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Long-chain ω-3 fatty acid supply in pregnancy and lactation

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Purpose of review

Long-chain ω-3 fatty acids are essential for the developing fetus. Docosahexaenoic acid, the most important ω-3 fatty acid, is an important component of neural and retinal membranes, and rapidly accumulates in the brain during gestation and the postnatal period. Positive associations have been shown between maternal intake of fish, seafood and ω-3 fatty acids during pregnancy and/or lactation and visual and cognitive development.

Recent findings

The review focuses on new findings by both observational and interventional studies on the influence of ω-3 fatty acids during pregnancy or lactation on gestation length and birth weight, preterm delivery, preeclampsia, maternal depression and infant visual function and neural development.

Summary

Omega-3 fatty acids have been associated with reduced risk of cardiovascular and other diseases. Observational and interventional studies indicate a significant association with prolonging gestation and reducing the risk of preterm delivery both in low-risk and in high-risk pregnancies. Further benefits have been suggested for intrauterine growth restriction, preeclampsia and postpartum depression, but the evidence is inconclusive. Higher maternal docosahexaenoic acid intake both in pregnancy and lactation is associated with positive infant neurodevelopmental outcomes. Women of reproductive age should achieve an average dietary docosahexaenoic acid intake of at least 200 mg/day.

Keywords

Docosahexaenoic acid, diet, fetus, lactation, long-chain polyunsaturated derivatives, pregnancy, supplementation

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Introduction

The dietary essential ω-3 fatty acid (FA), α-linolenic (ALA; 18:3n-3) is the precursor of long-chain polyunsaturated derivatives (LCPUFA), eicosapentaenoic (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), which are important structural elements of cell membranes that are needed for the normal development of the central nervous system and retina [1,2]. The biological roles of ω-3 FA involve eicosanoid metabolism, membrane properties and regulation of gene expression. DHA is the most important of these molecules, being incorporated into the membrane phospholipids of brain and retina against a concentration gradient [3,4].

In the past 20 years, a wealth of studies have investigated the effect of maternal intake of fish, seafood and ω-3 FAs during pregnancy and lactation on perinatal and infant outcomes.

Effects on maternal and pregnancy outcomes

The fact that ω-3 FA intake is particularly important in pregnancy is not surprising, as it has been shown to accumulate in fetal tissue at a particularly high rate in the second part of pregnancy [5]. As mammalian cells lack Δ-12 desaturase and Δ-15 desaturase enzymes, they depend on diet for the n-6 and n-3 polyunsaturated FAs. Although women of reproductive age appear to have a greater capacity than men to convert the essential n-3 FA ALA (obtained predominantly from unsaturated vegetable oils) to EPA and DHA [6], their overall capacity for de-novo synthesis is low, and therefore they need preformed DHA and EPA [7]. The major sources of ω-3 LCPUFA are fish and seafood, whereas seed oils, eggs, poultry and pig meat contain the greatest amount of n-6 FAs [8]. However, the average dietary supply of ω-3 in pregnancy is rather low both in Europe and in North America [9,10] and varies worldwide ranging from 0.89% to nearly 9% of energy [8].

Studies [11] performed on the Faroe Islanders, a secluded population with high-fish intake, reported longer gestations and higher birth weights together with lower incidence of low birth weight compared with those reported in Denmark. Since then a number of observational studies [12] have confirmed the association of high-fish intake with a slightly prolonged gestation. The rationale for this effect is that higher concentration of ω-3 will modify the balance of production of prostaglandins involved in the initiation of labor.

For this reason, the effect of n-3 LCPUFA supplementation to the diet of pregnant women has been evaluated in numerous randomized controlled intervention trials. Although differences exist between studies in terms of population, baseline ω-3 levels, amounts supplemented and timing of intervention, the results of two recent independent meta-analyses indicate gestation prolonged by an average of 1.6–2.6 days [13,14••]. In a randomized double-blind, placebo-controlled trial, published after these meta-analyses, 300 mg DHA supplementation of fish oil in 29 women, from gestation week 24, resulted in a significantly longer gestation (6 days on average) [15•]. A reduced risk of early preterm delivery was indicated in a meta-analysis of four randomized controlled trials [16••], evaluating the effect of LCPUFA supplementation in women with high-risk pregnancies.

Omega-3 LCPUFA intake during pregnancy has also been associated with a trend toward greater growth measures at birth by some observational studies [11,17,18]. However, the effect of ω-3 on fetal growth has been a matter of debate as some studies [19,20] have reported a potentially detrimental effect, with lower birth weight when adjusted for gestational age. When randomized trials were considered, the effect of supplementation showed slightly higher rates of birth weights and significantly greater head circumference [13,14••].

Recently, the relation between fish consumption during pregnancy and fetal growth was evaluated in a large cohort of Danish women, and higher rates of birth weights below the 10th percentile were found in women who consumed more than 60 g of fish per day [21••]. However, this was true in the case of consumption of fatty fish and not for consumption of lean fish, thus suggesting that the effect on fetal growth could be due to exposure to persistent organic pollutants highly carried by fatty fish [22]. A number of studies [23] have shown concerns about potential health risks from the environmental contaminants found in fish, suggesting the relevance of choosing the most suitable species in terms of levels of ω-3 FA and pollutants, the frequency of consumption and the meal size.

Changes during healthy pregnancy include inflammation, insulin resistance and hyperlipidaemia [24]. These are exaggerated in women with preeclampsia, and some are also features of the 'metabolic syndrome', representing a risk factor for cardiovascular disease in later life [25]. In recent years, ω-3 LCPUFAs have been specifically recommended for the secondary prevention of cardiovascular disease [26], and they have been the focus of considerable attention for the prevention and treatment of disorders with an inflammatory component, including mental disorders [27].

A potential beneficial effect of ω-3 FAs on preeclampsia has been hypothesized, with the theoretical rationale of a shift in production toward n-3 derived eicosanoids versus decreased synthesis of arachidonic acid-derived thromboxane A_2 [28]. A recent reappraisal of a large controlled study [29] that had already been conducted in London in the 1930s concluded that fish oil consumption might result in a lower incidence of preeclampsia. Moreover, a preventive effect on the incidence of edema, but not of hypertension and/or preeclampsia was reported when supplementing a combination of fish oil and evening primrose oil (supplying γ-linolenic acid) [30]. Six randomized intervention trials on supplementation of ω-3 involving 2783 women were recently evaluated [14••]. Although the authors concluded that there is not enough evidence to support the routine use of marine oil, or other prostaglandin precursor, as supplements to reduce the risk of preeclampsia or small-for-gestational-age (SGA) infant, some effects were found in terms of slightly greater birth weights and lower risk of giving birth before 34 weeks.

The success and failure of different clinical trials supplementing ω-3 FA are, however, influenced by baseline conditions and by habitual diets in different populations. Among low fish-eating pregnant women in India, fish intake in the third trimester was closely associated with birth weight, with a significant risk of low birth weight in women who did not eat fish [31•].

Moreover, suggested intakes should also be related to background intakes of the n-6 FAs, linoleic acid and arachidonic acid, as greater dietary intakes of n-6 FA increase tissue concentrations of arachidonic acid, while reducing tissue concentrations of EPA and DHA. Lower DHA together with a higher n-6 to n-3 ratio was reported in women who developed postpartum depression [32,33]. Evidence from worldwide diversity of dietary intakes also indicates that dietary intakes of ω-3 FA are inversely related to morbidity from postpartum depression [8]. In countries with low-ω-3 intake, the prevalence of postpartum depression is fifty-fold higher than that in those with the highest intake [34]. However, there are only few intervention trials designed to specifically address this endpoint. Two recent small trials on ω-3 FA intake of up to 2.8 g/day showed a significant reduction in depression during pregnancy and the postpartum period [35,36]. In

these studies, ω-3 FA appeared beneficial and improved depressive symptoms. A randomized, placebo-controlled trial is warranted to determine the efficacy of ω-3 FA in reducing the occurrence of depression in the peripartal period.

Placental transfer and fetal needs

The FA composition of tissue is known to change throughout development. The requirements for ω-6 and ω-3 FAs by the human fetus during the last trimester of fetal development through the early weeks of life have been estimated to be 400 mg/kg/day and 50 mg/kg/day, respectively [37,38], Phospholipids, in particular, are progressively enriched in DHA at the expense of the n-6 FA, with a significant increase in the n-3 to n-6 ratio in the third trimester of gestation. Although DHA is the main component of mature brain [39], and it has been recently shown to be incorporated directly into retinal phospholipids without further metabolism, *20*:5n-3 and *22*:5n-3 are the primary precursors of the very long chain FA C-24-C36 that are synthesized in the retina [40].

However, the quantitative degree to which the human fetus is capable of desaturation and elongation of precursor FAs is not clear. Therefore, the placental supply of LCPUFA is critical for the synthesis of structural lipids, and, hence, to normal fetal development [41,42•].

Preformed dietary DHA has been shown to be significantly more efficient as DHA source for the neonatal brain than ALA [43]. Delta 5-desaturase and Δ6-desaturase activities are not significantly detectable in the human placenta, leading to an inability of the placenta to convert the essential FA, ALA and linoleic acid into their LC derivatives, DHA and arachidonic acid [44]. Thus, the ability of the placenta to extract LCPUFA from maternal circulation and deliver them to the fetus becomes highly important. In pregnancy, both maternal metabolism and placental effects lead to a significant change in the umbilical cord plasma FA composition [41,45].

Numerous studies [46,47], both at delivery and *in utero*, have shown that the percentage of LCPUFA is higher in human fetal than in maternal circulation, suggesting that the placenta may play a role in the preferential transfer of LCPUFA, with a significant selectivity for DHA both in placental perfusion studies [48,49] and in stable isotope studies performed *in vivo* [50•,51].

FAs taken up by the placenta originate primarily from maternal triglycerides hydrolysed by lipoprotein lipase and from nonesterified fatty acids (NEFA) in the maternal circulation [45]. Oral supplementation of long-chain ω-3 FAs both from fish oil and from single cell organisms to women of childbearing age is effective in increasing DHA contents of blood lipids [52,53•]. The supplementation of a DHA rich oil to pregnant women from about 20 weeks of gestation until the time of birth in a randomized controlled clinical trial led to clearly higher DHA incorporation both into placental lipids [54] and maternal and cord blood lipids [55•], indicating that fetal supply can be enhanced by maternal dietary intake. Moreover, maternal dietary supply will affect the quality of maternal body fat accumulation, which occurs preferentially during the first half of pregnancy. An unbalanced dietary supply during this period not only restrains intrauterine development in the second half of pregnancy but also may have long-term consequences on glucose tolerance later in life [45].

Placental transfer involves binding to membrane proteins and cytoplasmatic transport proteins [56]. A different compartmentalization of individual FAs within the placenta might represent a powerful mechanism for selective transfer of certain FAs. In conditions associated with placental insufficiency, like intrauterine growth restriction, the ratios between the long-chain DHA and arachidonic acid and their precursors ALA and linoleic acid have been reported to be significantly reduced when compared with normally grown fetuses of similar gestational age [47]. Recently, Larque *et al.* [57] demonstrated the expression of FA binding and transport proteins in human placenta. The same group also showed that the expression of FA transport protein 4 (FATP-4) was correlated to DHA contents in cord blood at the time of birth, which suggests that FATP-4 might act as the specific DHA transporter in human placenta [58].

Effects on infant outcomes and neurodevelopment

DHA is enriched in brain grey matter and retina phospholipids, but its content decreases with low-dietary supply, leading to impaired neurogenesis, altered gene expression and neurotransmitters and decreased kinetics of the visual photocycle [59•,42•]. Experimental animal studies [60,61] have provided evidence that DHA deficiency during pregnancy causes disturbances in offspring brain development. Moreover, autopsies from infants who had received breast milk, known to contain DHA, showed significantly higher concentrations of DHA in the cerebral cortex than did infants fed with formulas without DHA [62].

The levels of DHA reported in breast milk show considerable variability worldwide (0.17–0.99% of total FAs) [63], which depend on maternal dietary intake [64]. A number of observational studies [12] have shown positive associations between maternal intake of fish, seafood and LCPUFA during pregnancy and/or lactation and visual and cognitive development as well as other functional outcomes. Similar associations have been found between indices of DHA status in infants and visual acuity and

language development [12]. Results from a large observational cohort study [65••] showed that maternal seafood consumption of less than 340 g per week (thus avoiding contaminants) in pregnancy did not protect children from adverse outcomes. Rather, strong beneficial effects on development of verbal intelligence quotient, fine motor function and social behavior were observed in the children up to 8 years of age with higher maternal seafood intakes during the last period of pregnancy. A dose–response relationship was found between the amount of seafood consumed and later verbal intelligence quotient development, with close-to-optimal outcomes at a fish intake providing approximately 200 mg DHA per day. The authors concluded that the risks from loss of biologically important nutrients by avoiding fish consumption were higher than the risks of harm from exposure to trace contaminants.

A recent review of a large number of human and animal studies [66] indicated that, within the context of specific experimental designs, changes in brain concentrations of DHA are positively associated with changes in cognitive or behavioral performance [66]. In addition, recent randomized controlled trials on the effects of LCPUFA supplementation during pregnancy and lactation suggest a beneficial effect on cognitive development of infants and children, but not on visual development [67•]. In the already mentioned recent randomized double-blind, placebo-controlled trial, 300 mg DHA supplementation of fish oil from gestation week 24, improved infant problem-solving but not recognition memory at 9 months, adding to the growing body of evidence that DHA has beneficial effects on some areas of cognitive development [15•].

Omega-3 FAs are also important biomediators that can affect growth and body composition through diverse mechanisms. Both ω-3 levels and the ratio between n-3 and n-6 FA can influence signaling processes and the expression of genes that regulate cell growth and differentiation. In a small randomized double-blind trial, 200 mg DHA supplementation to pregnant mothers starting at mid-gestation was associated with reduced weight and BMI of the children at 21 months of age [68•].

Omega-3 FAs appear to modulate also the synthesis of eicosanoids affecting bone metabolism [69]. Infant bone mass was found to be related to the AA status of the mother and neonate [70], suggesting that the maternal diet should be balanced in n-6 and n-3 status.

DHA supplementation during pregnancy was also shown to modulate the immune phenotype [71] and to decrease inflammatory cytokines, suggesting a potential role for primary allergy prevention [72•].

What is the appropriate intake of ω-3 FAs in pregnancy and lactation?

Many studies [12,42•] during pregnancy and lactation have shown that ω-3 FAs have a significant influence on pregnancy outcomes, nervous system function and development of the child [12,42•]. Therefore, it is an important topic for public health to address the appropriate amount of long-chain ω-3 FA supply in pregnancy and lactation.

Recently, evidence-based consensus recommendations on dietary fat intakes during pregnancy and lactation were developed, based on a systematic review of the available evidence and a formal consensus process, with support from the European Commission [73••]. These consensus recommendations conclude that pregnant and lactating women should aim to achieve an average DHA intake of at least 200 mg/day to reduce the risk of early preterm birth and to ensure adequate DHA deposition in brain and other tissues during critical developmental periods. This recommended intake of DHA can be reached by consuming one to two portions of sea fish per week, including oily fish as a good source of ω-3 LCPUFA. However, it is important to bear in mind the differences related to worldwide diversity in dietary intakes of both n-3 and n-6 FA and how these could affect baseline body composition and availability of FA [8]. As recognized in the consensus statement [73••], intakes of up to 1 g/day DHA or 2.7 g/day ω-3 LCPUFA have been used in clinical trials with no significant adverse effects. Recently, the question arose as to what is the right DHA level in the infant diet [74••], stimulated by data obtained on baboons showing significant increases in DHA content of different areas of the brain when DHA is added in amounts higher than those commonly utilized in term formulas [75]. Although breast feeding is associated with higher levels of DHA in the brain, at least 1 g of DHA is needed to reach a breast milk DHA level of 1 wt% [76]. This amount is much higher than the average dietary intake in most of the western countries [8,9,10].

Conclusion

The studies published to date and reviewed herein strongly suggest that the dietary intake of ω-3 FAs, and in particular of DHA, during pregnancy and lactation has biologically important effects on gestation length and the risk of preterm delivery and may have an effect on other pregnancy outcomes such as fetal growth, preeclampsia and postpartum depression. Similarly, DHA supply to the fetus and the neonate is associated with beneficial effects on later cognitive development and visual function. The resulting effects might be related to background diversity of dietary supplies. Dietary advice should be given to women of childbearing age

in order to achieve a regular intake of adequate amounts of DHA in their diets.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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