Effects of n−3 fatty acids during pregnancy and lactation[1–3]

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ABSTRACT

n−3 Fatty acids exert important effects on eicosanoid metabolism, membrane properties, and gene expression and therefore are biologically important nutrients. One n−3 fatty acid, docosahexaenoic acid, is an important component of neural and retinal membranes and accumulates rapidly in the brain and retina during the later part of gestation and early postnatal life. It is reasonable to hypothesize that maternal n−3 fatty acid intakes might have significant effects on several pregnancy outcomes as well as on subsequent infant visual function and neurodevelopmental status. Studies, both observational and interventional, assessing the influence of n−3 fatty acids during pregnancy or the early postpartum period on duration of gestation and infant size at birth, preeclampsia, depression, and infant visual function and neurodevelopment have been reported. n−3 Fatty acid intakes (both in terms of absolute amounts of docosahexaenoic acid and eicosapentaenoic acid and the ratio of these 2 fatty acids) varied widely in these studies, however, and no clear consensus exists regarding the effects of n−3 fatty acids on any of these outcomes. The available data suggest a modest effect of these fatty acids on increasing gestational duration and possibly enhancing infant neurodevelopment. Although data from earlier observational studies suggested a potential role of these fatty acids in decreasing the incidence of preeclampsia, this has not been confirmed in randomized, prospective trials. Because of the paucity of data from randomized, prospective, double-blind trials, the effect of n−3 fatty acids on depression during pregnancy or the early postpartum period remains unresolved. *Am J Clin Nutr* 2006;83(suppl):1452S–7S.

KEY WORDS n−3 Fatty acids, maternal DHA supplementation, docosahexaenoic acid, eicosapentaenoic acid, pregnancy, preeclampsia, maternal depression, infant visual function, infant neurodevelopment

INTRODUCTION

n−3 Fatty acids exert important effects on eicosanoid metabolism, membrane properties, and gene expression and therefore are biologically important nutrients. This is especially true for the long-chain n−3 polyunsaturated fatty acids docosahexaenoic acid (DHA; 22:6n−3) and eicosapentaenoic acid (EPA; 20:5n−3). DHA is an important component of neural and retinal membranes and accumulates rapidly in the brain and retina during the later part of gestation and early postnatal life (1-3). EPA competes with arachidonic acid (20:4n−6) for the enzymes responsible for eicosanoid formation (cyclooxygenase, lipoxygenase). EPA and DHA can be ingested as components of dietary lipid or can be synthesized from shorter, less unsaturated n−3 fatty acids, primarily α-linolenic acid (ALA; 18:3n−3), through a series of desaturations and elongations. n−3 Fatty acids compete with n−6 (and also n−9) fatty acids for the enzymes responsible for desaturation and elongation and probably for incorporation into membrane phospholipids as well.

The effect of pregnancy on maternal n−3 fatty acid status is likely to be dependent on prepregnancy n−3 fatty acid status and intake during pregnancy. The possibility of increased dietary requirements during pregnancy may be expected because of fetal accretion: ≈50–60 mg of n−3 fatty acids, mainly DHA, per day during the last trimester (1, 3). Maternal and fetal DHA synthetic capabilities are not known and the data are inconsistent regarding maternal plasma n−3 fatty acid status during pregnancy, with decreased long-chain n−3 fatty acid concentrations observed in some, but not all, studies (4–7). In one study, ALA supplementation from 14 wk of gestation until delivery did not increase either maternal or infant plasma phospholipid DHA concentrations, although EPA concentrations were higher (8).

Maternal plasma phospholipid DHA concentrations have been observed to decrease significantly after delivery (7). The concentration of DHA in human milk is related to maternal DHA status, which varies widely. Because the average n−3 long-chain polyunsaturated fatty acid intake of lactating women in the United States is quite low, mean breast milk DHA content in the United States is lower than that in many other populations (9–11). DHA supplementation of lactating women increases breast milk DHA content (12–14), whereas ALA supplementation of lactating women increases breast milk ALA content but has little effect on breast milk DHA content (15). DHA supplementation during lactation is much more effective in raising breast milk DHA content than is supplementation limited to pregnancy only (16).

Because of the biological activities of n−3 fatty acids, some investigators have hypothesized that maternal n−3 fatty acid intakes might have significant effects on several pregnancy outcomes, including duration of gestation and infant size at birth, preeclampsia, depression, cognition, and immunologic function. In addition, because DHA is present in high concentrations in the brain and retina, particularly in synaptic membranes and rod-cone outer membranes, adequate provision of DHA is thought to

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be essential for optimal visual and neurologic development during early life. Thus, maternal DHA supplementation may also affect infant visual function and neurodevelopment.

These hypotheses have been addressed in both observational studies and interventional trials. Some investigators view observational studies as hypothesis-generating rather than hypothesis-confirming and prefer that findings from observational studies be tested in appropriate double-blind, prospective trials if feasible. Other potentially relevant factors in evaluating the results of these studies include the amount and fatty acid composition (eg, amounts of DHA and EPA) of any supplements used, the duration and timing of the supplementation, the baseline n−3 fatty acid intakes of the populations studied, and other population differences (eg, potential genetic or environmental interactions) between studies.

The results of these types of studies have important public health implications. Currently, on numerous websites, n−3 fatty acid supplementation during pregnancy is encouraged as a means of preventing preeclampsia, preterm delivery, and postpartum depression. If n−3 fatty acid supplementation during pregnancy is considered, several factors, including the fatty acid composition of potential supplements, the possible presence of contaminants (eg, mercury, polychlorinated biphenyls, and dioxin), the availability of safety and efficacy data, and cost, may influence specific recommendations.

STUDIES ADDRESSING SPECIFIC OUTCOMES

Potential effects of n−3 fatty acids on duration of gestation and infant size at birth

Some evidence from both observational studies and interventional trials suggests that higher n−3 long-chain polyunsaturated fatty acid intakes during pregnancy may result in a small increase in the duration of gestation and, possibly, an increase in birth weight. However, the study results are inconsistent. The results of several studies addressing these questions are summarized below.

Olsen et al (17–20) suggested that higher n−3 fatty acid intakes may increase gestational duration and birth weight. Observational data supporting this hypothesis included the lower incidence of low-birth-weight infants in the Faroe Islands than in Denmark (3.5% compared with 5.9%), the suggestion of slightly longer gestational length, and the relation to erythrocyte n−3 fatty acid content (17, 18). Also, a reexamination of data from a large controlled trial of fish oil supplementation conducted in London in the late 1930s showed a 20.4% reduction in preterm delivery with supplementation (19). In an observational study of 965 women in Denmark, however, no association between n−3 fatty intake or n−3 to n−6 fatty acid status and either gestational length or fetal growth rate was found (20). The results of other recent observational studies have been mixed. In a study done in Vancouver, significant positive correlations were observed between triacylglycerol and cholesteryl ester arachidonic acid contents in cord plasma and length of gestation, birth weight, and birth length and between cholesteryl ester DHA and birth length (21). In an observational study of 182 pregnant women in the Faroe Islands, a higher intake of marine fats (fish and whale) was associated with a slight prolongation of gestation (≈1.5 d for each 1% relative increase in cord serum phospholipid DHA content) but possibly a lower birth weight adjusted for gestational age (22). In an observational study of 627 term newborns in the Netherlands, cord plasma concentrations of both DHA and arachidonic acid were negatively related to weight *z* scores at birth, whereas cord blood dihomo-γ-linolenic acid (20:3n-6) was positively related to weight *z* scores (23).

Several interventional trials assessing the effect of n−3 fatty acid supplementation on gestational length and infant size at birth have been reported. In a randomized controlled trial conducted in Denmark in which pregnant women received either fish oil (≈1.57 g EPA/d, ≈1.13 g DHA/d; n = 266), olive oil (n = 136), or no supplemental oil (n = 131) during the third trimester, gestation was ≈4 d longer and birth weight was slightly higher in the fish oil group than in the olive oil group (24). In a randomized, double-blind, placebo-controlled UK trial in which women with high-risk pregnancies received either fish oil (1.62 g EPA + 1.08 g DHA/d; n = 113) or placebo (n = 119) until 38 wk of gestation, there was no effect of fish oil on duration of gestation (25). In multicenter trials in which women with high-risk pregnancies were assigned to either fish oil or olive oil from ≈20 wk of gestation (≈2.7 g EPA + DHA/d) or ≈33 wk of gestation (≈6.1 g EPA + DHA/d), fish oil reduced the recurrence risk of preterm delivery from 33% to 21% in nontwin pregnancies, although there was no effect on intrauterine growth retardation or preterm delivery with twin pregnancies (26). In a Norwegian trial of cod liver oil (≈1200 mg DHA, ≈800 mg EPA) versus corn oil supplementation beginning at 18 wk of gestation that was designed primarily to examine effects on infant neurodevelopment, no effect on gestational length or birth weight was observed (27). In a prospective cohort study of 8729 pregnant women in Denmark, low dietary fish intake was a "strong" risk factor for preterm delivery and low birth weight (the incidence of preterm delivery was 7.1% for women who never ate fish compared with 1.9% for women who ate fish at least once per week) (28). In a UK study in which pregnant women were randomly assigned to receive either ≈323 mg fish oil (≈100 mg DHA) per day from a high-DHA, low-EPA fish oil or high-oleic sunflower oil from 15 wk of gestation until delivery, gestational length, birth weight, length, and head circumference were not significantly different between groups; however, gestational length was significantly greater in infants in the upper quartile for umbilical cord plasma DHA than in infants in the lower quartiles (29). Smuts et al (30) recently reported that relatively low-dose DHA supplementation with ≈1 high-DHA egg (≈133 mg DHA/egg) compared with a regular egg (≈33 mg DHA/egg) per day during the last trimester of pregnancy increased gestation by ≈6 d. Birth weight, length, and head circumference were higher in the DHA-supplemented group, but the differences between groups were not significant. Study subjects were predominantly African American and most received government assistance for health care.

Although the results of the studies summarized above are inconsistent, some evidence suggests that higher n−3 fatty acid intakes during pregnancy may increase gestational duration without obvious adverse effects. From a pediatric perspective, this would be viewed as a positive outcome.

Potential effects of n−3 fatty acids on preeclampsia or related conditions

There are theoretical rationales (eg, decreased synthesis of thromboxane A_2 from arachidonic acid versus synthesis of EPA-derived eicosanoids, etc) for a possible beneficial effect of n−3 fatty acids on preeclampsia. Higher blood concentrations of arachidonic acid in preeclamptic women were reported >20 y ago (31), and high-dose n−3 fatty acid intake has been shown to reduce maternal thromboxane A_2 synthesis and enhance maternal refractoriness to angiotensin II (32). However, despite some promising early observational data, there is little evidence from randomized, placebo-controlled trials of a significant effect on the incidence or severity of preeclampsia. Some related studies are summarized below.

A reanalysis by Olsen and Secher (19) of data from a previously mentioned large controlled study conducted in London >60 y ago suggested that fish oil consumption might result in a lower incidence of preeclampsia (a 31.5% reduction in the odds of developing preeclampsia was noted). In an observational study by Wang et al (33), total n−3 and n−6 polyunsaturated fatty acids were lower in women with preeclampsia, and the investigators speculated about the possible role of low EPA in the pathogenesis of preeclampsia. In a study done in Angola, a combination of fish oil and evening primrose oil (supplying γ-linolenic acid) or magnesium oxide versus olive oil had no appreciable effect on pregnancy-induced hypertension or proteinuric hypertension but did result in a lower incidence of edema (34). In a trial of 2.7 g of fish oil versus olive oil versus no oil supplementation during the third trimester of pregnancy, fish oil supplementation increased thromboxane B_3 and prostacyclin I_3, whereas analogues synthesized from arachidonic acid tended to be decreased; however, clinical benefits were not confirmed (35). An observational study of 22 women with preeclampsia and 40 control women in Seattle showed that low maternal erythrocyte concentrations of n−3 fatty acids and high concentrations of arachidonic acid were associated with a higher risk of preeclampsia (36). Finally, in the previously mentioned randomized, double-blind, placebo-controlled UK trial of Onwude et al (25) in which women with high-risk pregnancies received either fish oil (1.62 g EPA + 1.08 g DHA/d) or placebo until 38 wk of gestation, there was no significant effect on the incidence of hypertension with or without proteinuria. Although compelling evidence for a beneficial effect of n−3 fatty acids on preeclampsia from recent prospective, double-blind studies is lacking, the lower incidence of edema observed in one study might be relevant for many pregnant women.

Potential effects of n−3 fatty acids on depression or cognition during or shortly after pregnancy

As discussed in another article in this supplement (37), evidence suggests a potential role of n−3 fatty acids in the prevention or treatment of depression. At present, however, there is a paucity of data from controlled studies supporting the efficacy of n−3 fatty acids in the prevention or treatment of depression during pregnancy or in the postpartum period, although data from recent observational studies and open-label trials of n−3 fatty acid supplementation appear promising. Some relevant studies are summarized below.

An analysis by Hibbeln (38) of data pooled from several countries showed a negative correlation between the prevalence of postpartum depression and either seafood consumption or breast milk DHA concentrations. In 2003, Chiu et al (39) reported the case of a 34-y-old with a recurrent depressive episode in mid-pregnancy who appeared to respond to therapy with 4 g EPA + 2 g DHA/d. De Vriese et al (40) reported that shortly after delivery, DHA and total n−3 fatty acids in serum phospholipids and cholesteryl esters were lower, and the ratio of n−6 to n−3 fatty acids in phospholipids higher, in 10 women who developed postpartum depression than in 38 women who did not. In a study conducted in the Netherlands, the ratio of DHA to n−6 docosapentaenoic acid, which is an indicator of DHA status, was lower in a "possibly depressed" group than in a nondepressed group of women assessed by using the Edinburgh Postnatal Depression Scale (EPDS) shortly after delivery and at 32 wk postpartum (41). However, Llorente et al (42) reported no effect of supplementation with ≈200 mg of algal DHA from shortly after delivery through 4 mo postpartum on several indexes of depression. Note, however, that this was not the primary outcome of that study and a vulnerable population was not studied. A planned trial of n−3 fatty acid monotherapy (fish oil: 1730 mg EPA and 1230 mg of DHA/d starting between the 34th and 36th week of pregnancy and continued through 12 wk postpartum) for prevention of postpartum depression in women with a prior history of depression in the postpartum period was discontinued after 4 of the first 7 subjects had a major depressive episode during the study period (43). On the other hand, in a study of ≈14 000 women, self-report of lower seafood intake at 32 wk gestation was associated with an approximate doubling of the risk of severe depressive symptoms during pregnancy and in the postpartum period (44). Additionally, beneficial effects on symptoms of depression during pregnancy and the postpartum period were observed in recent, small open-label trials of EPA plus DHA supplementation (45, 46), which provides support for the further study of these fatty acids in larger, randomized controlled trials.

Few studies assessing the effect of n−3 fatty acids during pregnancy or the postpartum period on maternal cognitive function have been published. In the study of DHA supplementation of lactating women by Llorente et al (42), there was no statistically significant difference in performance on the Stroop Test (a measure of cognitive interference) between women in the DHA-supplemented group and those in the control group; however, it could be argued that a "trend" toward benefit with supplementation was present and that this effect would be detectable if larger groups were studied. In a study by de Groot et al (47), ALA supplementation during pregnancy, which had little effect on DHA status, did not affect cognitive performance at 14 wk of gestation or 32 wk postpartum.

n−3 Fatty acids and recurrent miscarriages associated with persistent antiphospholipid syndrome

In an open-label trial, the outcomes of 23 pregnancies in 22 women with persistent antiphospholipid syndrome and 3 or more miscarriages who were treated with fish oil (5.1 g DHA + EPA with an EPA:DHA ratio of 1.5) were reported (48). One intrauterine death occurred at 27 wk of gestation and 19 infants were born after 37 wk of gestation (all with birth weight > 2500 g). Two infants were delivered by cesarian section because of preeclampsia (at 30 and 35 wk of gestation). Although this study suffers from the weaknesses inherent in a small, nonblinded trial, the results suggest a potential application for n−3 long-chain polyunsaturated fatty acid supplementation in this clinical setting.

Effects of maternal n−3 fatty acid intakes or status during pregnancy or lactation on infant visual function or neurodevelopment

A limited number of studies of the effect of maternal n−3 fatty acid supplementation during pregnancy or lactation on infant visual or neurodevelopmental outcomes have been published to date. Summaries of some potentially relevant studies are given below.

Cheruku et al (49) reported that infants of mothers with higher versus lower plasma phospholipid DHA concentrations had a lower ratio of active to quiet sleep (which is suggestive of a more mature sleep pattern). Ghys et al (50) found no association between the cognitive development of 128 former full-term infants at 4 y of age and umbilical venous plasma or red blood cell phospholipid DHA or arachidonic acid contents. In another observational study, children whose mothers ate oily fish during pregnancy were more likely to develop high-grade stereoacuity at 3.5 y of age than were children whose mothers did not eat oily fish (51). Observational studies from Vancouver showed better visual acuity at 2 and 12 mo of age in breastfed infants with higher red blood cell phosphatidyl ethanolamine DHA content at 2 mo of age and statistically significant positive correlations between several indexes of infant DHA status at 2 mo of age and measures of language development at 9 and 18 mo of age (52, 53).

Results are available for a small number of interventional trials assessing the effect of maternal DHA intake during pregnancy on visual and neurodevelopmental outcomes. In studies by Malcolm et al (29, 54) conducted in the United Kingdom, pregnant women were randomly assigned to receive either ≈323 mg fish oil (≈100 mg DHA) per day from a high-DHA, low-EPA fish oil (n = 50; 28 completed the study) or high-oleic sunflower oil (n = 50; 27 completed the study) from 15 wk of gestation until delivery. Electroretinograms were assessed within the first week of life and pattern-reversal visual evoked potential (VEP) testing was done at 50 and 66 wk postconceptional age. This low-dose DHA supplementation did not increase DHA concentrations in umbilical cord blood significantly and there were no significant differences between groups on electroretinogram or VEP measures. However, maturation of pattern-reversal VEP and retinal sensitivity correlated with DHA status (29, 54). Infants with higher DHA status had shorter VEP peak latencies (a positive finding). In a study by Helland et al (55), mothers in Norway received either a cod liver oil (≈1200 mg DHA, ≈800 mg EPA) or a corn oil supplement from 18 wk of gestation through 3 mo postpartum, and the Kaufman Assessment Battery for Children (KABC) was administered to children at 4 y of age. Children whose mothers received the cod liver oil had a higher composite KABC score at 4 y of age. Colombo et al (56) assessed the effects of maternal DHA status on development of attention during infancy and toddlerhood in children born to mothers participating in the DHA supplementation trial of Smuts et al (30). Infant control habituation was assessed at 4, 6, and 8 mo of age, and free play attention and distractibility were assessed at 12 and 18 mo of age. Infants whose mothers had higher DHA status (ie, higher erythrocyte phospholipid DHA) at the time of delivery had an accelerated decline in looking over the first year of life and less distractibility in the second year.

A few interventional studies assessing the effect of maternal DHA supplementation during lactation on infant visual and developmental outcomes have also been reported. In the study by Gibson et al (12), breastfeeding women were assigned to a placebo group (n = 12) or groups receiving 200 mg (n = 10), 400 mg (n = 12), 900 mg (n = 10), or 1300 mg (n = 8) DHA/d during the first 12 wk postpartum. Visual acuity was assessed at 12 and 16 wk of age by VEP testing, and neurodevelopment was assessed at 1 and 2 y of age by using the Bayley Scales of Infant Development. There was no relation between visual acuity at either age tested and infant DHA status. Erythrocyte DHA status at 12 wk of age was associated with the Bayley Mental Development Index (MDI) at 1, but not 2, y of age. Lauritzen et al (57) supplemented lactating Danish women who had low habitual intakes of n−3 fatty acids with fish oil supplying 1.3 g of long-chain n−3 fatty acids per day (n = 53) or olive oil (n = 44) for the first 4 mo postpartum and assessed visual acuity by using sweep VEP testing at 2 and 4 mo of age. Visual acuity was not significantly different between groups but was positively associated at 4 mo with infant erythrocyte DHA. In a recent study by Jensen et al (58), infants whose mothers received 200 mg algal DHA versus placebo (with resultant breast milk DHA contents of 0.35 compared with 0.2 mol% of total fatty acids, respectively) during the first 4 mo postpartum performed significantly better on the Bayley Psychomotor Development Inventory at 30 mo of age.

RECOMMENDATIONS AND CONCLUSIONS

Several concerns regarding the safety of increasing n−3 fatty acid intakes during pregnancy or lactation have been raised, including the possible risk posed by potential contaminants in certain dietary sources of long-chain polyunsaturated n−3 fatty acids and possible problems with bleeding. It seems prudent for pregnant and lactating women to select dietary sources of n−3 fatty acids known to have a low mercury content as well as low levels of other potentially harmful contaminants. Although in the study by Olsen et al (24), women in the fish oil group had a greater estimated blood loss during delivery than did women in the olive oil (but not control) group, this was felt to be statistically but not clinically significant.

n−3 Fatty acids are biologically important nutrients that may have potential benefits on pregnancy outcomes and infant development. Although one can reasonably argue that the current data are insufficient to formulate specific recommendations for n−3 fatty acid intakes during pregnancy and lactation, several scientific groups have made such recommendations. One expert panel recommended a DHA intake of 300 mg/d during pregnancy and lactation (59). Other recommendations for 200–300 mg/d during this period have been made (60). Although intakes well in excess of these recommendations are the norm in many areas of the world and a case can be made for higher intakes, in view of the potential for DHA intakes at or even below those of the recommendations cited above to increase gestational duration (30) and improve infant neurodevelopment (58), such recommendations seem reasonable at this time, especially because the average intake of DHA by pregnant and lactating women in the United States is substantially lower than these recommended amounts (61).

Evidence exists that the relative abundance of n−3 fatty acids in our ancestral diet was much higher than in most modern Western diets (62), which lends some support to the view that intakes higher than those currently recommended may be preferable. Because of the potential importance of these fatty acids for pregnant or lactating women, fetuses, and newborn infants and the limited data from prospective trials assessing the effect of these fatty acids on pregnancy and infant outcomes, additional research is required to better define optimal intakes of specific n−3 fatty acids during these critical periods.

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