Omega-3 Fatty Acid Supplementation During Pregnancy

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Omega-3 fatty acids are essential and can only be obtained from the diet. The requirements during pregnancy have not been established, but likely exceed that of a nonpregnant state. Omega-3 fatty acids are critical for fetal neurodevelopment and may be important for the timing of gestation and birth weight as well. Most pregnant women likely do not get enough omega-3 fatty acids because the major dietary source, seafood, is restricted to 2 servings a week. For pregnant women to obtain adequate omega-3 fatty acids, a variety of sources should be consumed: vegetable oils, 2 low-mercury fish servings a week, and supplements (fish oil or algae-based docosahexaenoic acid).

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In the field of perinatal nutrition, polyunsaturated fatty acids (PUFAs) of the omega-3 and omega-6 groups have gained recent attention because of their important functions in fetal and newborn neurodevelopment and because of their roles in inflammation.[1-3]

Two PUFAs, arachidonic acid (AA) and docosahexaenoic acid (DHA), are critical to fetal and infant central nervous system (CNS) growth and development.[1,4] Embedded in the cell membrane phospholipid, AA is involved in cell signaling pathways and cell division, and serves as an inflammatory precursor for eicosanoids. The DHA concentration is high in retinal and brain membrane phospholipids, and it is involved in visual and neural function and neurotransmitter metabolism.[2] During the last trimester, the fetus accrues about 50 to 70 mg a day of 1 omega-3 fatty acid, DHA.[5,6] Both maternal DHA intake and circulating DHA concentrations are important determinants of fetal blood concentrations of DHA.[3] Babies accrue DHA into the CNS up until about 18 months of age.[7,8]

Although research into the specific pathways affected by these PUFAs is still in its infancy, there is enough understanding to draw conclusions and make recommendations about their dietary intake during the perinatal period. For the purposes of this review, we focus primarily on the omega-3 fatty acids, DHA and eicosapentaenoic acid (EPA), and the omega-6 fatty acid, AA. We present information about how the absolute and relative concentrations of these fatty acids affect pregnancy outcome and fetal neurodevelopment.

Background Nutritional Science

Of the 20 or so edible fatty acids, only omega-3 and omega-6 fatty acids cannot be synthesized by the body.[9] All of the omega-3 and omega-6 fatty acids accumulated by the fetus must ultimately be derived from the mother by placental transfer. *Omega* refers to where the first double bond appears on the fatty acid chain from the carboxyl end. The typical American diet is replete with omega-6 fatty acids, particularly linoleic acid, which is readily converted to AA. Omega-6 fatty acids can be found in the vegetable oils used in processed foods, fried foods, and condiments like salad dressings.[10,11] One teaspoon of corn oil can satisfy the daily omega-6 requirement, but most individuals eat 10 to 20 times that amount.[10,11]

In contrast, the intake of omega-3 fatty acids is suboptimal.[9-11] The richest dietary sources of omega-3 fatty acids are from marine sources, fish oil supplements, and selected vegetable oils like flaxseed (57% omega-3 fatty acids), canola (11% omega-3 fatty acids), and soybean (8% omega-3 fatty acids). Most individuals in the United States do not consume these omega-3–rich foods on a regular basis.[12] The ratio of dietary omega-6/omega-3 fatty acids in the American diet approximates 10 to 25:1; the Paleolithic diet was probably closer to 1:1.[10]

The omega-3 fatty acid EPA and the omega-6 fatty acid AA are essential structural components of every cell in the body. Both EPA and AA serve as precursors for biologically active compounds called eicosanoids. These fatty acids compete for the enzyme systems cyclooxygenase, which makes prostaglandins and thromboxanes, and lipoxygenase, which makes leukotrienes. Diets that are rich in omega-6 fatty acids produce potent eicosanoids, whereas a diet with a more balanced intake of omega-6 and omega-3 fatty acids makes less inflammatory and less immunosuppressive eicosanoids.[13]

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Specific to pregnancy, although both DHA and AA appear to be essential to fetal CNS development, the relatively poor intake of EPA coupled with the high intake of linoleic acid (which produces AA), may affect pregnancy outcome by altering the balance of the eicosanoids produced.[2,5,6,14-16] A high ratio of AA to EPA may promote untoward effects such as preterm labor and preeclampsia.[2,17] A linoleic acid–rich diet produces an abundance of AA, which serves as a precursor of the potent 2-series prostaglandins (PGs) E_2 and $PGF_2\alpha$, and the vasoconstrictor thromboxane (TX) A_2. Both PGE_2 and $PGF_2\alpha$ are closely associated with the initiation of labor and preterm labor, whereas thromboxane A_2 has been associated with preeclampsia.[18,19] Whereas the omega-3 fatty acid, DHA, is not usually considered to be involved with eicosanoid formation, EPA is a precursor for the 3-series of PGs and produces PGE_3 and PGI_3, which promote relaxation of myometrium.[20,21] Also, EPA and DHA competitively displace AA in the membrane phospholipids and thereby reduce production of 2-series eicosanoids.[22,23] Thus, a diet that provides a closer balance of omega-3 to omega-6 fatty acids may be as important to pregnant women as the absolute individual plasma levels of these fatty acids.

Nonetheless, in pregnancy, the real significance of EPA may be related to its role in mediating DHA and AA concentrations across the placenta rather than its production of the relatively less potent PGI_3. Free fatty acids need to be bound for transfer to the fetal circulation. Selective transport across the human placenta for individual fatty acids has been suggested as 1 mechanism to explain greater concentrations of some PUFAs like DHA and AA in the fetal, rather than maternal, circulation. In this regard, the effect of EPA on mRNA expression of fatty acid transport proteins (FATPs) becomes important.[24] EPA, but not DHA, has been positively correlated with mRNA expression of all membrane proteins. Thus, higher maternal EPA concentrations may increase FATP expression (FATP-4 in particular) that, in turn, has been shown to increase cord blood DHA levels.[24] In addition, the free fatty acids need to be bound to fatty acid binding proteins (FABPs) in order to gain entry into placental and fetal cells. Because, as noted above, EPA has been positively correlated with mRNA expression of all membrane proteins, higher EPA concentrations also lead to increased expression of FABPs including B-FABP, which is strongly expressed in developing brain cells and has a strong affinity for DHA.[25]

Much of the interest in omega-3 fatty acid intake and pregnancy began in the early 1980s, when Danish investigators determined that women living on the Faroe Islands delivered babies that were 194 g heavier and had gestation lengths 4 days longer than babies born in Denmark.

Because only about 4% to 11% of DHA is retroconverted to EPA,[10,11,26] pregnant women who just take DHA supplements, without any dietary EPA, may be unable to produce the right balance of eicosanoids and may limit the transport and uptake of DHA into fetal cells.[10,11,24-26]

Clinical Trials

Benefits of Omega-3 Fatty Acids

Much of the interest in omega-3 fatty acid intake and pregnancy began in the early 1980s, when Danish investigators determined that women living on the Faroe Islands delivered babies that were 194 g heavier and had gestation lengths 4 days longer than babies born in Denmark.[21] The Faroese diet had substantially more omega-3 fatty acids and less omega-6 fatty acids than a Danish diet. Red blood cell fatty acid content (expressed as the ratio of omega-3 to omega-6) was significantly higher in the Faroese pregnant women than in Danish pregnant women.[27] From this study, the authors theorized that a Danish woman who adjusted her diet to increase her blood ratio of these fatty acids by 20% would expect to increase gestation 5.7 days.[27]

Following up on their earlier epidemiologic work, the same Danish group then randomized pregnant women at week 30 of gestation to either a fish oil supplement (2.7 g omega-3 fatty acids, of which 920 mg were DHA), olive oil, or no supplement.[20] Women in the fish oil group had a gestational period 4 days longer than women taking either olive oil or no supplement. The babies born to the women in the fish oil group also weighed 107 g more than babies born to the women in the olive oil group, and 43 g more than those born to those mothers without supplementation. The supplemental amount of dietary omega-3 fatty acids used in this study was larger than a typical Danish diet, which only provided about 10% of this amount (ie, 270 mg of omega-3 fatty acids). Thus, it appeared that rather high amounts of omega-3 fatty acids need to be consumed to affect gestation and fetal weight.

Healthy pregnant women taking about 1 g of DHA a day from a marine oil supplement were able to deliver substantially more DHA to the fetus than those who were not given marine oils.

In a different Scandinavian trial, Norwegian pregnant women (n = 341) between gestational weeks 17 and 19 were randomized to consume omega-3 fatty acids from cod liver oil (ie, 2632 mg omega-3 fatty acids with 1183 mg as DHA) or corn oil daily, until 3 months after delivery.[28] Unlike the previous study, the primary outcomes of gestational length and birth weight did not differ between the two groups.[20] Interestingly, however, they did note that infants with the highest quartile concentration of DHA in the cord blood had a gestational period 9.3 days longer than those in the lowest quartile. Thus, it appeared that although increased delivery of DHA to the fetus may be of benefit, how much DHA gets to the fetus may be entirely related to maternal intake.

Later, these same investigators evaluated the fatty acid content of the blood of the mothers and babies from the previous study.[28,29] No maternal blood fatty acid differences occurred at baseline. However, at the end of pregnancy the maternal plasma omega-3 fatty acids (eg, EPA and DHA) and the ratio of omega-3 to omega-6 fatty acids were higher in the mothers who were assigned to the cod liver oil supplement compared with those in the corn oil group. In addition, fetal DHA umbilical cord plasma phospholipids were 23% higher in babies born to mothers in the cod liver oil group compared with those born to mothers in the corn oil group. Thus, healthy pregnant women taking about 1 g of DHA a day from a marine oil supplement were able to deliver substantially more DHA to the fetus than those who were not given marine oils. Finally, and most importantly, 4 years later, when these authors evaluated this same Norwegian cohort of infants, they concluded the children had higher mental processing scores when born to mothers supplemented with cod liver oil (rich in EPA and DHA, omega-3 PUFAs) during pregnancy and lactation, compared with children of mothers who were supplemented with corn oil (rich in linoleic acid, omega-6 PUFAs).[30]

In the same vein, an Australian group also looked at infant cognition in a similar trial and found similar results.[30,31] At 20 weeks of gestation until delivery, 98 women were randomized to receive either fish oil (2.2 g DHA and 1.1 g EPA/day) or olive oil. At birth, infants from mothers in the fish oil–supplemented group had higher DHA and EPA levels and lower AA levels in the cord blood compared with children born to mothers in the olive oil–supplemented group. When evaluated at 2.5 years of age, children in the fish oil–supplemented group (n = 33) had higher scores for eye and hand coordination compared with those in the olive oil group. In this study, as in others, eye and hand coordination scores and other tests of mental acuity correlated with omega-3 levels (EPA and DHA) in cord blood erythrocytes, and inversely correlated with omega-6 levels (AA).[23,31]

Benefits of DHA-Only Supplementation

The time of the most rapid neural and retinal development occurs in the second half of pregnancy, mainly during the third trimester. On this basis, supplementation of the maternal diet later in pregnancy with omega-3 fatty acids, especially DHA, was thought to be especially important.[3,7,11,14,15] In a trial focused on the benefits of naturally occurring DHA from food, a sample of pregnant Inuit women living in Arctic Quebec was assessed.[23] Maternal DHA blood concentrations were shown to be directly related to cord plasma phospholipid levels, and the correlation of the DHA/AA ratio in maternal and cord plasma was even stronger. In this study, higher DHA cord blood concentration was related to longer gestation, better visual acuity and mental and psychomotor skills at 6 months and 11 months, suggesting that raising DHA concentrations alone may independently yield some benefits. (It must be noted that the Inuit population has a dietary intake of EPA and DHA that is higher than most other nations because of their regular intake of fish and marine animals. Such foods are also rich in EPA, but it was not measured.)

A second study providing large amounts of DHA as a supplement explored its effects during pregnancy and, later, on fetal cognition.[3] From week 16 of gestation until delivery, healthy Canadian women (average age, 33 years) who were not taking supplemental fish oil capsules were randomized to 400 mg of algae-derived DHA or a blend of corn and soybean oil. The purpose of the study was to compare red blood cell (RBC) DHA levels, dietary intakes of DHA and other omega-3 fatty acids, and infant visual acuity at 60 days of age. At week 36, DHA in the supplemented women was 32% higher than the control group, and no differences were found between the groups for EPA and AA, both of which decreased. Infants were 3 times more likely to have low visual acuity scores in the placebo group than the DHA group, indicating that the usual diet may have had insufficient DHA to maximize visual acuity in infants. In fact, omega-3 fatty acid deficiency, as measured by RBC DHA, was more prevalent in the control group than in the DHA-supplemented group.

Lack of Omega-3 Fatty Acids in the Western Diet

The trials outlined above (and numerous others not mentioned) provide a compelling argument for the essential nature of omega-3 PUFAs during pregnancy. Yet, the typical Western diet is notably deficient with respect to them. Three studies demonstrated that pregnant women likely consume inadequate omega-3 fatty acids.[7,32,33] In a Canadian study, pregnant women were found to consume only 1.5 g of omega-3 fatty acids per day, of which only 117 mg were from EPA and DHA.[7] This is below what is considered adequate for a nonpregnant woman, and quite inadequate in DHA.

A Danish survey study conducted in high-risk pregnant women showed that dietary omega-3 fatty acids were inversely related to the risk of preterm delivery.[33] Women consuming less than 150 mg of omega-3 fatty acids a day (ie, less than 0.5 oz of fish per day) were at the highest risk of delivering prematurely. Of those who ate no seafood and did not use fish oil supplements, the rate of preterm delivery was 7.1%, compared with 1.9% in those who regularly ate fish. Thus, for high-risk pregnant women, omega-3 fatty acid intake seemed to have an important effect on reducing spontaneous premature births. Unlike the Canadian study, the Danish women who regularly ate fish appeared to obtain adequate omega-3 fatty acids from the diet alone and did not require supplementation.

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Finally, in the United States, there is considerable evidence of inadequate seafood consumption. In a review of the 1999-2000 National Health and Nutrition Examination Survey, Smith and Sahyoun concluded that only 19% of American adults consume the recommended 2 servings of fish each week.[34] Furthermore, Oken and colleagues reported that after a well-publicized January 2001 federal advisory regarding methylmercury contamination in certain fish species, seafood consumption of all species decreased in pregnant American women, even as recommendations were publicized by nutritional groups as to the benefits of seafood for pregnant women.[35]

Dietary Sources of Omega-3 Fatty Acids

As noted above, the typical Western diet is deficient in omega-3 PUFAs, in general, and in DHA in particular. Although seafood is a good source of both DHA and EPA, concerns about mercury contamination have led to both fear and confusion about whether to recommend it during pregnancy. Both the Environmental Protection Agency and The American College of Obstetricians and Gynecologists recommend that women consume 12 ounces of seafood per week from low-mercury species (Table 1).[36,37]

The mercury found in 2 servings of the approved seafood poses little risk to the fetus.[38,39] The only evidence of fetal neuron-developmental abnormalities was seen in infants whose mothers consumed known, high amounts of mercury-rich seafood. The mercury intake of these women was much higher than what an American woman would get from eating 2 servings of low-mercury fish per week (10-30 ppm vs $<$ 0.05 ppb, respectively). These conclusions are further corroborated by the Project Viva data where children born to mothers eating more than 2 weekly servings of fish performed better on language and visual and motor tests at 3 years of age compared with children born to mothers who ate less than this amount.[40] Only 12% of the 341 pregnant women consumed more than 2 servings of fish per week. No adverse effects of maternal mercury concentrations were observed. Maternal consumption of fish lower in mercury resulted in stronger benefits to the offspring, and thus underscores the importance of consuming low-mercury seafood during pregnancy.

The typical Western diet is deficient in omega-3 PUFAs, in general, and in DHA in particular.

For those seeking to avoid seafood, there are few nonsupplement options. Plant-based omega-3 fatty acids (ie, α-linolenic acid [ALA]), like flaxseed oil, are poorly converted to the biologically active omega-3 fatty acid EPA, and converts even less to DHA.[3,10,11,26,41] The range of conversion of ALA to EPA is generally between 0.2% and 9%, although some authors have suggested that women of childbearing age may be able to convert up to 21% of their dietary ALA to EPA. Regardless of which conversion factor is correct, trying to obtain all omega-3 fatty acids from plant-based oils requires ingestion of too many fat calories.

Unfortunately, it is impossible for pregnant women to meet their omega-3 fatty acid requirements from omega-3-rich vegetable oils and 2 servings of seafood a week (Table 1). Two servings of fish per week only provide about 100 to 250 mg per day of omega-3 fatty acids, of which 50 to 100 mg is from DHA; plant-based oils supply insignificant amounts of EPA and no DHA. During pregnancy, the dietary goal for omega-3 fatty acids is 650 mg, of which 300 is DHA.[42] Thus, in order make up the omega-3 fatty acid deficit in the diet, pregnant women are left with essentially 2 choices: fish oil supplements supplying EPA and DHA, or algae-derived DHA. Specifically, depending upon the omega-3 content of the seafood consumed during the week, each day pregnant women would need an additional 400 to 550 mg of omega-3 PUFAs (EPA and DHA), of which about 225 mg should be DHA.

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Fish oil supplements are commercially available from multiple companies. The amount of EPA and DHA per capsule varies, but most contain one-third to one-half of these omega-3 fatty acids (eg, in a 1000-mg capsule, 300 or 500 mg would come from EPA and DHA). Most commercially available fish oil supplements contain less than 1 to 2 ppb of mercury compared with less than 0.05 ppb in seafood, but because the amount of fish oil used (1-2 g a day) is much smaller than what is consumed when eating seafood (200 g twice a week), the risk of mercury toxicity is inconsequential. Cod liver oil is considered a less desirable source of EPA and DHA, because it is also rich in vitamin A, unlike other fish oils. Long-term use of vitamin A has been associated with an increased risk of osteoporosis.[45]

Meaningful vegetarian sources of DHA are essentially limited to algae-derived DHA from Martek Biosciences (Columbia, MD). Using a strain of algae, *Crypthecodinium cohnii*, which is a naturally high producer of DHA, DHA oil is produced in US Food and Drug Administration–inspected, environmentally controlled manufacturing facilities. Although free of any environmental contaminants such as mercury, the oils do not contain any EPA and data demonstrating the benefits in pregnancy of DHA alone are lacking.

Table 1
How to Meet Omega-3 Fatty Acids Needs During Pregnancy[10,12,38,39,43,44]

Daily Needs for Omega-3 Fatty Acids	How to Meet Need
1.4 g of omega-3 fatty acids as linolenic acid from vegetable oils	Choose vegetable oils that are rich in the omega-3 fatty acid linolenic acid and low in the omega-6 fatty acid, linoleic acid Meet 1.4 g linolenic acid via 1/2 tsp flaxseed oil, 1 tbsp canola oil, or 1 tbsp + 1 tsp soybean oil
650 mg omega-3 fatty acids as EPA and DHA, of which 300 mg are from DHA	Reduce intake of vegetable oils rich in omega-6 fatty acids (eg, sunflower oil, corn oil, cottonseed oil)
Consume 2 servings of low-mercury (< 0.05 μg/g [ppb]) seafood per week	Total milligrams of omega-3 fatty acids in 1 6-oz serving (milligrams of DHA in parentheses). Unless noted each entry below has < 0.05 ppb of mercury Shrimp 880 mg (320 mg)[39] Salmon 620 mg (260 mg)[39] Pollock 520 mg (360 mg)[39] Catfish 340 mg (180 mg)[39] Scallops 740 mg (360 mg)[39] Sardines 2.2 g (1.2 g)[44] Light tuna 380 mg (170 mg) (<0.12 ppb)[39] Based on consuming 2 fish servings a week, the average intake per day of omega-3 fatty acids is 100-250 mg omega-3 fatty acids and 50-100 mg DHA
Remainder of the 650 mg EPA and DHA	Use fish oil capsules containing EPA and DHA Require 400-550 mg omega-3 fatty acids, with 225 mg as DHA each day Use 1 or 2 capsules/day to meet these needs Examples of commercially available products in milligrams Total omega-3 / DHA / Amount 300 / 120 / 2 capsules 640 / 260 / 1 capsule

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Recommendations

There is little doubt that pregnant women need at least as many omega-3 fatty acids as nonpregnant women, and likely need more DHA.[10,14,42] The recommendations for dietary omega-3 fatty acids should be adopted at the onset of pregnancy, but there may be benefits for all women who are considering becoming pregnant. Given concerns for mercury toxicity with overconsumption of certain fish, in order to meet these recommendations, pregnant women will need to consume omega-3 fatty acids from 3 sources: vegetable oils, 2 servings of seafood per week, and omega-3 fatty acid supplements containing EPA and DHA or DHA alone. Intake of omega-6–rich oils found in sunflower, corn, and cottonseed oils should be minimized because they are converted to substrates that compete with EPA. Pregnant women should reduce their intake of these oils and substitute others that are rich in omega-3 fatty acids like flaxseed, canola, and soybean oil.[42,46] ■

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Main Points

- Docosahexaenoic acid (DHA) is a major structural fat in the human brain and eyes, representing about 97% of all omega-3 fats in the brain and 93% of all omega-3 fats in the retina.
- DHA is particularly important for fetal development of the brain and retina during the third trimester and up to 18 months of life.
- The balance between omega-3 fatty acids and omega-6 acids may be important, and the omega-3 fatty acid eicosapentaenoic acid (EPA) may play an important role in DHA transplacental transport and intracellular absorption.
- Pregnant women likely have an increased need for essential omega-3 fatty acids compared with women who are not pregnant.
- Fish consumption, although an excellent source of both DHA and EPA, may contain mercury contamination and should therefore be limited to 2, 6-ounce, low-mercury seafood servings a week, such as shrimp, salmon, pollock, catfish, scallops, and sardines.
- Both fish oil supplements, containing both EPA and DHA, and algae-derived DHA-only oils are good, mercury-safe means of supplementing the diet of a pregnant woman.

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