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Kar S, Wong M, Rogozinska E, Thangaratinam S. Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies. *European Journal of Obstetrics, Gynecology and Reproductive Biology*. 2016;198:40-46.

What We Know, Think We Know, or Are Starting to Know

Whatever debate may exist about the role of the long-chain marine omega-3 fatty acids, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA], for outcomes like cardiovascular disease, the one area where there is widespread acceptance of their importance is in relation to pregnancy [1–3].

However, if we drill even further into the relative importance of these fatty acids for pregnancy related outcomes, DHA emerges as the primary focus; along with arachidonic acid [AA], DHA plays a vital role in the development of the central nervous system and brain, a process which rapidly accelerates from 20-24 weeks gestation [1,3,4].

One important factor that is distinct but related to DHA for pregnancy outcomes is gestational age at birth, which itself is independently one of the most important variables in determining overall infant health and cognitive development [5].

However, there may be a relationship with DHA as supplementation with this fatty acid has been shown to increase gestational age at delivery [3,6]. The present study was a meta-analysis of the effects of omega-3 fatty acid supplementation during pregnancy on gestational age at

The Study

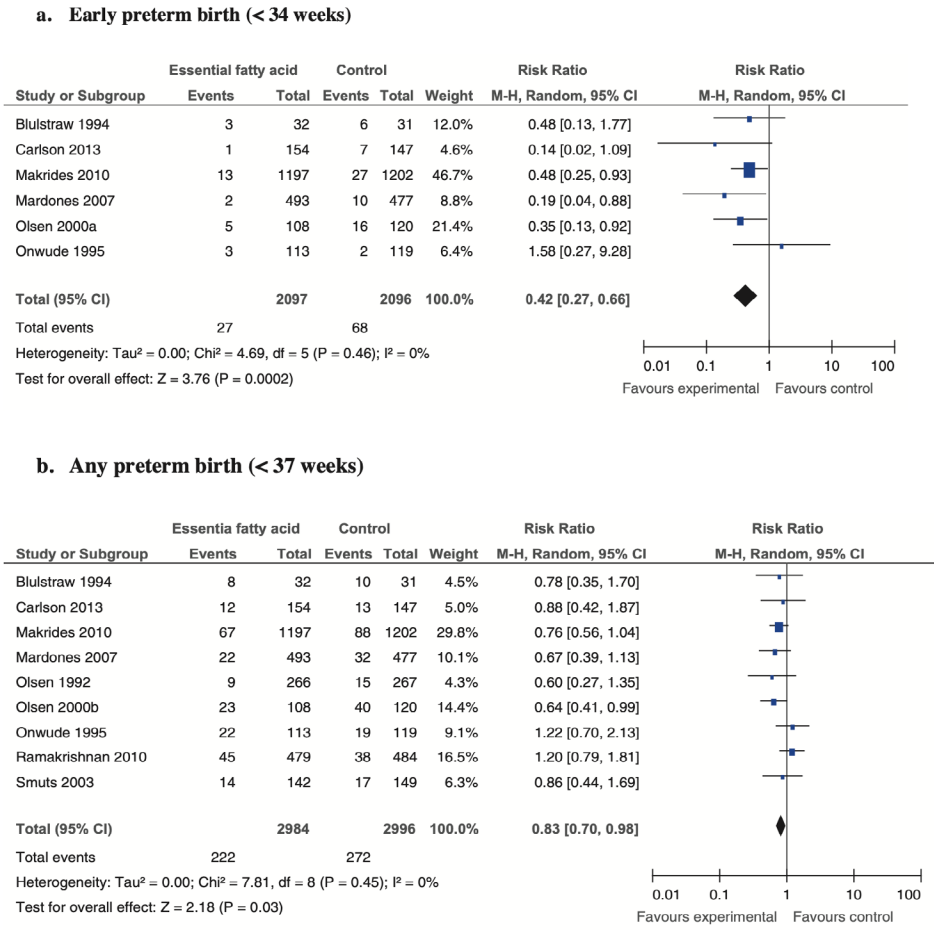
The investigators conducted a systematic review and meta-analysis of studies meeting the following criteria:

- **Design**: Randomised controlled trials
- **Exposure**: Omega-3 supplementation
- **Outcome**:
  - early preterm birth ['ePTB' , defined as delivery at <34-weeks' gestation]
  - overall preterm birth ['PTB' , defined as delivery at <37-weeks' gestation]
- **Population**: Women with singleton pregnancies

Pre-planned subgroup analyses assessed the effect of the trials based on preterm risk factors, supplement timing, and supplemental dose. Preterm birth risk included pre-eclampsia, pregnancy induced hypertension, small for gestational age baby, unexplained still birth or preterm birth in previous pregnancies; women were considered high risk if they exhibited any of these risk factors.

Results: 6 RCTs on ePTB, which totalled 9 RCTs when overall PTB was the outcome, were included. The RCTs with ePTB as an outcome included 4,193 women, and 5,980 women including the RCTs on overall PTB. Trials used either EPA in isolation, DHA in isolation, or mixed EPA+DHA, with a dosage range of 300-1,300mg/d. 7/9 studies began supplementation before 24-weeks' gestation.

- ***Effects of Omega-3 on ePTB*:** Omega-3 supplementation resulted in a 58% [RR 0.42, 95% CI 0.27–0.66] lower risk of early preterm birth. In women at high risk of a preterm birth, the effect was a 64% [RR 0.36, 95% CI 0.18–0.71] lower risk.
- ***Effects of Omega-3 on Overall PTB*:** Omega-3 supplementation resulted in a 17% [RR 0.83, 95% CI 0.70–0.98] lower risk of overall preterm birth. Doses of >400mg/d showed a 17% [RR 0.83, 95% CI 0.69–1.00] lower risk [more under ***Interesting Finding***, below].



***Forest plot** from the paper showing [**top**] the effects of omega-3 supplementation on early preterm birth and [**bottom**] the effects of omega-3 supplementation on overall preterm birth. While both findings were significant in favour of omega-3 supplementation, the magnitude of effect was substantially greater for prevention of early preterm birth of delivery <34-weeks' gestation.*

- ***Effects of Omega-3 on Gestational Age*:** Based on data from 6 studies, there was a significant increase in gestational age at term of 2.43 weeks [95% CI 0.93–3.93 weeks]. Excluding women at high risk of a preterm birth, there remained a significant increase in gestational age of 1.35 weeks [95% CI 0.39–2.31]. There was also a significant increase in infant birth weight of 122.1 g [95% CI, 47.4–196.8g].

The Critical Breakdown

Pros: The systematic review included a search of relevant research databases. The quality of the included trials was high overall, and intention-to-treat analysis was used in 7/9 trials [where the last value recorded for a participant is included in the statistical analysis, as if that value represented the data point the participant finished the trial with, to ensure balance is maintained between groups in the trial]. The subgroup analyses were pre-planned to avoid cherry-picking, and provided useful insights on factors like supplemental dose [more under ***Interesting Finding***, below].

Cons: Some typical issues for a meta-analysis in nutrition, the trials differed in terms of timing of initiating supplement use, duration of supplement use, and importantly, type of supplement [EPA, DHA, or EPA+DHA] and dose. The overall number of trials was small, although the total number of participants was larger than many other meta-analyses and may have overcome this limitation. The authors note there was limited data from the included studies on compliance with taking omega-3 supplements.

Key Characteristic

The fact that 6/9 studies reported specifically on ePTB provides the present study with its most persuasive finding, including data on 4,193 women. It is important to distinguish between ePTB [<34-weeks] and overall PTB [>37-weeks] as the magnitude of effect of omega-3 supplementation, and DHA in particular, consistently appears to differ between these respective outcomes.

For example, a 2018 meta-analysis found that while risk of PTB was 11% [RR 0.89, 95 CI 0.81–0.97] lower from omega-3 supplementation, there was a 42% [RR 0.58, 95% CI 0.44–0.77] lower risk of ePTB, a similar effect size to that found in the present study.

This finding is not merely academic; compared to PTBs of 34 to 37-weeks, ePTB <34-weeks are associated with longer hospitalizations, increased risk of additional hospitalizations during the first year of an infant's life, and greater short and long term healthcare costs [(7)].

Interesting Finding

Teasing out dose thresholds is one of the most crucial aspects of reconciling apparent conflicts in the evidence, and particularly in parsing "null" findings in RCTs. The present meta-analysis undertook several potentially insightful subgroup analyses, specifically the stratification of dose comparing >400mg/d to <400mg/d.

The analysis found that doses of >400mg/d showed a 17% [RR 0.83, 95% CI 0.69–1.00] lower risk of PTB, while doses <400mg/d showed a 13% [RR 0.86, 95% CI 0.44–1.69]. While there was no statistically significant difference between these dose thresholds, the direction of effect for >400mg/d is clear [the upper bound of the confidence touches 1.0, but is otherwise <1.0], and the analysis of <400mg/d was based on only 291 women from a single study [hence the clear imprecision in the confidence intervals].

This is where we look to wider research. For example, an RCT which used a dose of exactly 400mg/d found no effect of DHA on reducing PTB [8]. A prior RCT showed significant reductions in ePTB and low birthweight at a dose of 600mg/d [3], while another RCT using 800mg/d also showed significant reductions in ePTB and low birthweight [9].

Following up on this, Carlson *et al*. [10] analysed dose-thresholds using data from two RCTs, indicating that 600mg/d may be where the maximum benefit of DHA supplementation is observed. Thus, the findings of the present meta-analysis of effects >400mg/d are congruent with the wider evidence.

Relevance

Recently, the results of the Omega-3 to Reduce the Incidence of Prematurity [ORIP] RCT were published, indicating that 900mg/d of total omega-3 did not reduce risk of ePTB or PTB [11]. Ah, a 'null' finding! See, we can't trust nutrition science at all.

Sophistry aside, how do we reconcile such findings against what appears to be quite a persuasive and comprehensive body of evidence supporting the efficacy of omega-3 fatty acid supplementation [DHA in particular] in reducing risk of preterm births?

There are two factors that I try to hammer home with Deepdives on nutrient RCTs: dose thresholds *and* baseline nutrient status. The former is sometimes considered; the latter, unfortunately, is seldom considered. Yet baseline nutritional status is a crucial determinant of effect because *nutrients are not drugs;* giving people more of a nutrient when they have sufficient levels of that nutrient will not yield any greater effect of that nutrient [see **figure**, below].

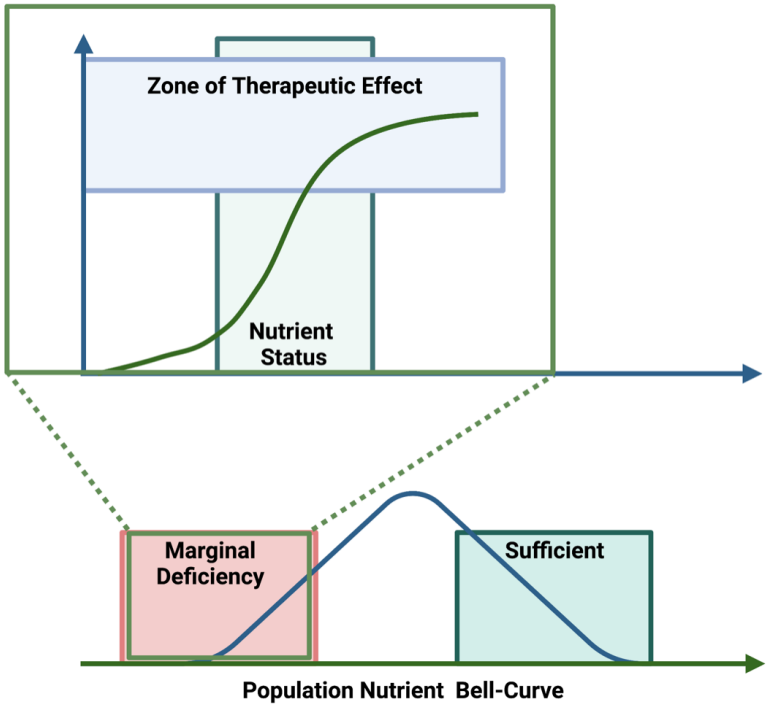


***Figure** illustrating the relationship between the bell-curve of nutrient action [**bottom**], and the expected zone of therapeutic effect for a nutrient [**top**]. The bottom represents the population, and the red-shaded box represents the proportion of the population with insufficient intakes of a nutrient. Within that range of insufficient intake, if a nutrient is provided it will increase the levels of that nutrient [**nutrient status box in top graph**] to a **zone of therapeutic effect** within which the functions associated with that nutrient will increase and effects of that nutrient will be observed. As you can see from the curve [**green line**] of nutrient status, this effect will plateau, and no further benefit will be derived from providing more of the nutrient. Graph adapted from Carlson et al. [12].*

Thankfully, the investigators behind the ORIP trial were live to these issues for nutrient RCTs and explored their data in a secondary analysis to determine whether baseline levels of omega-3 fatty acids in the blood influenced the results of the trial [13].

And guess what? In women with an omega-3 status of <4.1% of total fatty acids at baseline, supplementation with omega-3 reduced risk of ePTB by 77% [RR 0.23, 95% CI 0.07–0.79]. Conversely, in women with baseline omega-3 of >4.9% there was an *increased* risk of ePTB. Remember, *nutrients are not drugs,* and more does not mean better; in fact, there can be potential adverse effects where excess levels are reached.

Application to Practice

There is a summary from the most recent meta-analysis on the topic of omega-3 supplementation and preterm birth [6], which sums up the application nicely for those of you who work with women considering [or indeed already] pregnancy:

"Omega-3 long-chain polyunsaturated fatty acids (LCPUFA), particularly docosahexaenoic acid (DHA), supplementation during pregnancy is a simple and effective way to reduce preterm, early preterm birth and low birthweight, with low cost and little indication of harm."

It does appear that it is DHA that is the specific omega-3 desired, and a dose of 600mg/d from ~20-weeks' gestation appears to be the effective dose [10]. Nevertheless, given the potential for too much of a good thing to be a bad thing, it would be important to drill down with a client to determine their habitual intakes of oily fish, and whether they are currently supplementing with omega-3's and at what dose; the evidence suggests it is women with low levels/intakes that are likely to benefit.

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