

Reducing the risk of early preterm birth: Omega-3 status test screening and targeted advice

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On behalf of the Omega-3 Implementation Group



15 million babies are born preterm each year



Preterm birth (<37 weeks)

- 85% of all perinatal complications and death
- leading cause of death in children <5 years

Early preterm birth (< 34 weeks)

- ~20% of preterm births
 - ~75% occur spontaneously
-
- Observational and RCT evidence suggests omega-3 fatty acids extend the period of gestation and may reduce prematurity

Omega-3 marine fats and pregnancy duration

- Omega-3 long chain polyunsaturated fatty acids (LCPUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are most commonly found in fish and fish oils
- Population comparisons in Denmark vs Faroe Islands
 - Increased length of gestation in islanders with high fish intake
- Influence length of gestation by
 - counteracting pro-inflammatory prostaglandins
 - delaying the initiation of labour and cervical ripening
 - relaxing the myometrium

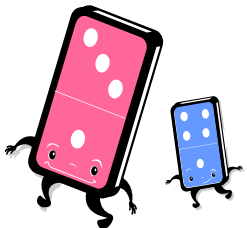
DOMInO Birth Outcomes

(800mg DHA, 100mg EPA)

	Omega-3 (n=1197)	Control (n=1202)
Early preterm birth <34 weeks	1.1%	2.3% p=0.03
Birth <37 weeks	5.6%	7.3% p=0.09
Post-term induction or post-term pre-labour C-section	18%	14% p<0.01

Omega-3 intervention was also associated with:

- Fewer admissions to neonatal intensive care
- Fewer cases of brain injury
- Fewer perinatal deaths



Makrides et al. JAMA 2010;304:1675-83
Zhou et al. AJCN 2012;95:1378-1384



The path to reduce the risk of preterm birth...

- **Synthesising all the available intervention studies in a systematic review and meta-analysis**
- **Conducting a new modern intervention study that aims to retain the benefit while minimising the risk**



The 2018 Cochrane Review

- 70 RCTs with 19,927 pregnant women (+23 on-going trials)
- Mainly from high income countries, but some from low-middle income countries
- Most trials included women with **singleton pregnancies**
- Test dose range 200mg - 2,700mg/d ω -3 LCPUFA
- Mainly as fish oil capsules; also oil, fish, eggs, bars, dairy products
- Mainly throughout second half of pregnancy

Primary Outcomes of Cochrane Review

Variable	Effect size
Birth <34 weeks	RR 0.58 (95% CI 0.44 to 0.77) 42% reduction from 4.6% to 2.7% 11 trials with 5,409 women
Birth <37 weeks	RR 0.89 (95% CI 0.81 to 0.97) 11% reduction from 13.4% to 11.9% 25 trials with 10,256 women
Birth >42 weeks	RR 1.61 (95% CI 1.11 to 2.33) 61% increase from 1.6% to 2.6% 6 trials with 5,141 women

Some Other Important Outcomes of the 2018 Cochrane Review

Variable	Effect size
Gestational length	MD 1.67 days (0.95 to 2.39), 41 trials with 12517 women
Pre-eclampsia	RR 0.84 (0.69 to 1.01), 20 trials with 8306 women
Perinatal death	RR 0.75 (0.54 to 1.03), 10 trials with 7416 women
Birth Weight	MD 76g (38 to 113), 42 trials with 11584 women
Low birth weight <2500g	RR 0.90 (0.82 to 0.99), 15 trials with 8449 women
SGA	RR 1.01 (0.90 to 1.13), 8 trials with 6907 women
LGA	RR 1.15 (0.97 to 1.36), 6 trials with 3722 women

What's Important About The Cochrane Review?

- Includes studies with low-risk, normal risk and high-risk women but almost all women have singleton pregnancies
- Dose: Most studies used >500mg ω -3 LCPUFA/day
- Reporting biases may underestimate or overestimate omega-3 effect on prematurity and other adverse birth outcomes
- But, sensitivity analysis with high quality trials only indicate consistent effect of omega-3 supplementation on prematurity

Omega-3 LCPUFA to Reduce the Incidence of Prematurity



- Blinded RCT in 6 centres
- **5544** women with singleton or multiple pregnancies
- Supplementation from <20 weeks until 34 weeks of gestation to reduce incidence of early preterm birth and prevent the need of obstetric intervention for post-term dates
- **Broad based strategy – few exclusions**
- DBS fatty acid profiles at entry and 34 weeks

PLEASE COMPLETE ALL DETAILS
- write clearly within the boxes

Surname
[S][A][M][P][L][E]

First Name
[P][U][E][A][C][O][A][T]

Date of Birth
[1][1][0][2][1][2]
Day Mth Yr

Collection Date
[1][3][0][2][1][2]
Day Mth Yr

Collection Time
[0][3][0][0]
24hr clock

Study Name
[N][3][R][0]

Research Purposes
[1][2][3][4][5][6]

Study ID number
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SPOT BLOOD/MILK THIS SIDE
ATTENTION: The drops will take some time to soak into the filter paper.



Makrides et al. NEJM 2019;381:1035-45

ORIP Results

- **Primary outcome - There was little difference between the DHA and control group on the incidence of early preterm birth (<34 weeks)**

Primary Outcome	Omega-3 (n=2734)	Control (n=2752)	Adjusted RR (95% CI)	Adjusted P Value
Early Preterm Birth (<34w)	2.25%	1.98%	1.13 (0.79, 1.63)	0.50

- **Secondary birth outcomes**

Outcome	Omega-3 (n=2734)	Control (n=2752)	Adjusted RR (95% CI)	Adjusted P Value
Pre-term Birth (<37w)	7.71%	8.93%	0.86 (0.72, 1.03)	0.11
Post term induction or pre-labour LSCS	5.16%	5.66%	0.91 (0.73, 1.14)	0.42
Gestational Age at birth (mean)	273.18	273.16	-	0.96



Interpretation

- ORIP (largest RCT) contrasted most other studies in the Cochrane review
 - singleton pregnancies and/or
 - focused mainly on women with low intakes
- Further analyses for ORIP singleton pregnancies
 - Does baseline omega-3 status predict the risk of EPTB?
 - Does baseline omega-3 status modify the effect of omega-3 LCPUFA supplementation on EPTB?



OMEGA MUM: Mother-to-be Meghan supports fish oil research. Picture: TRICIA WATKINSON

BRAD CROUCH HEALTH REPORTER

ADELAIDE researchers studying fish oil supplements to prevent preterm births are searching for the "sweet spot" to achieve the best effect for individual women.

Research by the South Australian Health and Medical Research Institute's Women and Kids Theme has proved supplements of omega-3 – found in fish oil – can prevent preterm births.

However, the latest study

published today in the New England Journal of Medicine of a trial involving more than 5500 pregnant Australian women found drawbacks with using a universal "one dose fits all" approach.

Lead researcher Dr Karen Best said the latest results indicate the benefits for preventing preterm birth might be best achieved through a targeted supplementation strategy.

She said the work is now focusing on developing a simple test to check the level of omega-3 in women, so individ-

uals can know if they need a supplement and also how much they need.

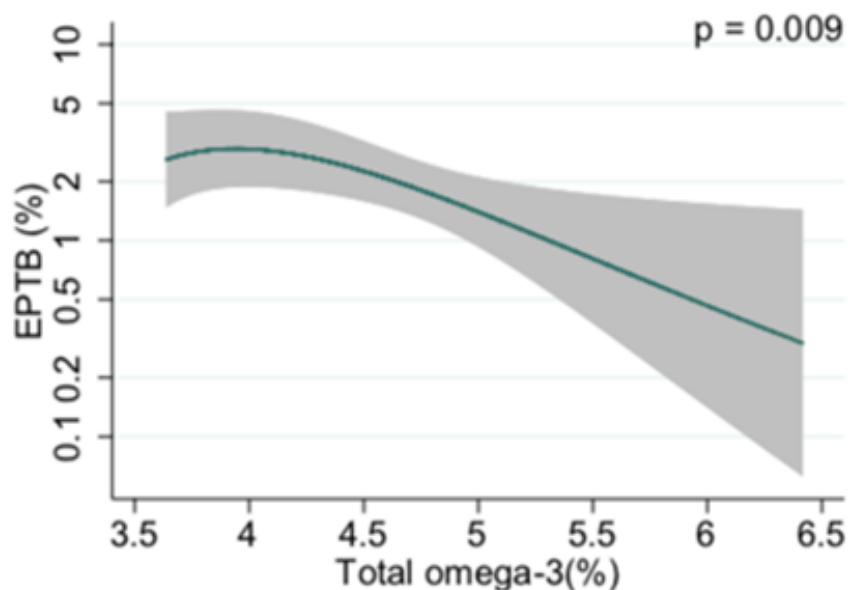
"We are trying to find the sweet spot women need to be at," Dr Best said. "If women are eating fish once or twice a week, or taking a different supplement – that contains omega-3, they may not need a supplement at all."

Adelaide mum-to-be Meghan, 28, is 31 weeks pregnant with her first baby and strongly supports the research.

"The work they are doing is fantastic," she said.

Does baseline omega-3 status predict the risk of early preterm birth?

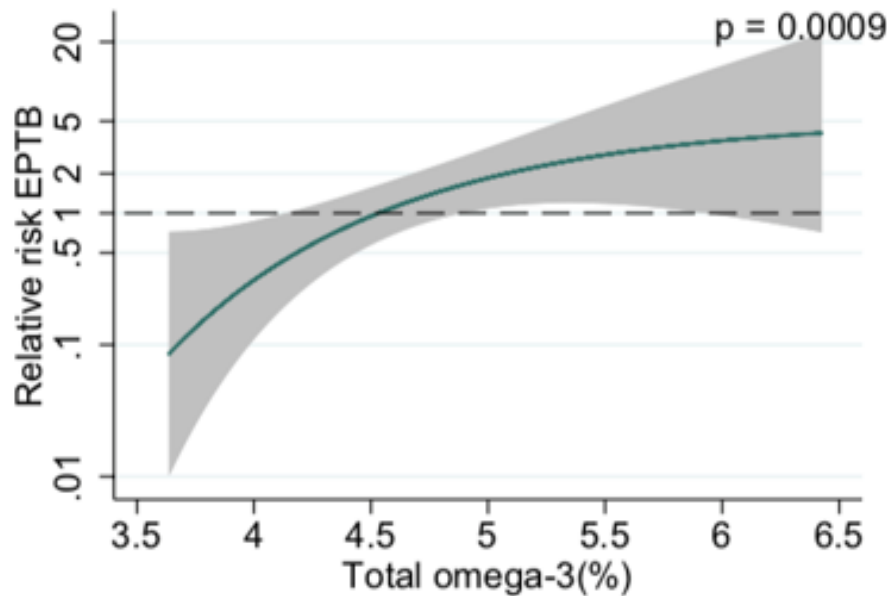
- Risk of EPTB in singleton pregnancies in the **control group** (n=2545) by baseline omega-3 status in DBS



- Low n-3 status in early pregnancy is associated with a higher risk of EPTB

Does baseline omega-3 status modify the effect of supplementation on early preterm birth?

- Relative risk of EPTB (intervention vs. control) in singleton pregnancies by baseline total omega-3 status (**n=5070**)

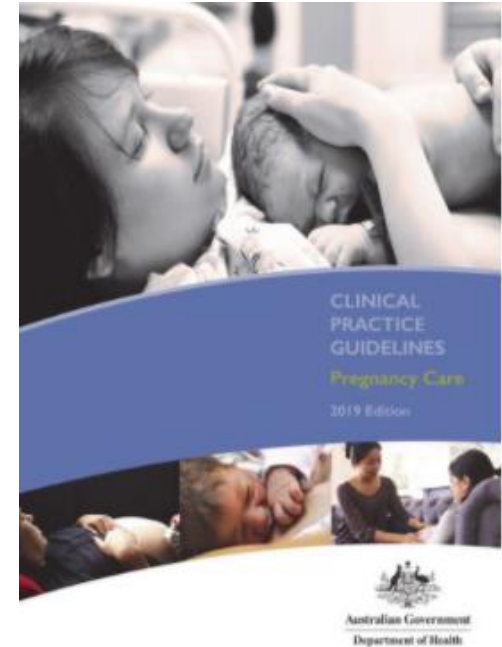


Omega-3 status <4.2% + supplementation **reduced** risk of EPTB (RR 0.23, 0.07 - 0.79)

Omega-3 status >4.9% + supplementation **increased** risk of EPTB (RR 2.27, 1.13 - 4.58)

Summary ... & actions

- Women with **low** omega-3 status are at higher risk of prematurity and supplementing these women reduces their risk of EPTB
- Women with higher omega-3 status do not need extra omega-3 supplementation, and extra supplementation may increase their risk of early preterm birth
- Updated recommendations for omega-3 in pregnancy



“assess omega-3 status and supplement pregnant women with low omega-3”

***New Omega-3 test for all pregnant women
in South Australia - personalised advice
based on omega-3 status***



How to implement into practice?

MATERNAL SERUM SCREENING TEST
Down syndrome, Neural Tube Defects and other Pregnancy Pathologies

SA PATHOLOGY

Patient Details Ethnic Group: Caucasian Aboriginal Asian African-Caribbean

Family Name: _____ Given Name(s): _____

Date of Birth: _____ UR Number: _____ Medicare Number: _____

Address: _____

Suburb: _____ State: _____ Postcode: _____

Clinical Details – Mandatory

First Trimester Screen Second Trimester Neural Tube Defect only **Omega-3 status (SAHMRI)**

EDD/LMP: ____/____/____ Cycle length (days): _____ Maternal weight (Kgs): _____

GA Clinical weeks + days: _____ on ____/____/____

GA Ultrasound weeks + days: _____ on ____/____/____

Crown-rump length (CRL) mm: _____ on ____/____/____

Pregnancy: Singleton Twins Triplets IVF: Yes No Age at egg retrieval/age of egg donor: _____

Pregnancy complications: Diabetes (IDMM only) Yes No Smoker Yes No Previous T21 T18/13

Name of Imaging Practice: _____

For first trimester screening risk assessment an Ultrasound request form is required for Nuchal Translucency, 11-14w0d.

Patient status at the time of the service or when the specimen was collected:

a private patient in a private hospital or approved day hospital facility
 a private patient in a recognised hospital
 a public patient in a recognised hospital
 an outpatient public of a recognised hospital
 an outpatient private of a recognised hospital

Privacy Disclosure SAMSAS requires the personal information contained in this request form for the purpose of Risk assessment and Program Audits. SAMSAS may therefore request copies of ultrasound and cytogenetic reports from your doctor in order to complete its testing and audits.

5-10ml CLOTTED BLOOD SAMPLE Gel or plain tube - no anticoagulant
 First trimester blood sample 9-14w0d Second trimester blood sample 14w1d-20w6d

I have verified FULL NAME, DOB and URN on the sample label and request form verbally with the patient and/or checking the patient's ID band.

Collector's Signature: _____ Specimen Collected: ____/____/____ : Hrs

Requesting Doctor SAMSAS risk assessment calculation not required

Name: _____ Provider No: _____ Address: _____ Tel: _____ Fax: _____ Email: _____ Signature: _____ Request Date: ____/____/____

Copy of report to:
 Name: _____ Address: _____

Deliver to: South Australian Maternal Serum Antenatal Screening (SAMSAS) Program
 SA Pathology, Specimen Reception Area, Level 3, Royal Adelaide Hospital, Port Rd ADELAIDE SA 5000.
 T (08) 8161 7285 F (08) 8161 8085 samsas.program@health.sa.gov.au www.wch.sa.gov.au/samsas.html

Enquiries 8222 3000 www.sapathology.sa.gov.au

- Collaboration with SA Pathology
- SA Maternal Serum Antenatal Screening Program covers 80-85% of women in SA with testing before 16 weeks
- No additional blood test and no cost to women or health service
- Omega-3 testing not currently offered by SA Pathology, so testing will be done at SAHMRI



Omega-3 Status Test Results

- Stand alone reports (with omega-3 recommendation) sent to requesting doctor
- Results also available on OACIS

- SA Pathology Report -|

Omega-3 Status is % total fatty acids
xx weeks of gestation

Omega-3 Status ¹	Recommendation
Omega-3 Status <3.7%	Take omega-3 fatty acid supplements until 37 weeks to reduce the risk of early preterm birth. Suggested dose: 800 mg DHA and 100 mg EPA per day. Typical suitable supplements include <u>Infantem</u> (algal oil supplement from <u>Pharmamark</u>) and Omega Brain (fish oil supplement from Blackmores)
Omega-3 Status 3.7 to 4.3%	No action required. If already taking omega-3 fatty acids as part of a multivitamin and mineral supplement, this may continue.
Omega-3 Status >4.3%	Stop any omega-3 fatty acid supplements. Risk of early preterm birth is low and additional omega-3 supplementation may increase this risk.

¹ Percentage of omega-3 fatty acid in serum

Omega-3 status is being measured as part of a research evaluation to determine its utility in identifying women with low omega-3 status and advising supplementation to reduce their risk of early preterm birth.

Evaluation of omega-3 screening program

It is important to assess how many women have low omega-3 levels and how many babies were born early to see if screening has reduced the number of premature births in South Australia. We will electronically link the omega-3 test results with birth data in a secure way, without identifying you or your baby in any way. You may decline to have your data linked without affecting you or your baby's care.

Opting out: If you do not want your data included in the statewide evaluation of the screening program, please telephone (08) 8128 4444 or email omega3@sahmri.com.

The evaluation has been approved by the Women's and Children's Health Network (WCHN) Human Research Ethics Committee (HREC/20/WCHN/138). Should you wish to discuss the study with someone not directly involved, you may contact the executive secretary of the Human Research Ethics Committee, Mr Luke Fraser, WCHN (08) 8161 6521.

Further Information

- sahmri.org/omega3
- Speak to your doctor or midwife



If you would like further information about the evaluation of the omega-3 screening program, please contact

omega3@sahmri.com

(08) 8128 4444

Omega-3 screening to help prevent premature births

? Information for families



SA Pathology and the South Australian Health and Medical Research Institute (SAHMRI) are evaluating the effectiveness of omega-3 screening for pregnant women from 2021 to reduce the number of babies born prematurely.

Why Omega-3 Screening?

Omega-3 fats are nutrients commonly found in fish and algae. The right amount of omega-3 in your body during pregnancy can help you have a full-term pregnancy. Babies born too soon (premature), particularly those born before 34 weeks of pregnancy, may have lengthy stays in hospital and may experience long-term health problems and delays in development.

Women expecting one baby who have low omega-3 levels in their blood are at higher risk of having their baby born prematurely. They are most likely to benefit from omega-3 supplements. Women who have sufficient omega-3 levels are already at lower risk of having a premature baby and so should not take additional omega-3 supplements.

Screening for omega-3 levels before 20 weeks of pregnancy will identify women who require omega-3 supplements and those who will not.

We do not yet have a screening test for women expecting twins or triplets.

Blood collection

Your health professional will give you the SA Maternal Serum Antenatal Screening (SAMSAS) request form to take to a blood collection centre. Your omega-3 level will be measured using the blood collected for the SAMSAS program. The test is provided free to families.



Omega-3 Results

Your health professional will discuss your omega-3 test results with you.

Omega-3 test result	Health professional advice
Less than 3.7%	<p>If you have a low omega-3 level (less than 3.7%), your health professional will recommend you take omega-3 supplements (fish oil or algal oil) to reduce your risk of a premature birth:</p> <ul style="list-style-type: none"> You can take supplements after receiving omega-3 results up until 37 weeks of pregnancy. The suggested dose is 800 mg of DHA and 100 mg of EPA every day. Omega-3 supplements you can take include: Infantem* (Pharmamark) and Omega Brain (Blackmores). <p>PLEASE NOTE: If you are already on prescription medication to stop your blood clotting (like heparin), speak with your doctor before taking omega-3 supplements.</p>
Between 3.7 and 4.3%	<p>If you have a moderate omega-3 level:</p> <ul style="list-style-type: none"> You do not need to do anything different from what you usually do. If you are already taking omega-3 fatty acids as part of a multivitamin and mineral supplement or an omega-3 supplement, you can continue to do so.
Above 4.3%	<p>If you have a sufficient omega-3 level:</p> <ul style="list-style-type: none"> Your risk of a premature birth is low and additional omega-3 supplements may increase this risk. Your health professional will advise that you stop taking any omega-3 supplements.

*Algal oil supplement of DHA and EPA.

Omega-3 blood sample and cost

No additional blood sample is required as omega-3 analysis will be performed on serum collected as a part of the established SAMSAS program. The omega-3 fatty acid analyses will be performed at no cost to the patient or health service.

How to order the Omega-3 status test

- 1 Discuss the omega-3 status test and refer woman to the *Information for Families* sheet.
- 2 Order using the updated SAMSAS request form.
- 3 Tick the omega-3 status test on the SAMSAS request form.
- 4 Refer woman to the Privacy Disclosure on the SAMSAS request form.
- 5 The omega-3 status test results will be reported to the requesting provider as a standalone report and will be available on OACIS.

Further Information

For further information regarding omega-3 status testing or results interpretation:

📍 Visit sahmri.org/omega3

☎ Call the omega-3 status test hotline
0438 273 155

Evaluation of Omega-3 status testing program

This SA Pathology SAHMRI collaboration will assess the feasibility and reach of identifying women with low omega-3 status, providing appropriate advice and ultimately assessing success in reducing the rates of early preterm birth. This will be done by deidentified linkage of the omega-3 status test results with relevant pregnancy outcome data. Women who do not want their data linked will need to contact (08) 8128 4444 or email omega3@sahmri.com.

The evaluation has been approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/138). Should you wish to discuss the study with someone not directly involved, you may contact the executive secretary of the Human Research Ethics Committee, Mr Luke Fraser, WCHN (08) 8161 6521.

For request forms:

☎ Call the SAMSAS Program
(08) 8161 7285



Omega-3 status test for prematurity risk

SA Maternal Serum Antenatal Screening (SAMSAS) Program

🔍 Information for health professionals



SA Pathology, through the SA Maternal Serum Antenatal Screening (SAMSAS) program, and the South Australian Health and Medical Research Institute (SAHMRI) are evaluating serum omega-3 testing for women with singleton pregnancies in South Australia from 2021.

Why do omega-3 status testing?

Women with a singleton pregnancy and low omega-3 status (concentration) in their blood are at higher risk of early preterm birth and most likely to benefit from omega-3 supplementation. Screening before 20 weeks' gestation will identify women who require omega-3 supplementation.

The latest National Health and Medical Research Council and Department of Health National Pregnancy Care guidelines recommend assessing omega-3 fatty acid status and supplementing pregnant women with low omega-3 intakes.

There is high quality evidence for omega-3 status testing

- A Cochrane systematic review of 70 randomised controlled trials of almost 20,000 women with mainly singleton pregnancies indicated that omega-3 supplementation from early-mid pregnancy until

birth reduces the risk of early preterm birth by 42% (from 46 per 1000 to 27 per 1000 births) and preterm birth by 11% (from 134 per 1000 to 119 per 1000 births)¹.

- As the Cochrane review included many studies that were conducted before prenatal supplements with low dose omega-3 were commonly taken by women, a large randomised trial, with 5540 women, was undertaken to test if a universal supplementation strategy would be successful with contemporary practice. Overall this trial showed that supplementation of all women would not be effective², but secondary analyses revealed that reductions in early preterm birth are best achieved by a targeted approach to omega-3 supplementation based on omega-3 status before 20 weeks³. Women with low omega-3 status are at higher risk of early birth and more likely to benefit from supplementation^{2,3}.

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:CD003402.

² Makrides M, Best K, Yelland L, McPhee A, Zhou SJ, Quinlivan J, et al. A randomized trial of prenatal omega-3 fatty acid supplementation and preterm delivery (ORIP trial). *New England Journal of Medicine.* 2019;381:1035-45. <https://doi.org/10.1056/nejmoa1816832>

³ Simmonds LA, Sullivan TR, Skubisz M, Middleton PF, Best KP, Yelland LN, et al. Omega-3 fatty acid supplementation in pregnancy – baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial (ORIP). *BJOG.* 2020;27(8):975-981. <https://doi.org/10.1111/1471-0528.16168>

⁴ Percentage of total omega-3 fatty acid status in serum

Omega-3 status test results: how to advise women

Omega-3 test result ^{3,4}	Recommendation
Less than 3.7%	<p>For a low status, take omega-3 fatty acid supplements after receiving the omega-3 results until 37 weeks to reduce the risk of early preterm birth.</p> <p>Suggested dose: 800 mg DHA and 100 mg EPA per day</p> <p>Typical suitable supplements include Infantem* (Pharmamark) and Omega Brain (Blackmores)</p>
Between 3.7 and 4.3%	<p>For a moderate omega-3 status, no action required.</p> <p>If already taking omega-3 fatty acids as part of a multivitamin and mineral supplement or a standalone supplement, this may continue.</p>
Above 4.3%	<p>For a sufficient status, stop any omega-3 fatty acid supplements.</p> <p>Risk of early preterm birth is low and additional omega-3 supplementation may increase this risk.</p>

*Algal oil supplement of DHA and EPA.

Contraindications to omega-3 fatty acid supplements

- Omega-3 fatty acid supplements should be avoided for women requiring heparin because of possible additive anti-coagulant effects.
- Low dose aspirin can be taken with omega-3 fatty acid supplements. Recent randomised trials of omega-3 fatty acid interventions have included women on low dose aspirin without increase in adverse events.

What next?

- Go live date 19th April 2021
- Updated SAMSAS forms on SA Pathology website and hard copy
- Resources for more information
 - SAHMRI website
 - Health professional hotline/email
 - Consumer email
 - Newsletters
 - In-services as required
- Ongoing Evaluation
 - deidentified linkage of the omega-3 status test results with pregnancy outcome to see if specific advice can reduce the rate of EPTBs in SA.
 - Partnership with APBPA to consider extension nationally and internationally

Omega-3 status test for prematurity risk

Further Information

- Visit sahmri.org/omega3
- Call the omega-3 hotline 0438 273 155
- For order forms call the SAMSAS Program (08) 816 7285