The role of omega-3 polyunsaturated fatty acids in the prevention of preterm birth

Preterm birth, defined as delivery before 37 completed weeks' gestation, is the leading cause of death in children under five years of age. Preterm birth affects nearly 15 million babies worldwide,[1] of which 26 000 are in Australia.[2] Of these, an estimated 30% are defined as early preterm birth (< 34 completed weeks' gestation),[2] with this subgroup experiencing the highest rates of mortality and morbidity.[1] Despite targeted research and interventions, preterm birth rates have remained mostly unchanged.[1,2]

Decades of research involving more than 70 randomised controlled trials (RCTs) have reported that omega-3 supplementation during pregnancy reduces the rate of preterm birth.[3,4] These data have potential to be translated into an effective population-based strategy to prevent preterm birth globally. Unfortunately, implementation of this strategy is not straightforward, as recent data suggest that the benefit of omega-3 supplementation appears to be limited to individuals with low omega-3 levels and may cause harm to pregnant women who are replete.[5]

Role of omega-3 polyunsaturated fatty acids on preterm birth

Long-chain polyunsaturated fatty acids (LCPUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are naturally occurring omega-3 fatty acids. For pregnant women, Australian guidelines recommend a daily intake of 250–500 mg of DHA or EPA which can be met by consuming two to three servings of seafood per week or from fish or algal oil supplements.[6]

The mechanisms by which omega-3 LCPUFAs influence the timing of birth remain unclear. It has been postulated that higher omega-3 LCPUFAs intake may increase the production of omega-3 prostaglandin derivatives, interfering with omega-6 prostaglandin derivatives (prostaglandins E_2 and $F_{2\alpha}$) that are known to contribute to premature uterine contractions and cervical ripening. Further, omega-3 may regulate myometrial contractility, delaying early labour, and may inhibit trophoblastic inflammatory pathways, reducing the placental inflammation contributing to some preterm birth.[7]

Over the past 30 years, the effect of omega-3 LCPUFAs on preterm birth has been examined in observational studies, interventional trials, and meta-analyses. Initial positive associations between gestational duration and maternal omega-3 status were first observed in the 1980s.[8] Since publication of these findings, cohort and case–control studies have reported reduced rates of preterm birth outcomes with increased omega-3 levels.[9-11] Pooled results from studies involving nearly 159 000 women across 19 European countries reported a 13% reduction in preterm birth when fish was consumed at least once a week.[11] At a population level, a 2019 cross-sectional analysis examining the relationship between omega-3 intake and preterm birth rates in 184 countries reported a decreased rate of preterm birth by 1.1% in countries where omega-3 intake was greater than 600 mg per day compared with countries that consumed 600 mg per day or less.[12] Multiple meta-analyses have demonstrated reduced rates of preterm birth with omega-3 supplementation.[3,4] The most current Cochrane review reported an 11% reduction in preterm birth rates (relative risk [RR], 0.89; 95% confidence interval [CI], 0.81–0.97), and a 42% reduction in early preterm birth (RR, 0.58; 95% CI, 0.44–0.77).[3] Since the Cochrane review, several RCTs (including three key trials[13-15]) have been published. Inclusion of these RCTs to the 2018 Cochrane meta-analysis reaffirmed the association between omega-3 intervention and preterm birth risk reduction reporting a 12% and 35% reduction in preterm birth (RR, 0.88; 95% CI, 0.81–0.95) and early preterm birth rates (RR, 0.65; 95% CI, 0.46–0.92) respectively.[7]

Adverse effects

With all interventions, it is important to consider adverse effects. For mothers, data from 70 RCTs evaluating various obstetric outcomes found no significant increases in adverse outcomes with omega-3 intervention when compared with placebo or controls.[3] For neonates, pooled data from nine RCTs suggest a possible increase in the risk of large-for-gestational-age babies (RR, 1.13; 95% CI, 1.01–1.28) with omega-3 intervention versus placebo.[7] Neonates may also be at an increased risk of post-term delivery (RR, 1.31; 95% CI, 1.01–1.70). No significant difference on post-term caesarean deliveries was observed, and the evidence is unclear for post-term induction of labour.[7] Based on these data, it is currently recommended that omega-3 supplementation ceases at 37 weeks' gestation.[16]

Limitations of broad-based omega-3 implementation

Despite increasing evidence to support omega-3 use for preterm birth prevention, there are several key limitations that require careful consideration before widespread implementation across Australia. Omega-3 supplementation may not be appropriate for all pregnant women. Evidence suggests that the baseline omega-3 status of pregnant women may affect the outcome of supplementation on preterm birth risk. Observational and interventional studies have suggested that mothers with low omega-3 status or intake receive the greatest reduction in preterm birth risk with omega-3 intervention.[5,10,14] In contrast, supplementation in mothers with sufficient or higher baseline omega-3 status may have no benefit on early preterm birth risk.[5,14,17] The largest RCT examining the effects of omega-3 supplementation on preterm

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birth outcomes to date reported a 77% reduction (from 3.16% to 0.73%; RR, 0.23; 95% CI, 0.07–0.79) in early preterm birth rates with 900 mg omega-3 LCPUFA supplementation in women with low omega-3 status. Women with sufficient omega-3 levels were at low risk of early preterm birth (0.97%), and 900 mg omega-3 LCPUFA was associated with a 2.27-fold increase (2.2%; 95% CI, 1.13–4.58) in early preterm birth rates.[5] Currently, the mechanism responsible for increased rates of preterm birth with supplementation in women who are replete remains unclear. These data highlight the critical importance of testing omega-3 status before supplementation in pregnancy as Australian data report that about 60% of women are replete with omega-3;[5,18] supplementation of these women may inadvertently increase their rate of preterm birth.

National guidelines

Current national guidelines reflect the evidence from meta-analyses in their recommendations.[19-21] The 2020 Australian *Clinical practice guidelines: pregnancy care*, developed in conjunction with the National Health and Medical Research Council, recommend mid-dose omega-3 supplementation (800 mg DHA + 100 mg EPA daily) for pregnant women with low omega-3 status as it may reduce their risk of preterm birth.[19] The Royal Australian College of General Practitioners has published similar recommendations, with advice to use an omega-3 supplement with at least 500 mg of DHA per day during pregnancy.[20] Recommendations by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists regarding omega-3 supplementation in pregnancy are due to be reviewed. Their most recent statement from 2019 provided consensus-based recommendations for women who consume small amounts of dietary omega-3 to consider additional supplementation; the dose and frequency of supplementation is not clearly defined.[21]

Although national guidelines recommend omega-3 supplementation in pregnancy for women with low omega-3 status, the definition of a low status remains unclear.[19,21] Recently, the South Australian Health and Medical Research Institute (SAHMRI) published recommendations for omega-3 LCPUFA supplementation in women with singleton pregnancies specific to baseline omega-3 status in early pregnancy.[16] These recommendations are based on data from the largest RCT examining the role of omega-3 supplementation on preterm birth,[5,15] and are the basis of an evaluation of an omega-3 screen and treat approach linked with routine first trimester antenatal screening to assess the effectiveness of omega-3 supplementation to reduce preterm birth in the South Australian community.[16] Omega-3 serum levels should be established before 20 weeks' gestation. After this, significant pregnancy-related haemodilution may affect the validity of blood tests and their relevant cut-offs. For women with low omega-3 status (serum total omega-3 < 3.7% of total fatty acids), omega-3 LCPUFA supplementation (800 mg DHA + 100 mg EPA per day) should be initiated before 20 weeks' gestation and continued until 37 weeks' gestation.[16] In contrast, for women with sufficient omega-3 status (serum total omega-3 > 4.3% of total fatty acids), omega-3 supplements are not required (as part of pregnancy multivitamins or a standalone supplement). If women are already taking omega-3 as part of a multivitamin, the dose of DHA + EPA should not exceed 250 mg per day.[16] For women with serum total omega-3 levels between 3.7% and 4.3%, no changes are required for their use of supplementation.[16] Alternative thresholds for omega-3 depletion and sufficiency that are linked to other clinical outcomes from omega-3 supplementation in pregnancy are currently unavailable. Further, data analysing the effects of omega-3 supplementation in very early pregnancy are limited.

Measuring omega-3 status in Australia

Current methods to estimate omega-3 status involve screening maternal dietary intake or direct measurement through blood testing. Unfortunately, dietary screening is only modestly related to omega-3 status[18] because it fails to consider maternal age, body mass index, smoking and the effect of genetic polymorphisms on omega-3 status.[22] Blood testing remains the gold standard to determine omega-3 status in early pregnancy;[22] however, this is expensive, and most laboratories do not report total serum omega-3 levels as a percentage, leading to confusion for clinicians providing clinical care. In New South Wales and Queensland, it costs about $200 in out-of-pocket expenses to measure omega-3 levels, as the test is not currently eligible for Medicare benefit.[23,24] Recently, an alternative approach has become available using dried blood spot collection cards (www.omega3index.com.au), which quantifies whole blood omega-3 levels. This method is approved by the Therapeutic Goods Administration and has been validated against traditional gas chromatography methodology with remarkable accuracy (r^2, 0.99).[25] This testing approach is more affordable (~$60) and has a three-day turnaround time for both analysis and reporting. Although preterm birth outcomes are linked to different reference ranges for omega-3 levels in whole blood compared with serum, this test as well as others can convert whole blood levels to equivalent serum levels to mirror reporting standards of SAHMRI to facilitate smooth implementation. For the first time in Australia, there is a more affordable option.

Conclusion

Measurement of omega-3 levels is required before the initiation of omega-3 supplementation to reduce the risk of preterm birth in pregnant women with low omega-3 status and to minimise potential harm in those who are omega-3 replete. Affordable and accessible testing and consistent approaches to reporting are required to implement nationwide programs to reduce preterm births.

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1 Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019; 7: e37-e46.

2 Australian Institute of Health and Welfare. Australia's mothers and babies [website]. Canberra: AIHW, 2023. https://www.aihw.gov.au/reports-data/population-groups/mothers-babies/reports (viewed Aug 2023).

3 Middleton P, Gomersall JC, Gould JF, et al. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev* 2018; (11): CD003402.

4 Serra R, Peñailillo R, Monteiro LJ, et al. Supplementation of omega 3 during pregnancy and the risk of preterm birth: a systematic review and meta-analysis. *Nutrients* 2021; 13: 1704.

5 Simmonds LA, Sullivan TR, Skubisz M, et al. Omega-3 fatty acid supplementation in pregnancy-baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial. *BJOG* 2020; 127: 975-981.

6 National Heart Foundation of Australia. Fish and omega-3: questions and answers for health professionals. National Heart Foundation of Australia, 2015. https://www.heartfoundation.org.au/getmedia/4adbe011-db9a-4777-8a99-db6365e27cb1/Consumer_QA_Fish_Omega3_Cardiovascular_Health.pdf (viewed May 2023).

7 Best KP, Gibson RA, Makrides M. ISSFAL statement number 7 — omega-3 fatty acids during pregnancy to reduce preterm birth. *Prostaglandins Leukot Essent Fatty Acids* 2022; 186: 102495.

8 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: 367-369.

9 Olsen SF, Halldorsson TI, Thorne-Lyman AL, et al. Plasma concentrations of long chain n-3 fatty acids in early and mid-pregnancy and risk of early preterm birth. *EBioMedicine* 2018; 35: 325-333.

10 Olsen SF, Secher NJ. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *BMJ* 2002; 324: 447.

11 Leventakou V, Roumeliotaki T, Martinez D, et al. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. *Am J Clin Nutr* 2014; 99: 506-516.

12 Ciesielski TH, Bartlett J, Williams SM. Omega-3 polyunsaturated fatty acid intake norms and preterm birth rate: a cross-sectional analysis of 184 countries. *BMJ Open* 2019; 9: e027249.

13 Olsen SF, Halldorsson TI, Li M, et al. Examining the effect of fish oil supplementation in Chinese pregnant women on gestation duration and risk of preterm delivery. *J Nutr* 2019; 149: 1942-1951.

14 Carlson SE, Gajewski BJ, Valentine CJ, et al. Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: a randomised, double-blind, adaptive-design superiority trial. *EClinicalMedicine* 2021; 36: 100905.

15 Makrides M, Best K, Yelland L, et al. A randomized trial of prenatal n-3 fatty acid supplementation and preterm delivery. *N Engl J Med* 2019; 381: 1035-1045.

16 South Australian Health and Medical Research Institute. Information for health professionals [website]. Adelaide: SAHMRI, 2023. https://sahmri.org.au/information-for-health-professionals (viewed Aug 2023).

17 Olsen SF, Secher NJ, Tabor A, et al. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. *BJOG* 2000; 107: 382-395.

18 Fu JY, Wang CA, Liu G, et al. Development and internal validation of a non-invasive clinical tool to predict sufficient omega-3 levels in early pregnancy. *BMC Pregnancy Childbirth* 2023; 23: 442.

19 Department of Health and Aged Care. Clinical practice guidelines: pregnancy care. Canberra: Commonwealth of Australia, 2020. https://app.magicapp.org/?language=en#/guideline/jm83RE (viewed May 2023).

20 HANDI Project Team. Omega-3 fatty acid addition in pregnancy to reduce the risk of preterm birth [website]. Melbourne: Royal Australian College of General Practitioners, 2019. https://www.racgp.org.au/clinical-resources/clinical-guidelines/handi/handi-interventions/nutrition/omega-3-fatty-acid-addition-in-pregnancy-to-reduce (viewed May 2023).

21 Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Vitamin and mineral supplementation in pregnancy. Melbourne: RANZCOG, 2019. https://ranzcog.edu.au/wp-content/uploads/2022/05/Vitamin-and-Mineral-Supplementation-and-Pregnancy.pdf (viewed July 2023).

22 de Groot RHM, Meyer BJ. ISSFAL official statement number 6: the importance of measuring blood omega-3 long chain polyunsaturated fatty acid levels in research. *Prostaglandins Leukot Essent Fatty Acids* 2020; 157: 102029.

23 NSW Health Pathology. Essential fatty acid (blood), [updated 20 July 2023; website]. https://catalogue.pathology.health.nsw.gov.au/test/1c9cefb5-9732-4a3e-83cd-75009947f8f4/specimenCollection?searchValue=Omega%203&searchType=startsWith&page=1&pageSize=10&testingLocation=9d780502-b4cd-4dd2-a672-f2e46e340047&testingLaboratory= (viewed July 2023).

24 Mater Pathology. Non-CMBS tests not covered by Medicare. https://www.mater.org.au/Mater/media/page-template/mater-health/pathology/Non-CMBS-Price-List_190919-pdf.pdf (viewed July 2023).

25 Jackson KH, Harris WS. Harmonizing blood DHA levels in pregnancy studies: an interlaboratory investigation. *Prostaglandins Leukot Essent Fatty Acids* 2022; 179: 102417. ■