Docosahexaenoic Acid and Preterm Birth

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Key Messages

- Preterm birth is one of the leading causes of infant deaths worldwide. There is a growing need to identify safe, effective, easily available primary prevention strategies to prevent preterm delivery, especially ‘early preterm birth’ before 34 weeks of gestation.
- Epidemiological and randomised controlled trial evidence exists to support an effect of increased omega-3 long-chain polyunsaturated fatty acid intake during pregnancy on length of gestation.

Key Words

Preterm birth · Omega-3 · Pregnancy · Nutritional supplements · Fatty acids · Primary prevention

Abstract

Preterm birth accounts for more than 85% of all perinatal complications and deaths. There are many short- and long-term consequences of being born too soon. These infants often require intensive care and are at increased risk of early morbidities often with life-long sequelae. Approximately 50% of all preterm births have unknown or unclear causes, and there are no effective primary prevention strategies in widespread clinical use. Epidemiological studies have observed an increased length of gestation in populations with high fish consumption. These findings have led to randomised controlled trials of omega-3 (n-3) long-chain polyunsaturated fatty acid (LCPUFA) supplementation which show that these dietary agents may delay the timing of birth and may have value as a prophylactic intervention in some women. This review presents the available evidence and discusses the relationship between prenatal n-3 LCPUFA supplementation during pregnancy and the incidence of preterm birth.

Introduction

Preterm birth (before 37 completed weeks of gestation) complications are now the leading cause of under-five deaths globally, accounting for 17% of all such deaths [1] and more than 85% of all perinatal complications [2]. It is estimated that 11% of births (15 million babies each year worldwide) are premature (table 1), with half of these due to unknown or unclear causes [3–5]. Advances in perinatal and neonatal care have resulted in greatly improved survival rates for preterm babies; however, there is an increasing awareness that, even in high-income countries, many of these children suffer short- and long-term consequences of being born too soon [6]. These infants often require intensive care and are at increased risk of early morbidities such as respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, blindness and cerebral palsy. In early childhood, developmental difficulties may emerge in preterm children and later manifest as low educational achievement, high unemployment and other deficits in social
and emotional wellbeing, as well as having wider societal and economic impacts [7, 8].

One quarter of preterm births are due to medical intervention following pregnancy-related complications including pre-eclampsia, intra-uterine growth restriction or maternal disease [9]. The remainder of preterm births occur spontaneously and are due to multifactorial processes causing the uterus to change from quiescence to active contractions and birth. The precise cause of spontaneous preterm labour is of unknown aetiology in up to half of all cases [10]. Whilst tocolytic drugs to inhibit uterine contractions are available in an emergency situation to stop or delay premature labour, there are currently no effective primary prevention strategies for preterm birth in widespread clinical use. More than 10 Cochrane systematic reviews have investigated treatments ranging from dietary supplements to therapeutic drugs such as betaimetics, magnesium sulphate and calcium channel blockers. Despite the wide range of treatments investigated in the reviews, none have been shown to be effective in reducing the risk of spontaneous preterm birth.

### n-3 LCPUFA and Preterm Birth

In recent decades, omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA), specifically docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3), have emerged as efficacious dietary agents that moderate a number of clinical conditions through their known anti-inflammatory activity. This action may also apply to pregnancy and the inflammatory cascade of labour where the maternal immune response to the fetus is crucial. The feto-placental unit is supplied with n-3 and omega-6 (n-6) LCPUFA from the maternal circulation, which is influenced by maternal dietary intake and endogenous synthesis. The prostaglandins derived from n-6 arachidonic acid (AA, 20:4n-6) within the utero-placental unit in normal pregnancy are countered by local production of prostaglandins derived from n-3 LCPUFA within the same tissues. The balance between the metabolites of n-3 and n-6 fatty acids plays an important role in the maintenance of normal gestation length and is a critical element in cervical ripening and the initiation of labour [11]. If local production of n-6-derived prostaglandins within the feto-placental unit is too high, or local accumulation of n-3 LCPUFA is too low, the cervix may prematurely ripen and uterine contractions increase, which may in turn lead to preterm birth, particularly in susceptible women [12].

### Maternal DHA Intake

Modern Western diets are low in n-3 LCPUFA and high in n-6 fatty acids, leading to a predominance of AA in tissues. The prenatal period is a time of increased risk for n-3 LCPUFA deficiency as DHA is preferentially transferred from maternal tissue stores to the developing fetus [13]. The World Health Organization recommends an intake of 300 mg/day of n-3 LCPUFA for pregnant women [14]; however, women in many low-, middle- and high-income countries do not achieve this amount, with the exception of coastal countries where fish and other

<table>
<thead>
<tr>
<th>Region</th>
<th>Livebirths, n</th>
<th>Estimated mean preterm birth rate, %</th>
<th>Preterm births, n</th>
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<tbody>
<tr>
<td>Developed regions</td>
<td>14,300,000</td>
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<td>Eastern Asia</td>
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<td>Northern Africa</td>
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<td>259,200</td>
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<td>Oceania</td>
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<td>South-Eastern Asia</td>
<td>38,700,000</td>
<td>13.3</td>
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<td>Sub-Saharan Africa</td>
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<td>12.3</td>
<td>3,936,800</td>
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<td>Caribbean</td>
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<tr>
<td>Caucasus and Central Asia</td>
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<td>9.2</td>
<td>151,300</td>
</tr>
<tr>
<td>Total worldwide</td>
<td>135,000,000</td>
<td>11.1</td>
<td>14,936,700</td>
</tr>
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</table>

Source: Blencowe et al. [32].
Fish oil and largely targeted women with higher-risk pregnancies. A 2006 Cochrane review of marine oil supplementation during pregnancy included data from 6 trials and measured a variety of maternal and neonatal health outcomes including preterm birth [22]. Two of these trials (n = 860 women in total) measured preterm birth outcomes of women with high-risk pregnancies. A meta-analysis showed that the fish oil intervention resulted in an approximate 2-day increase in the mean duration of gestation, a nonsignificant 8% reduction in preterm birth <37 weeks’ gestation and a significant 31% reduction in early preterm birth <34 weeks’ gestation. More recent trials of prenatal n-3 supplementation have included women with normal-risk pregnancy and have intervened with DHA because of the association with early childhood developmental outcomes [23–25]. The strongest evidence to support the efficacy of DHA supplementation to reduce preterm birth comes from the DOMInO trial, the largest trial to date of n-3 LCPUFA supplementation in pregnancy (n = 2,399) [23]. This trial was designed to assess the effect of n-3 LCPUFA supplementation (predominantly as DHA) during the last half of pregnancy on the prevalence of postnatal depression in women and on early childhood neuro-developmental outcomes. A preplanned secondary analysis showed a reduction in early preterm birth (<34 weeks) in the DHA-supplemented group compared with the control group, corresponding to a 50% reduction in the incidence of early preterm birth (1.09 vs. 2.25%, adjusted RR 0.49, 95% CI 0.25–0.94, p = 0.03). These findings concur with results of the 2006 Cochrane review, and when combined in an updated meta-analysis including two other trial recent trials (n = 3670) [24, 26], the numbers of included women increase 2.5- to 3-fold and the effect sizes remain remarkably similar and are increasingly compelling (table 2).

Collectively, data from the Cochrane systematic review [22] combined with more recent reviews [27–29] imply that the effects of n-3 LCPUFA are not attributable only to prostaglandins arising from EPA, as newer trials have used DHA-based supplementation. Clearly the mechanisms underlying the effects of n-3 LCPUFA on the duration of gestation are complex, and this is perhaps not surprising when one considers that multiple mechanisms often underpin important biological pro-
cesses, and it is likely that birth is no exception. Doses of n-3 LCPUFA supplementation used in RCTs during pregnancy range from 133 to 3,000 mg/day, and the intervention period has commenced between 16 and 30 weeks’ gestation until delivery or beyond. Overall, systematic reviews show that supplementation with marine oil or n-3 LCPUFA is safe in pregnancy and is generally well tolerated. Rates of serious adverse events were similar between treatment groups and occurrence of side effects (e.g. vomiting, nausea and diarrhoea) was generally similar except for belching and bad taste, which occurred more frequently in the marine oil-supplemented groups. No differences have been shown in the incidence of antepartum hospitalisation, caesarean section, eclampsia or other serious maternal morbidity between treatment and control groups [22, 27, 28]. However, a number of trials did report a significant increase in the incidence of post-term inductions or post-term pre-labour caesarean section in women supplemented with n-3 LCPUFA until delivery compared with control. This is a concern because post-term birth is also associated with increased perinatal mortality and morbidity in both infants and mothers [30]. Animal studies demonstrate that as the duration, dose and timing of n-3 LCPUFA supplement administration are altered, the levels accumulated within the feto-placental unit change in a timed dose-response relationship [11]. It has been shown that within 6 weeks, people who stop taking fish oil supplements have their plasma and red cell n-3 LCPUFA return to levels which are similar to those of the general population of low fish consumers [31]. Current trials are investigating the optimal timing of n-3 LCPUFA supplementation targeting the critical period before 34 weeks when preterm delivery has the poorest outcomes and easing treatment to reduce the risk of post-term intervention (Australian New Zealand Clinical Trials Registry number 12613001142729).

**Conclusion**

Preventing preterm birth remains one of the most challenging issues in obstetric and neonatal care. Whilst a level of concordance is evident between epidemiological studies and RCTs, inconsistencies remain. This is perhaps not surprising when one considers that maternal n-3 LCPUFA exposure in observational studies is most likely based on a lifetime of exposure compared to a defined period of n-3 LCPUFA supplementation in RCTs. The evidence to date consistently demonstrates that n-3 LCPUFA supplementation during pregnancy increases the mean duration of gestation by 2 days and produces a 40–50% reduction in early preterm birth (<34 weeks’ gestation) [22, 23]. Future directions for research in this area include refinement of dosing and timing of n-3 LCPUFA supplementation. It is important to identify and evaluate (by RCT) other agents and sustainable food-based dietary interventions that are thought to influence similar pathways. In addition, further studies to understand the mechanisms surrounding individual response to n-3 LCPUFA supplementation and the relationship to immune profile/inflammatory indicators, as well as social and clinical characteristics will be vital in optimising future treatment recommendations.

**Disclosure Statement**

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References


