
SPECIAL ARTICLE

Docosahexaenoic Acid and Preterm Birth

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ABSTRACT

Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid. DHA can be synthesized from α -linolenic acid or directly derived from maternal milk (breast milk), cold-water fatty fish such as salmon, fish oil, or algae oil. DHA has mechanisms that may help reduce the risk of premature birth, smaller for gestational age infants, and preeclampsia. Pregnant women should receive at least 200 mg of DHA per day. Several studies have found that low plasma DHA levels during pregnancy increase the risk of premature birth, and DHA supplementation during pregnancy (1,000 mg per day) has been shown to be effective in preventing premature birth and early preterm delivery in cases of low DHA levels.

Keywords: docosahexaenoic acid, DHA, fatty acid, preterm birth, pregnancy

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What is docosahexaenoic acid?

Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid (PUFA)^(1, 2). It is essential for the growth and functional development of the brain in infants. DHA is also required for the maintenance of normal brain function in adults⁽³⁾. It is also essential during pregnancy to support fetal growth and maternal health⁽³⁾.

Omega-3 fatty acids have a carbon-carbon double bond located three carbons from the methyl end of the chain. Omega-3 fatty acids, sometimes called n-3s, are present in certain foods such as flaxseed and fish, as well as in dietary supplements

such as fish oil. Omega-3 fatty acids are composed of three fatty acids: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and DHA. ALA contains 18 carbon atoms, while EPA and DHA are considered long-chain omega-3 fatty acids because EPA contains 20 carbons and DHA contains 22^(1, 2, 4).

Source of DHA

DHA can be synthesized from α -linolenic acid or directly derived from maternal milk (breast milk), cold-water fatty fish such as salmon, fish oil, or algae oil^(5, 6). The consumption of DHA (e.g., from fatty fish such as salmon, herring, mackerel and sardines)

contributes to numerous physiological benefits⁽²⁾. Foods that have omega-3 EPA/DHA > 1,000 mg/100g include herring, salmon, anchovy, mackerel, and gilthead sea bream⁽⁷⁾. Some Thai fish have high omega-3 (> 1000 mg / 100 mg): striped catfish (pla sawai, Thai mackerel (pla tu), striped snakehead fish (pla chon)⁽⁸⁾.

Mechanism of DHA

DHA has several mechanisms: 1. DHA regulates connexin 43 expression and reduces PGE2 and PGF2 α levels. 2. DHA can reduce inflammation by regulating the interaction between ligands and receptors on the cell surface. 3. DHA has a proangiogenic effect, stimulating the production of proangiogenic factors and improving the development of capillary buds. Then improve deep placental dysfunction⁽³⁾. These mechanisms may reduce the occurrence of preterm birth, small for gestational age infants and preeclampsia.

DHA and preterm birth

A Danish case-control study in 2018 evaluated the percentage of plasma DHA + EPA in total fatty acids at 9 and 25 weeks of pregnancy in 376 pregnant women with early preterm birth (< 34 weeks) and 348 pregnant women with term pregnancy. Women with concentrations < 1.6% had a 10.27-fold increased risk of early preterm birth when compared with women with DHA + EPA concentrations $\geq$ 1.8%. This result suggests that low plasma DHA and EPA concentrations during pregnancy may be a strong risk factor for early preterm birth⁽⁹⁾. A cross-sectional study from Indonesia in 2021 also found that the plasma DHA levels of preterm pregnant women at birth were significantly lower than those of full-term pregnant women⁽¹⁰⁾.

Regarding the three mechanisms of DHA, it is speculated that DHA supplementation during pregnancy is a potential way to prevent preterm birth. In 2018, the Cochrane study included 70 RCTs to analyze the association between omega-3 PUFA supplementation during pregnancy and pregnancy

outcomes. The results found that pregnant women with omega-3 PUFA supplementation during pregnancy reduced the incidences of preterm birth and early preterm birth compared to those without DHA supplementation⁽¹¹⁾. The Subgroup analysis of this Cochrane study also found dose of 500-1,000 mg/day of DHA/EPA and when starting DHA / EPA $\leq$ 20 weeks of gestational age significantly reduced the incidences of preterm birth and early preterm birth⁽¹¹⁾. A randomised, multicentre, double-blind, adaptive-design, superiority trial was conducted in three medical centres in the United States: "assessment of DHA on reducing early preterm birth" (ADORE) trial. The study found that a higher dose (1,000 mg) of DHA had a lower rate of early preterm birth. [1.7% vs 2.4%, $pp = 0.81$] especially if participants had low DHA status (< 6%) at enrolment⁽¹²⁾. An exploratory analysis of a randomised controlled trial from six Australian hospitals: "omega-3 to reduce the incidence of prematurity" (ORIP) trial found that women with singleton pregnancies and low total omega-3 PUFA status early in pregnancy have an increased risk of early preterm birth and are most likely to benefit from omega-3 supplementation to reduce this risk. While women with higher total omega-3 status are at lower risk and additional omega-3 supplementation may increase their risk⁽¹³⁾. Recently, Yakah et al performed a secondary analysis, obtained data from the large, prospective Nulliparous Mother-to-be (nuMoM2b) cohort study of 9,461 nulliparous individuals from eight clinical sites across the United States. They compared adverse birth outcomes between those taking additional omega-3 supplements beyond standard prenatal vitamin intake (PNV-OM) versus prenatal vitamins alone (PNV). PNV-OM intake was associated with significantly lower rates of preterm birth (5.04% vs 8.41%, $p < 0.001$) and SGA (2.84 vs 4.48%, $p = 0.004$). After adjustment for demographic and clinical differences, PNV-OM use remained associated with reduced odds of preterm birth (aOR, adjusted odds ratio 0.64, 95% CI 0.47, 0.86, $p = 0.004$) and SGA (aOR 0.64, 95% CI 0.42, 0.95, $p = 0.03$)⁽¹⁴⁾. Carvajal, et al performed a randomized, double-blind,

placebo-controlled trial (DEEPER trial) to evaluate whether early DHA supplementation modifies clinical phenotypes associated with impaired placentation. They found that daily DHA supplementation (600 mg) from early pregnancy was safe and well tolerated but did not demonstrate a statistically significant effect on clinical phenotypes of impaired placentation⁽¹⁵⁾.

From these articles in the literature, it may imply that low plasma DHA levels during pregnancy increase the risk of preterm birth, and DHA

supplementation during pregnancy (1,000 mg/day) has a preventive effect on preterm birth and early preterm birth in the case of low DHA levels.

Recommendation of DHA intake in pregnant women

Many world organizations recommend the intake of DHA during pregnancy. The summary of each organization's recommendation is shown in Table 1.

Table 1. Recommendation on the intake of DHA in pregnant women of world organizations.

Organization	Population	Recommendation
AJOG MFM 2023 ⁽⁷⁾	All pregnant women	An average intake of ≥ 250 mg/d of DHA+EPA and an additional intake of ≥ 100 –200 mg / d of DHA
	Pregnant women with low DHA intake or blood levels at the beginning of pregnancy	Average intake of approximately 600–1000 mg/d of DHA+EPA, or DHA alone, preferably beginning in the second trimester of pregnancy and not later than approximately 20 weeks of gestation, and continuing until childbirth or approximately 37 weeks of gestation
EBCOG 2024 ⁽¹⁶⁾	Women of childbearing age	should be encouraged to obtain a regular supply of omega-3 fatty acids from foods rich in these fatty acids. The daily target intake during pregnancy should aim to reach within the range of 350–450 mg/day
	Pregnant women at increased risk of preterm births due to inadequate DHA intake	should receive a regular supply of approximately 600 to 1000 mg/day of DHA plus EPA, or DHA alone, start before 20 weeks of gestation, and should be sustained until approximately 37 weeks of gestation.
Bureau of Nutrition, Department of Health, Ministry of Public Health, Thailand 2020 ⁽¹⁷⁾	Pregnant women and breastfeeding mothers	should receive DHA 200-1,000 mg/day (at least DHA 200 mg /day)
Australian Pregnancy Care Guideline 2025 ⁽¹⁸⁾	Pregnant women with low omega-3	800 mg of DHA and 100 mg of EPA may reduce the risk of preterm birth
Polish Society of Gynaecologists and Obstetricians 2020 ⁽¹⁹⁾	All pregnant women	Should take at least 200 mg/day of DHA
	Pregnant women at risk of preterm birth	Should intake 1,000 mg/day of DHA
European Food Safety Authority 2010 ⁽²⁰⁾	All pregnant women	250-mg/day DHA+EPA and additional 100–200-mg/day DHA
International Society for the Study of Fatty Acids and Lipids 2004 ⁽²¹⁾	All pregnant women	≥ 200 -mg/day DHA

DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid.

Pregnant women should receive at least 200 mg/day of DHA, while pregnant women with low DHA intake or blood levels at the beginning of pregnancy should receive 600-1000 mg/day of DHA plus EPA, or DHA alone, before 20 weeks of gestation and should be sustained until approximately 37 weeks.

Conclusion

DHA is an omega-3 PUFA. DHA can be synthesized from α -linolenic acid or directly derived from maternal milk (breast milk), cold-water fatty fish such as salmon, fish oil, or algae oil. DHA has mechanisms that may help reduce the risk of premature birth, smaller for gestational age infants, and preeclampsia. Pregnant women should receive at least 200 mg of DHA per day. Several studies have found that low plasma DHA levels during pregnancy increase the risk of premature birth, and DHA supplementation during pregnancy (1,000 mg per day) has been shown to be effective in preventing premature birth and early preterm delivery in cases of low DHA levels.

Potential conflicts of interest

The author declares no competing interests.

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