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## Reducing early preterm birth for 25 cents a day

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## **Reducing early preterm birth for 25c a day**

### **Invited Editorial**

Preterm birth (before 37 weeks of gestation) is the most common direct cause of death and disability in children (1). Early preterm birth (EPTB) (less than 34 weeks) is the main cause of neonatal death and severe disability (2). Most women who experience early preterm birth are low risk (1). In those women who have already experienced one early preterm birth, we can involve tertiary hospital clinics and implement strategies such as cervical screening and either vaginal progesterone therapy or cervical suturing (3). However, these measures require levels of clinical expertise that are not available at a global level. Even within Australia, some rural women do not have access to trained ultrasonographers who can perform reliable transvaginal scanning necessary to detect cervical shortening. In many countries in the world, any sort of ultrasound scan in pregnancy is not feasible, let alone access to secondary interventions following on from discovery of a short cervix such as progesterone therapy or cervical suturing. Tertiary hospital clinics are simply a dream.

The severe consequences of early preterm birth and high cost and need for clinical expertise in existing strategies of prevention, has led to calls for a public health approach to reduce the rate of early preterm birth (3). Implementation of omega 3 long chain polyunsaturated fatty acids (omega-3 LCPUFA) supplements in pregnancy is now a feasible and cost effective public health strategy (4,5,6).

The omega 3 LCPUFA story is remarkable and involves multidisciplinary researchers from around the world. The discovery is a gold standard in progressing from benchtop to bedside in medical research. The journey started with basic

science studies evaluating the mechanisms of initiation of labour, progressed through observational and epidemiological studies of populations, advanced into randomised trials testing a specific hypothesis and culminated in a Cochrane Review.

Understanding the omega-3 LCPUFA story begins with knowledge of factors leading to the initiation of cervical ripening and labour (3, 7-11). Omega-3 LCPUFA enter the materno-feto-placental unit from the maternal circulation. Tissue concentrations are heavily influenced by diet (3,7,9). Increases in omega-3 LCPUFA levels in cervical tissues directly counter local production of pro-inflammatory 2-series prostaglandins such as PGE<sub>2</sub> and PGF<sub>2α</sub> within those same tissues, resulting in a delicate balance in hormonal drivers that inhibit cervical ripening and those that augment these processes. The balance plays a critical role in the duration of gestation (9). Omega-3 LCPUFA are a direct dietary antagonist of the production of 2-series prostaglandins in the cervix. Arachidonic acid directly competes with omega-3 LCPUFA for incorporation into cells. Diets that are high in omega-3 LCPUFA result in preferential incorporation of the 3-series prostaglandins into cellular phospholipids and the displacement of arachidonic acid and this results in lower outputs of 2-series prostaglandins (3,10). If endogenous levels of 2-series prostaglandins within the cervix are too high, or local availability of omega-3 LCPUFA to act as an antagonist are too low, the cervix may prematurely ripen, basal uterine contractions increase in strength, and the outcome may be preterm birth (7,8,9,10,11).

A population strategy to reduce preterm birth would therefore need to target either:

a) reducing endogenous levels of pro-inflammatory series 2 prostaglandins such as PGE<sub>2</sub> and PGF<sub>2α</sub> in the cervix and the underlying disease processes that lead to these; or

b) increase materno-feto-placental levels of omega-3 LCPUFA through diet or supplementation.

Research into the human microbiome and specifically the role of the materno-feto-placental microbiome on altering endogenous concentrations of pro-inflammatory 2-series prostaglandins as measured using new molecular technologies is an emerging field of research for the former intervention (12,13). However the development of drugs and obstetric management based upon microbiome and pro-inflammatory markers is still at least a decade from fruition. In contrast, increasing materno-feto-placental tissue levels of omega-3 LCPUFA could be easily implemented through dietary modification or supplementation.

The next step in the scientific journey was to investigate whether dietary deficiency of omega-3 LCPUFA was a clinical concern and whether there was any association between diet and preterm birth. This heralded the need for observational and epidemiological studies. Observational studies consistently documented that many pregnant women did indeed have a diet low in omega-3 LCPUFA (10,14,15,16). In Australia, there was evidence that diets were poor and most pregnant women did not consume sufficient omega-3 LCPUFA. Despite a long standing global recommendation for an intake of 300 mg/d of omega-3 LCPUFA per day in pregnancy, most Australian and American women consumed less than a third of the recommended daily intake (17).

Epidemiological studies also found a consistent association between populations with poor dietary intake of omega-3LCPUFA and preterm birth (14,15,16). One interesting early epidemiological study evaluated the rates of preterm birth in the Faro Island and Denmark. These closely linked geographical and genetic populations differed only in dietary fish intake and rates of preterm birth and provided an excellent case study to support the hypothesis (15).

The observational and epidemiological studies were an important step in developing the hypothesis to be tested in randomised trials that a dietary supplement might reduce preterm birth. They also helped identify the type of supplement that would work best. The largest early study was the Australian DOMInO Trial (Docosahexaenoic acid (DHA) to Optimise Mother Infant Outcomes)(4). In a pre-planned analysis, it was reported that omega-3 LCPUFA supplementation halved the rate of early preterm birth (RR 0.49; 95% CI 0.25-0.94) and the need for admission to a neonatal intensive care unit (RR 0.57, 95% CI 0.34-0.97, p=0.04)(4).

A second key outcome of the DOMInO study was the safety evaluation. There was no increase risk of hospitalisation, caesarean section, pre-eclampsia or other serious morbidity. Of note side effects that might be attributable to omega-3 LCPUFA such as maternal nose bleeds, vaginal blood loss, constipation, nausea or vomiting were also not elevated in supplemented women (4). However, there was an increased risk of post dates pregnancy and therefore the ORIP study was designed to address whether ceasing supplementation at term might be beneficial (17).

Following publication of DOMInO, there was a call for more randomised trials to establish the generalisability of findings. These trials have now been performed and an updated Cochrane review involving 19,787 women reported a 42% reduction

in early preterm birth and 11% reduction in preterm birth with the implementation of prenatal supplementation with omega-3 LCPUDFA (6). The Cochrane team advise that no new trials to evaluate the benefits in singleton pregnancy should be performed (6). They outlined that further research into the impact in multiple pregnancy and on supplement timing remain outstanding questions.

Omega-3 LCPUFA are not a drug. They are not covered by a patent. They can be manufactured easily in accredited health food supplement factories. Mass production brings the retail cost of tablets to 20 cents a day. The Cochrane review concluded the minimum effective dose is 500mg of DHA each day from week 12 of pregnancy (6). A widespread public health message should now try and implement this advice.

It is important the message provided to pregnant women is clear. They need to buy the right omega-3 LCPUFA in the right dose and take it from 12 weeks of pregnancy. We need to recommend brands with validated manufacturing controls to avoid unscrupulous traders. One way to help ensure pregnant women do take the correct dose, type and purity of supplement may be to consider implementation of a PBS subsidized prescription for a 24 week supply of 500mg of DHA taken once daily. This would help ensure our most vulnerable pregnant women can access the right intervention. An alternative would be to create a mechanism by which health care professionals and pregnant women could ensure a supplement met obstetric requirements and was manufactured in an accredited facility.

Obstetric care providers have been very supportive of previous public health nutritional supplementation strategies such as use of folic acid to prevent neural tube

defects. The cost benefit ratio of omega-3 LCPUFA supplementation is even greater, and widespread adoption into clinical practice should now occur.

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