcome of early preterm birth <34 weeks' gestation, the trials that assessed mixed EPA/DHA were also the same trials that tested a dose of >1000 mg per day omega-3 LCPUFA. Further work is needed to differentiate LCPUFA dose from the balance of EPA and DHA.

4.6. Timing of supplementation

The gestational age at which omega-3 supplementation commenced

(≤ 20 weeks or >20 weeks) had no clear effect of prematurity outcomes, although supplementation starting before 20 weeks was associated with larger effect sizes in prematurity outcomes. This was observed in both the 2021 Cochrane update and the 2018 Cochrane review [11]. Interestingly, the two trials [10,19], with over 10,000 participants, that stopped supplementation before delivery, showed no effect of prolongation of pregnancy with omega-3 supplementation and no effect on obstetric intervention because of post-term dates. Furthermore, Olsen et al [19] suggest that the effect of omega-3 LCPUFA supplementation on delaying birth ceases rapidly once supplementation is stopped. The reduction in effect size on prolonged gestation is noted in **Table 1** between the 2018 and 2021 Cochrane reviews with the inclusion of these two trials.

4.7. Baseline omega-3 status and efficacy of omega-3 LCPUFA supplementation

Changes in consumer behavior in recent years have resulted in increased consumption of prenatal supplements with low dose DHA (≈ 200 mg per day), especially in high-income countries. This has led to the hypothesis that more recent trials in population groups where prenatal supplementation is more common may show smaller effect sizes. However, there is no trend to support a reduction in effect size in either preterm or early preterm birth with trial publication date in either the 2018 Cochrane review [11] or the 2021 Cochrane update. Rather, individual studies have suggested that the background omega-3 LCPUFA intake or status of women may predict the response to supplementation. Data from both the 1995 and 2000 Olsen trials indicate that omega-3 LCPUFA supplementation extended the duration of gestation and reduced the risk of spontaneous preterm delivery in low fish consumers but had no effect in higher fish consumers [22,23]. This is consistent with Olsen's 2019 trial in China that reported no overall effect of omega-3 LCPUFA (both 700 mg DHA + 1,100 mg EPA and 185 mg DHA + 275 mg EPA compared with control) on the risk of preterm birth, but among low fish consumers, they observed potentially clinically important delays in timing of delivery by 5 –10 days [19]. Similarly, the ORIP Trial (n = 5544), conducted in Australia, showed no overall effect of omega-3 LCPUFA (800 mg DHA + 100 mg EPA) supplementation on risk of early preterm birth [10]. A pre-specified per protocol analysis also showed no difference between intention to treat analysis and women who completed the trial per protocol [10]. However, secondary analyses in singleton pregnancies (n = 5070) demonstrated that response to omega-3 LCPUFA supplementation was dependent on omega-3 status at study entry (< 16 weeks' gestation). Women with low omega-3 status at study entry were at higher risk of early preterm birth and omega-3 supplementation significantly reduced this risk by 77% (0.73%, [3/411] vs 3.16%, [15/474], RR 0.23; 95% CI 0.07 – 0.79) [24]. Conversely, women with replete omega-3 status at study entry were already at low risk of early preterm birth and supplementation with 900mg LCPUFA per day increased this risk (2.20%, [25/1138] vs 0.97%, [11/1139]; RR 2.27, 95% CI 1.13–4.58) [24]. The ADORE trial (n = 1100) conducted in the United States showed an effect of 1000 mg vs 200 mg DHA per day on early preterm birth rates, if participants had low blood DHA status at enrolment (2.0% vs 4.1%, pp = 0.93) compared with results of the overall trial population (1.7 % vs 2.4%, pp = 0.81) [9]. Consistent with the ORIP trial, ADORE also suggested that women with sufficient DHA status in early pregnancy are at lower risk of early preterm birth [9]. Furthermore, a quartile analysis based on red cell EPA+DHA from the Harper trial [25] indicated that recurrent preterm birth was lowest in the second quartile of EPA+DHA status [26]. Although the types of analyses and the numbers of women included in the different trials varied, the results consistently imply a reduction in early birth with omega-3 LCPUFA supplementation in women with low status, while women with higher or replete status are already at lower risk of early birth and additional supplementation will result in a null or possible increased risk of early birth. As with many nutrient interventions, reports of a response curve dependent upon basal status is not uncommon [27]. Further work to define optimal omega-3 status in pregnancy linked with low rates of prematurity is desirable.

4.8. Summary of evidence synthesis for nutritional advice

The subgroup and secondary analyses reported here [9,24] indicate the complexity of what may be hidden in meta-analysis or aggregate analyses in individual large-scale trials. Nevertheless, the consistency in outcomes of the RCTs indicate that omega-3 LCPUFA has a role to play in extending the duration of gestation and reducing the risk of both preterm and early preterm birth. The 2018 Cochrane review included studies that were not generally representative of pregnant women with a higher proportion being at increased risk of poorer pregnancy outcome [11]. The latest three trials with over 11,000 women across three countries, which included general populations of pregnant women, show little or no benefit of routine omega-3 LCPUFA supplementation, with modestly high doses, on prematurity risk [9,10,19]. Rather the effectiveness of these modestly high omega-3 LCPUFA interventions is most evident in women with singleton pregnancies who are identified as having a low or depleted omega-3 status. Therefore, in higher income societies with good obstetric care, policies of targeted or tailored supplementation based on an individual's omega-3 status may be more effective than universal approaches.

Few data are available regarding the efficacy of omega-3 supplementation in reducing prematurity risk in lower income countries and societies. Women in such settings often have a higher incidence of preterm birth. Although it is attractive to extrapolate the results from higher income settings, risk factors for prematurity differ in lower income settings. Lower income regions with both low and adequate omega-3 intakes are known to have high prematurity rates with infection being a common factor related to prematurity. Understanding the role of omega-3 fatty acid nutrition in influencing prematurity risk in such contexts is an urgent priority and is actively being investigated (CRTI/2020/08/027146).

Data from upper-middle and high-income settings support the following nutritional advice to minimize the risk of early birth:

- Encourage adequate intakes of omega-3 LCPUFA for all women of childbearing age, in line with existing dietary guidelines, with special attention given to the increased omega-3 LCPUFA requirements for pregnant women. https://www.issfal.org/assets/globalrecommendationssummary19nov2014landscape_-3-.pdf
- Identify omega-3 LCPUFA deficits in early pregnancy as is common for other nutrients vital for pregnancy health (such as iron, vitamin D).
- Address nutritional deficits in omega-3 LCPUFA by advising supplementation with a total of about 1g of EPA+DHA, taken daily from before 20 weeks' gestation.
- Encourage women with adequate omega-3 LCPUFA to maintain their adequate intakes.

5. Contextual and situational considerations for evidence-based advice

Evidence-based guidance for clinical settings is often general in nature to allow regions, health services and individual health practitioners to consider contextual factors that impact local practices and assess and refine implementation strategies. There are important considerations for implementing omega-3 targeted or tailored nutritional approaches to reduce prematurity risk. These include determining the best methods to identify women with low omega-3 status, defining low status requiring intervention, availability of appropriate supplements, and equity and access issues for women who are disadvantaged even in higher income settings.

5.1. Determining the best methods to identify pregnant women with low omega-3 status

Two common methods have been used to identify women with low omega-3 status; dietary recall or direct measurement of omega-3 fatty acids in blood. While a dietary assessment has the advantage of being easy and immediate, accurately and precisely measuring omega-3 status from diet alone is difficult. At best only 30–40% of the variance in measures of omega-3 status is predicted by food frequency questionnaires [28–30]. Furthermore food frequency questionnaires generally do not meet the criteria for sensitivity and specificity required for a definitive measure of status and are therefore considered screening tools. [28, 31–33]. Based on current knowledge, the most reliable method to measure omega-3 status is an assessment of omega-3 fatty acids in blood [32]. A research priority is to develop and validate low-cost, minimally, or non-invasive methods to assess the omega-3 fatty acid status, preferably at the point of care.

5.2. Defining low omega-3 status

Numerous methods exist for the measurement of omega-3 fatty acids in blood samples and different fractions can be measured, all of which can give reliable measures of omega-3 status [34,35]. The range of omega-3 values obtained for human blood samples vary according to the blood fraction monitored (whole blood, plasma/serum, red cells). However, measurement of fatty acids from all these fractions has been formalized [36] and exchange of samples between labs indicates high comparability [35]. An area of contention is the actual biomarker used that will provide the most robust prediction risk of early birth and response to supplementation that will reduce this risk. With blood samples and prematurity outcomes from over 5000 women, the ORIP team investigated a range of omega-6 and omega-3 fatty acid biomarkers in being able to predict early birth and response to supplementation [34]. It was only the omega-3 related biomarkers (total omega-3, DHA+EPA, DHA) that could identify women at risk and most likely to benefit from supplementation. However, total omega-3 status was the more robust biomarker compared with EPA+DHA and DHA alone. Total omega-3 status identified 17.5% of women as being low in omega-3 status and supplementation reduced their risk of early preterm birth by 77% [24]. This compared with 14.7% of women with low status and a 46% reduction in early preterm birth for the EPA+DHA biomarker and 5% of women and a 69% reduction for the DHA biomarker [24]. The definitions for low, moderate and replete status are outlined in **Table 2** for both whole blood (measured as dried blood spots) or serum/plasma [34]. While the suggested definitions for low omega-3 status are derived from the largest trial to date there is no internationally agreed cut-off to define omega-3 depletion in pregnancy [34]. It would be worthwhile for future investigations to confirm the validity of different measures of omega-3 status for decision-making around omega-3 supplementation to reduce risk of early birth.

Table 2
Suggested blood levels of total omega-3 fatty acids to define low, moderate and replete status in whole blood and serum/plasma[1].

Definition	Total omega-3 fatty acids* in whole blood (as % total fatty acids)	Total omega-3 fatty acids* in serum or plasma (as % total fatty acids)
Low	<4.2	<3.7
Moderate	4.2 – 4.9	3.7 – 4.3
Replete	>4.9	>4.3

* Total omega-3 fatty acids = sum of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and alpha linoleic acid (ALA).

[1] Simmonds LA, Yelland LN, Best KP, Liu G, Gibson RA, Makrides M. Translating n-3 polyunsaturated fatty acid status from whole blood to plasma and red blood cells during pregnancy. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2022;176:102367

5.3. Availability of appropriate supplements

For women with low omega-3 status in early pregnancy, supplements are the most practical way to ensure omega-3 status is restored as effectively as possible. While increases in omega-3 fatty acid status could be achieved by increasing oily fish intake, cost, preference, limitation in food variety, lack of cooking skills, or philosophical and ecological concerns are all potential barriers for women [37]. Micro-algae or plant bioengineered sources of omega-3 fatty acids may be suitable for vegan or vegetarian women or those who have concerns about depleting fish stocks.

An important consideration when recommending omega-3 supplementation to reduce preterm birth is the appropriate regulation of supplement manufacturing to ensure pregnant women can obtain high quality supplements that meet accepted safe international standards for heavy metals, pesticides and oxidation levels [38].

5.4. Equity considerations

Good general nutrition during pregnancy, consistent with existing dietary guidelines, is important and provides an adequate omega-3 LCPUFA intake for most women. However, even in well-nourished populations, food insecurity is an issue for some families, and women who are socially disadvantaged have a tendency for lower omega-3 LCPUFA status [39] on top of already having greater rates of prematurity [8]. Contributing to this inequity is that families who are socially advantaged have the resources to purchase commercial omega-3 testing and supplementation as needed. It is, therefore, vital that any omega-3 test and treat program is inclusive of women who are disadvantaged, assesses subsidization strategies, and is appropriately evaluated for cost effectiveness.

6. Summary

Pregnancy is a time of major physiological change. Interventions with the capacity to alter pregnancy outcomes, such as omega-3 LCPUFA supplementation, should have the appropriate medical oversight and be incorporated into the pregnancy care plan. Due consideration will be required regarding interaction with other pregnancy risk factors and potential contraindications. For example, the value of omega-3 LCPUFA supplementation to reduce preterm birth in multiple pregnancies and women who have had a previous preterm birth is not clear. Data regarding effectiveness in these situations are limited and the pathophysiology of prematurity is most likely different from that of unexplained spontaneous preterm birth in otherwise seemingly well singleton pregnancies. Furthermore, modern medical management may also alter the pregnancy course [8,11,40]. With these considerations, the following statements are made:

6.1. Implications for policy and practice

- Omega-3 LCPUFA (DHA and EPA) have an important nutritional role to play in determining gestational length in singleton pregnancies.
- Adequate intake of omega-3 LCPUFA in early pregnancy, consistent with existing nutritional guidelines, is associated with a lower risk in preterm and early preterm births for women with singleton pregnancies.
- Women with adequate intake of omega-3 LCPUFA in early pregnancy should be encouraged to maintain their intakes.
- Women who are low in omega-3 fatty acids will benefit most from omega-3 LCPUFA supplementation to reduce their risk of early birth. In such cases supplementation with a total of about 1000 mg of EPA plus DHA is recommended. Supplementation should commence before 20 weeks' gestation.

- Routine maternal screening for omega-3 depletion in early pregnancy is recommended to identify women who would benefit from specific supplementation. Assessment of omega-3 status in blood is ideal.

6.2. Implications for priority research

- International agreement for specific reference ranges for low and replete status in blood fractions needs to be developed.
- Developing and validating novel, standardized omega-3 assessment tools and methodology that are robust, equitable and cost effective and can be widely implemented as a routine part of antenatal care.
- Further work is needed to evaluate the minimum effective omega-3 LCPUFA dose, the optimal balance of DHA and EPA for supplementation, the role of omega-3 LCPUFA in multiple pregnancies, and potential interactions with increasingly common interventions, such as aspirin and progesterone used to reduce prematurity.

Declaration of Competing Interest

The 2020 Australian Pregnancy Care Guidelines included an evidence-based recommendation for omega-3 supplementation to reduce the risk of prematurity for women who are low in omega-3. The Australian Pregnancy Care Guidelines was made by an independent multidisciplinary committee, which included a range of health professionals with expertise in providing, developing, and researching antenatal care, a consumer representative with experience of antenatal care and a methodology expert. The authors of this ISSFAL report were not involved in the Australian Pregnancy Care Guideline development. In response to the omega-3 evidence-based recommendation in the Australian Pregnancy Care Guidelines, the authors are currently evaluating the adoption and effectiveness of an omega-3 test-and-treat approach, embedded with routine antenatal screening, in the state of South Australia. All methods linked with the omega-3 test-and-treat program are published and the authors have no financial interests.

Acknowledgments

We thank Professor Philippa Middleton for providing updated analysis for the Cochrane Review.

Supplementary materials

Supplementary materials associated with this article can be found in the on-line version at 10.1016/j.plefa.2022.102495.

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