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# Nutritional roles of omega-3 fatty acids during pregnancy and neonatal development

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**FACULTY DISCLOSURES**

Dr. McGregor has served on the speaker's bureau for Ther-Rx Corp and 3M Pharmaceuticals. Dr. Carlson has served as a consultant to Mead Johnson Nutritionals and Wyeth Laboratories and has received research grants from Omega Tech, Inc (Martek Biosciences). Dr. Hobel receives grant/research support from PROP-10 Commission, Los Angeles; the National Institute of Child Health and Human Development; and serves on the speaker's bureau of Cedars-Sinai Medical Center. Dr Meis and Dr Ogburn have nothing to disclose.

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Preterm birth of low-birth-weight infants (<2,500 g) is the commonest cause of preventable neonatal morbidity and lifetime disability in the United States. Babies born "too soon" contribute to direct and indirect health care costs and health professional liabilities.[1] Despite advances in obstetrical care, the number of low-birth-weight infants in the United States increased by 11.8% between 1980 and 2000. The number of very-low-birth-weight infants (<1,500 g) increased even more dramatically (24.3%).[2]

Recent research suggests effective and practical nutrition-based strategies to reduce risks of preterm delivery and optimize child development. The Second Nutrition Special Interest Group addressed these important issues at the 2003 meeting of the Society of Maternal-Fetal Medicine. Highlights of the meeting, including recent research, are outlined, along with rationales and means for providing greater quantities of omega-3 fatty acids in the diet, including supplementation with prenatal vitamins.

**New findings suggest pregnant women and lactating mothers should pay close attention to nutrition, including ensuring sufficiency with omega-3 fatty acids.**

# Omega-3 fatty acids in fetal development

By James A. McGregor, MD

Ensuring maternal and prenatal nutritional sufficiency represents a practical, inexpensive strategy to optimize pregnancy and perinatal and lactational outcomes. New findings suggest that pregnant women and lactating mothers should pay close attention to their nutrition, including ensuring sufficiency of omega-3 fatty acids, especially docosahexaenoic acid (DHA). These fatty acids can be obtained by consuming

**Omega-3 fatty acids are particularly important for healthy pregnancy and brain and vision development and functioning in the baby.**

safe fish or DHA supplements, including selected prenatal vitamins. Randomized controlled trials and observational studies have confirmed that supplementation during pregnancy with the omega-3 fatty acids DHA and eicosapentaenoic acid (EPA) is associated with increased length of gestation, higher birth weight and term birth rates, and reduced risk of short gestation and low birth weight in women with prior preterm birth.

These long-chain polyunsaturated fatty acids, required for health, must be consumed in the diet, since the human body is generally unable to synthesize them in sufficient amounts. The omega-3 fatty acids DHA and/or EPA are particularly important for healthy pregnancy and brain and vision development and functioning in the baby (**Table 1**). The biosynthesis and principal physiologic roles of essential fatty acids (EFAs) are illustrated in **Figure 1**.

Modern diets are typically deficient in omega-3 fatty acids, which are most easily obtained by eating oily fish. Instead, contemporary diets are high in omega-6 fatty acids (dairy products, meats, fried or "fast" foods, and animal and vegetable oils). In contrast, the diets of our preindustrial ancestors consisted of unprocessed or wild foods characteristically available in grassy, forest, or shore environments. These foods provided an optimal 1:1 ratio of omega-3 to omega-6 fatty acids.

Maternal deficiency of omega-3 fatty acids may

**TABLE 1**

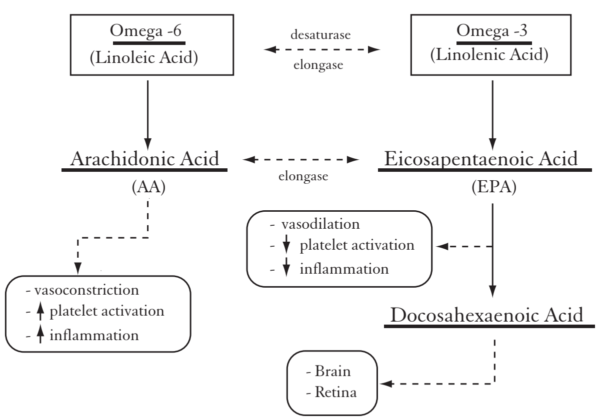
**Important omega fatty acids**

| | |
|---|---|
| *Omega-3 fatty acids* | |
| Alpha-linolenic acid | LNA |
| Eicosapentaenoic acid | EPA |
| Docosahexaenoic acid | DHA |
| *Omega-6 fatty acids* | |
| Linoleic acid | LA |
| Arachidonic acid | AA |

Adapted with permission from McGregor JA, et al. *Obstet Gyn Survey.* 2001;56:S1-S13.[1]

**FIGURE 1**

**Biosynthesis and physiologic roles of essential fatty acids**



be involved in the growing number of preterm births and other developmental problems in industrialized societies.

New research suggests activities that pregnancy care providers can take today:

1. Ensure nutritional sufficiency prior to conception as well as during pregnancy, lactation, and the interconceptional period;
2. Advise pregnant women and those trying to conceive to avoid missing meals, especially breakfast;
3. Stress the importance of an appropriate body mass index (BMI) prior to pregnancy, as well as appropriate weight gain during pregnancy; and
4. Encourage women to avoid smoking and other substance use prior to and during pregnancy.

Increased dietary or supplementary omega-3 fatty acids may become "the new folic acid" in terms of their fetal and neonatal benefits, which may persist through childhood and beyond. Animal studies focusing on prenatal nutrition suggest that benefits may even extend through several generations.

Clinical studies show that the omega-3 fatty acids may help to:

- Optimize the length of gestation,
- Reduce the risk for repeated prematurity,
- Optimize birth weight,
- Increase nutritional value of mother's milk,
- Contribute to early development of the infant brain and retina, and
- Produce the omega-3-derived eicosanoids required for relaxation of uterine smooth muscles and vessels during pregnancy (**Figure 1**).

Clinicians should also note that fetal nutritional deficiencies early in pregnancy are not necessarily offset by dietary improvements later in pregnancy. Moreover, maternal deficiencies of omega-3 fatty acids (DHA, EPA) tend to be compounded in the fetus.[1]

**Long-term maternal benefits of EFAs.** Well-established benefits of EFAs include improved vascular function, reduction in triglycerides, inhibition of pro-inflammatory molecules, improved gastric function, and reduced risk for such conditions as coronary artery disease, sudden cardiac death, and possibly depression.

The positive relationship between high consumption of omega-3 fatty acids and low cardiovascular mortality rates was initially revealed during studies of the Greenland Inuit, who tradi-

**TABLE 2**

### Essential fatty acids in history

| |
|---|
| 1920s |
| • Burr and Burr fed a fat-free diet to rats and observed scaly skin and reproductive problems |
| 1940s-1960s |
| • Holmon made strides in research on omega-3, -6, and -9 fatty acids |
| 1960s-1980s |
| • Crawford and others studied role of EFAs in fetal brain development |
| • Bergstrom and Samuelsson discovered EFAs were precursors to the prostaglandins involved in relaxation of uterine smooth muscle |
| 1980s |
| • Walsh and others described role of prostacyclin in vascular relaxation in pregnancy |
| • Holman and colleagues noted that normal pregnancy has an EFA deficiency pattern |
| 1990s-2000s |
| • Broadhurst suggested that omega-3 fatty acids were important in the evolution of Homo sapiens, who lived near bodies of water and ate fish |

EFA = essential fatty acid

Ogburn PL Jr. Essential fatty acids and prostaglandins in pregnancy. *In*: Cowett RM, ed. *Principles of Perinatal Metabolism*. 2nd ed. New York: Springer-Verlag; 1998:259-280.[3]

**Increased omega-3 fatty acids may become 'the new folic acid' in terms of fetal and neonatal benefits.**

tionally consume high quantities of oily fish and marine mammals. Their consumption of omega-3 fatty acids is very high, averaging 10 g for each 3,000 kcal. These populations have a very low incidence of coronary artery disease and myocardial infarction despite their high cholesterol intake.

**Classic symptoms of EFA deficiency.** The importance of EFAs in the diets of pregnant animals and humans was recently reviewed.[1] Deficiency can deter growth; produce dry, flaky skin; cause hair loss; lead to diarrhea; contribute to infections; retard wound healing; cause anemia; produce behavioral changes; and cause neurologic disorders.

**In animal experiments, DHA and EPA deprivation leads to impaired brain development.**

### EFAs and the fetus

Given the importance of EFAs, it is not surprising that they are essential for intrauterine growth and development.

**The cellular level.** Both arachidonic acid (AA) and DHA are essential structural components of biomembranes.[4] Accordingly, the developing fetus has a high demand for these substances, particularly during third-trimester formation of vascular and neural tissues. Products of DHA and EPA stimulate vasodilation, decrease platelet aggregation, and reduce inflammation (**Figure 1**).

**Neural formation.** Most human brain and special sensory development occurs before birth. In fact, the number of brain cells peaks at 20 weeks' gestation. In the latter half of the second trimester and throughout the third trimester, up to 70% of the nutrients that cross the placenta are directed toward development of the central nervous system. Both DHA and AA are abundant in the brain and retina, and accretion rates increase as gestation progresses.[5-7] It has been estimated that the fetus accumulates around 400 mg per kilogram per day of omega-6 and 50 mg per kilogram per day of omega-3 fatty acids during the third trimester.[8] Demand for both omega-3 and omega-6 fatty acids remains high for at least 2 years after birth.[5,9-10]

In animal experiments, DHA and EPA deprivation leads to impaired brain development. Conversely, omega-3 fatty acid consumption during gestation improves the performance of the offspring in multiple test regimens.

**Cognitive development.** The high fatty-acid content of infant brain and neural tissues suggests that DHA and AA consumption play an important role in cognitive development during pregnancy and lactation. In a randomized, controlled, blinded study, 341 pregnant women were given omega-3 supplementation (EPA and DHA) from 18 weeks of pregnancy to 3 months postpartum.[11] Supplementation led to a substantial increase in the DHA level in breast milk. In addition, the children's mental processing scores at 4 years of age showed a significant correlation with maternal intake of DHA and EPA during pregnancy.

**Visual acuity.** Studies have assessed the potential relationship between visual development and fish oil (DHA, EPA) consumption. In one study, children aged 3.5 years who had been healthy, full-term infants were evaluated. Breastfeeding over 4 months and the daily intake of oily fish by the mother during pregnancy were both associated with higher levels of visual development in infants.[12]

**Lower diabetes rates.** A trial in Scandinavia shows that offspring of women who consume a cod liver oil supplement during pregnancy experience a reduction in type 1 diabetes.[13]

**Overall health.** Clearly, the polyunsaturated fatty-acid status of the developing fetus and breastfeeding baby depends on the cumulative effects of maternal nutrition and supplement use. Given the current lack of omega-3 fatty acids in the American diet, many women who become pregnant have an existing deficit that will only increase during pregnancy, often leading to a relatively low neonatal status of omega-3 fatty acids.

Potential means to promote nutritional sufficiency or optimization include consumption of oily fish without mercury or polychlorinated biphenyls (PCBs), and supplementation with omega-3 (DHA, EPA) fatty acids and multivitamins containing folate and antioxidants. While no specific minimal daily requirement for EFAs exists, a number of international health organizations have recommended levels for individual populations (**Table 3**).[1]

**TABLE 3**

**Recommended daily values/intake for omega-3 fatty acids**

| POPULATION / DAILY RECOMMENDED VALUE OR INTAKE | ORGANIZATION / REFERENCE |
|---|---|
| **Adults**: eat at least 2 portions of fish per week. **Patients with CHD**: Consume 1 g omega-3s (EPA/DHA) daily; supplement as needed | American Heart Association, Feb. 25, 2003 |
| EPA/DHA 0.5% energy (1.2 g/day); LNA 1% energy (2.5 g/day) | British Nutrition Foundation Briefing Paper: Omega-3 Fatty Acids and Health, July 1999 |
| **Adults** (based on 2,000 kcal diet): EPA/DHA 0.65 g/day 0.3% energy DHA minimum, 200-300 mg/day EPA minimum, 200-300 mg/day **Pregnant women:** 300 mg/day | International Study for the Society of Fatty Acids and Lipids. Workshop on the Essentiality of and Dietary Reference Intakes (DRIs) for Omega-6 and Omega-3 Fatty Acids. National Institutes of Health, April 7-9, 1999 |
| **Term infants:** 20 mg/kg body weight **Preterm infants:** 40 mg/kg body weight | World Health Organization. Fats and Oils in Human Nutrition; Report of a Joint Expert Consultation. FAQ Food and Nutrition Paper 57. Rome: FAQ and WHO, October 1993 |

Adapted with permission from McGregor JA, et al. *Obstet Gyn Survey.* 2001;56:S1-S13.[1]
CHD = coronary heart disease; LNA = alpha-linolenic acid

## Stressors, preterm birth, and EFAs

By Calvin J. Hobel, MD

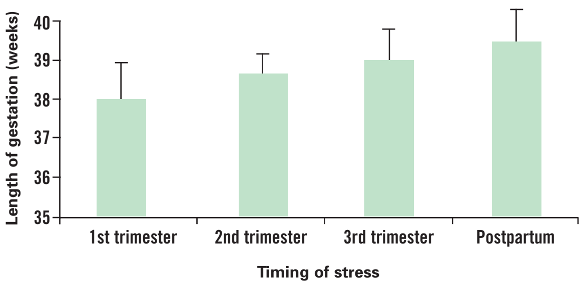
Preterm birth is a complex disorder that may involve a range of stressors including fasting, psychosocial and environmental stress, and irregular eating habits. Nutritional deficiencies in pregnant women and their timing are important parts of this paradigm. Prenatal stress can produce an adverse effect on the fetal neuroendocrine system as early as 13 weeks. Additionally, specific medical conditions increase the risk for preterm birth and are associated with higher levels of stress-related hormones, including corticotropin-releasing hormone (CRH). Although some stressors cannot be controlled, proper nutrition during pregnancy is one factor that may help to reduce or counter their adverse effects.

**Fasting.** Generally considered to mean not eating for more than 13 hours, fasting is a potent stressor in pregnant women.[14] Food withdrawal stimulates the hypothalamic-pituitary-adrenal (HPA) axis.[15] The resulting increase in cortisol secretion stimulates an increase in CRH, which is associated with the onset of labor and preterm birth.

Pregnant women with higher CRH concentrations tend to be African American, poor, and married; they also tend to have a high BMI and more than 3 children.[16] Studies of glucose excursions over 24 hours and insulin excursions after eating suggest hypoglycemia as another possible stressor in pregnancy.

**FIGURE 2**

**Shorter gestation associated with environmental stress in 1994 California earthquake**




Source: Glynn LM, et al. *Am J Obstet Gynecol.* 2001;184:637.[17]

**Irregular eating habits.** About 30% of pregnant women fail to eat the recommended 3 meals and 2 snacks per day.[15] Patients must understand that missing breakfast can result in a fasting period of 13 hours or longer for both the woman and her fetus (since dinner the previous night), with possible negative consequences including short gestation and low birth weight.

**A meta-analysis showed that a higher consumption of omega-3 fatty acids was associated with lower rates of postpartum depression.**

**Environmental stressors.** The physician should assess potential environmental stressors that may affect both the maternal and fetal neuroendocrine systems. For instance, women in their first trimester during the 1994 earthquake in Northridge, California, had shorter gestations (**Figure 2**).[17] Currently, there is interest in the World Trade Center disaster as a major stressor during pregnancy. Inclusion of omega-3 fatty acids in the diet and avoidance of fasting or elective weight loss are strongly recommended for women who have experienced unavoidable stressors.

**Postpartum depression.** Studies suggest that a dietary deficiency of DHA or other omega-3 fatty acids may be associated with depressive disorders such as postpartum depression.[18] A meta-analysis of 14,532 women in 22 countries showed that a higher consumption of omega-3 fatty acids in seafood was associated with lower rates of postpartum depression.[19] Also, higher concentrations of DHA in breast milk were linked to low rates of postpartum depression. An investigation of the effects of omega-3 supplementation in postpartum depression is under way at the University of Arizona.

**Mental status in nonpregnant women.** The administration of DHA has been variously linked to improvements in postpartum depression, schizophrenia, attention deficit disorder, bipolar disorder, and borderline personality disorder, suggesting a possible psychotropic effect. Studies are being developed to determine whether DHA is a safe and effective antidepressant or antipsychotic agent.[18]

**Preeclampsia.** Preeclampsia is characterized by enhanced platelet aggregation and vasoconstriction and is related to an elevated ratio of thromboxane $A_2$ to prostacyclin $I_2$. Differing levels of certain fatty acids have been found in the umbilical arteries, veins, and platelets of women with preeclampsia versus those without preeclampsia.[20]

In a case-control investigation, women with the lowest measured levels of omega-3 fatty acids relative to omega-6 fatty acids were 7.6 times more likely to develop preeclampsia than women with a more normal balance of these substances.[21] Increasing the ratio of omega-3 to omega-6 fatty acids reduced the risk of preeclampsia by 46%. (The ideal ratio for these substances is 1:1.) This indicates a potential benefit of increased dietary consumption of omega-3 fatty acids before and during pregnancy.

**Multiple pregnancies and progressive EFA losses.** During pregnancy, the mother loses 50% of her EFA stores. If she breastfeeds, she will lose 50 to 80 mg of EFAs daily from lactation alone.[22] An average of 26 weeks is needed to recover EFA stores lost during pregnancy.[22]

Further, the neonatal DHA status is generally lower in infants born later in the birth order.[23] This suggests that, given the prevailing dietary habits in this country, maternal transfer of EFAs to the fetus is not sufficient to ensure optimal fetal development.[24] Neonatal EFA status can be improved by supplementation during pregnancy. For optimal results, the supplement should contain both omega-3 and omega-6 fatty acids.[22]

### EFA requirements during pregnancy: A guide

In the United States, the recommended amount of EFAs for pregnant women is approximately 200 to 300 mg per day (**Table 3**). In one study, less than 2% of women met the recommended intake.[25] The average daily intake of omega-3 fatty acids among American women is only about 54 mg of DHA and 22 mg of EPA per day. This is about 20% to 60% of the daily intake recommended by the International Study for the Society of Fatty Acids and Lipids at the National Institutes of Health in 1999 (see **Table 3**). In contrast, the mean daily intake of omega-6 fatty acids (e.g., as contained in various vegetable oils used in cooking) exceeds by 200% the recommended upper limit proposed by that authoritative group.

**Infants with low fat reserves.** Adipose tissue reserves are usually attained during the third trimester. Premature infants with their low fat reserves require special attention. While EFA deficiency has been associated with low birth weight, some studies have also revealed EFA insufficiencies in high-weight and large infants.[24]

Accumulating evidence (discussed below) shows that dietary consumption and/or supplementation with omega-3 fatty acids can extend gestation and reduce the incidence of preterm births. It would also be informative to measure CRH levels in pregnant women who eat DHA-enriched eggs, or who take fish oil supplements containing omega-3 fatty acids. These supplements may reduce the production of pro-inflammatory cytokines and levels of CRH in the mother, which may explain the lower risk of preterm birth with increased omega-3 fatty acid supplementation.

**A study of Colorado women who delivered preterm showed low omega-3 levels, suggesting dietary deficiency.**

## Increasing gestation by feeding omega-3 fatty acids

By Susan Carlson, PhD

Interventions for optimizing the length of gestation with omega-3 fatty acids have been evaluated in randomized, controlled clinical trials. In their review, McGregor et al[1] provide a detailed analysis of key studies on omega-3 and omega-6 fatty acids in pregnancy conducted between 1996 and 1998. Results of other trials—including more recent studies—are discussed below and provide important information for clinicians.

**Reduced omega-3 levels in Colorado mothers and preterm infants.** Fatty acid levels in the erythrocytes and plasma of Colorado women during pregnancy were measured by Reece and McGregor,[26] who also analyzed amniotic membranes from preterm births. The mothers consumed large amounts of omega-6 fatty acids in food but ate little or no fish and thus ingested little or no omega-3 fatty acids.

▪ **Results.** Both mothers and preterm babies showed reduced levels of omega-3 fatty acids suggestive of a dietary deficiency. When 37 preterm babies were compared with 34 control term infants, the mothers of the preterm babies showed:

- A 42% greater level of arachidonic acid (omega-6) in maternal plasma and a 10% increase in linoleic acid (omega-6) in maternal plasma.

**TABLE 4**

**Foods high in omega-3 fatty acids**

| |
|---|
| Fish and fish oils—high in both DHA and EPA<br>• Ocean fish preferred to avoid mercury and PCBs<br>• Avoid eating shark, mackerel, swordfish, tilefish, and most freshwater fish unless harvested from fish farms; fresh tuna is preferable to canned |
| Eggs enriched with DHA |
| Canola, soy, flaxseed, walnut oils |
| Meat from beef cattle or bison fed on grass or a flaxseed additive |
| Web: Omega-3 Information Service (www.omega-3info.com) |

- A decrease of 34% in omega-3 fatty acid concentrations in maternal plasma.

## Fish oil consumption associated with lower rates of preterm delivery and increased birth weight

Several groundbreaking studies in Denmark, especially those by Olsen and colleagues, have evaluated the effects of fish oil on gestation.

**1986 study.** Olsen et al[27] compared the duration of gestation in women who lived on the Faroe Islands off Denmark (and who typically consume large amounts of marine lipids rich in omega-3 fatty acids) with that of women who lived on mainland Denmark and consume high levels of omega-6 fatty acids.

**These supplements may reduce the production of pro-inflammatory cytokines and CRH levels in the mother.**

▪ **Results.** Women who lived on the Faroe Islands had significantly longer gestations and higher birth weights than women of mainland Denmark. A 20% increase in the omega-3:omega-6 ratio in erythrocytes of women who consumed a diet high in fish was correlated with a significant 5.7-day increase in length of gestation.

**1992 study.** Olsen's group[28] randomized 533 pregnant women to receive 4 g of fish oil, 4 g of olive oil, or no supplementation, beginning at 30 weeks of gestation.

▪ **Results.** The group taking fish oil showed an increase of 4 days of gestation, and there was a significant increase in birth weight of 107 g.

**2000 study.** Olsen et al[29] evaluated the preventive effects of omega-3 fatty acids given as capsules containing fish oil versus control capsules containing olive oil in 232 women with a history of preterm delivery. The randomly assigned supplement was administered from about 20 weeks' gestation until delivery.

▪ **Results.** Women with a history of preterm deliveries who received the fish oil supplement, which contained 2.7 g of omega-3 fatty acids as prophylaxis, showed an increase in gestation of 8.5 days.

**2002 study.** A recent prospective study by Olsen[30] enrolled 5,000 pregnant Danish women who completed questionnaires regarding fish intake at gestation and weeks 16 and 30. Data on birth weight and premature deliveries were evaluated.

▪ **Results.** A significant decrease in the number of premature deliveries was seen in the mothers who consumed 150 mg per day or more of omega-3 fatty acids from fish or fish oil. Birth weights of their infants were also significantly higher. A 4-day increase in gestation was observed in women who consumed 2.7 g per day of omega-3 fatty acids given as fish oil from the 30th week of gestation.

When these women were classified by the amount of fish in their diet, the risks of preterm delivery were nearly 4 times higher (7.1%) in the group that never ate fish, compared with the group that consumed fish at least once a week (1.9%). Risks were greatest below a daily intake of 150 mg of omega-3 fatty acids or 15 g of fish. A low consumption of fish in early pregnancy increased the risk for preterm delivery by a factor of 4. These findings agree with those of Olsen's previous randomized trials.

## US studies show DHA supplementation lengthens gestation

Studies in the United States show that even small increases in omega-3 fatty acids given as DHA lengthen gestation. Eggs enriched with DHA are commercially available in this country and are produced by feeding hens a diet containing 1% DHA-rich marine algae. We conducted a pilot study to determine whether increased amounts of DHA in the diets of pregnant women would influence the length of gestation.[31]

**Pilot study.** A small randomized, controlled, double-blind pilot study was conducted in 1995[31] to determine the acceptability of eggs as a means of increasing DHA intake. Participants were gravidas in Memphis, Tennessee, who had a low prestudy dietary intake of DHA of about 50 mg per day. They received 12 ordinary eggs or 12 enriched eggs from hens fed a diet high in DHA. Both groups of women consumed about 9 eggs per week.

▪ **Results.** The group that received the high-DHA eggs (135 mg DHA per egg) from 24 to 28 weeks showed an increase in length of gestation as well as infant birth weight, compared with the group that received the ordinary eggs (18 mg DHA per egg). These findings suggest that DHA supplementation at levels as low as 117 mg could significantly improve pregnancy outcomes.

A later study conducted in Kansas City between 1998 and 2001 and published in 2003 was powered to determine whether high-DHA eggs could increase gestation.[32] The study was powered to determine an increase in gestation of 5.25 days.

**1998-2001 study.** In this double-blind, controlled investigation, we enrolled 350 pregnant women from 1998 to 2001, and 291 (83%) completed the study.[32] Duration of gestation was the primary outcome evaluated. Participants were randomized to consume either high-DHA eggs (a mean of 133 mg DHA per egg; 176 women) or ordinary eggs (mean of 33 mg DHA per egg; 174 women). Subjects were given 12 eggs per week throughout the study, starting between weeks 24 and 28 of pregnancy. Gestational age was determined by ultrasound examinations performed between 15 and 20 weeks. The mean intake was just over 7 eggs per week.

▪ **Results.** After controlling for risk factors, gestation was significantly increased by 6 days ($P<.009$) in the women who ate enriched eggs. Infant birth weight, body length, and head circumference showed clinically important increases that did not achieve statistical significance. These data indicate that even relatively low intakes of DHA—in the range recommended by the groups listed in **Table 3**—can increase gestation, body length, and head circumference.

**Similar findings from DHA-enriched egg and fish oil studies.** The extent of the increase in gestation seen with high-DHA eggs in our study in American women resembled increases obtained with fish oil in Danish women by Olsen et al,[28,29] even though the test eggs contained only DHA, while the fish oils contained both DHA and EPA. Increased duration of pregnancy was associated with a modest intake of omega-3 fatty acids. Although the total intake of omega-3 fatty acids in the studies with DHA-enriched eggs was less than 10% of that in the studies with fish oil, we observed a significant extension of gestation by 6 days. Thus, even supplementation with a relatively low dose of DHA showed a beneficial effect on gestation.

## Influence of DHA on cognition

Many published studies demonstrate a positive effect of omega-3 fatty acids on cognition.[33-37] We completed an observational study on the early development of attention in infants whose mothers had received high-DHA eggs. Infants born to women who had a red-blood-cell phospholipid level of DHA above the median at delivery—compared with those below the median at delivery—showed evidence of more mature attention development through 18 months of age.[38] Willats and Forsyth reported similar observations.[35] Although interventional studies are needed to determine whether improving maternal DHA status can improve the infant's cognitive development, these 2 observational studies suggest that a higher maternal DHA status would enhance infant development.

**The effects of poor nutrition on the fetus in early pregnancy cannot be offset by improving nutrition later.**

### Research with progesterone and omega-3 fatty acids

In a recent investigation in women at very high risk for short gestation and premature delivery supported by the National Institutes of Health, Meis and colleagues showed that daily injections of 17-hydroxyprogesterone caproate lengthened gestation and reduced preterm births.[39] Meis is now considering a randomized, controlled trial to determine whether daily supplementation with 2.7 g of omega-3 fatty acids, in addition to weekly injections of 17-hydroxyprogesterone caproate, might further reduce the rate of preterm births in high-risk women beyond what would be expected with the hormone alone. Findings may lead to a novel combination of nutritional and hormonal means of preventing preterm births in high-risk women.

## Clinical recommendations

Given the accumulating clinical evidence that omega-3 fatty acids are essential to the normal development of the fetal brain and retina, a number of strategies can be suggested to enhance the likelihood of an uncomplicated full-term pregnancy and improve fetal health and normal brain and retina development and functioning.

### Prevent or correct nutritional deficiencies before pregnancy

The effects of poor nutrition on the fetus in early pregnancy cannot be offset by initiating nutritional improvements later in pregnancy. Therefore, pre-pregnancy or interconceptional planning visits should be the standard of care for women who are likely to become pregnant. Breastfeeding women should receive similar nutritional support.

**Assess health and nutritional status.** Health and nutritional status should be evaluated, and primary prevention techniques initiated, to ensure adequate nutrition. Interventions should include daily intake of omega-3 fatty acids. Fish are a rich source of these substances. Other good sources include vegetable oils such as canola, soy, flaxseed, and walnut oil (**Table 4**).

The patient should eat 3 meals and 2 snacks per day, follow a healthy diet, and consume about 2 portions of omega-3-rich fish per week. Eggs enriched with DHA or prenatal supplementation containing omega-3 fatty acids present another option. A food diary also may prove helpful.

To ensure an adequate intake of omega-3 fatty acids, a daily supplement is recommended. One available formulation consists of a capsule containing omega-3 fatty acids to be taken in the morning, and a multivitamin tablet that is taken in the

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* PrimaCare® (Ther-Rx Corp, St Louis, Mo) is a prenatal/postnatal multivitamin/mineral supplement with essential fatty acids available by prescription. It consists of 2 dosage forms designated as AM (morning) and PM (evening). The AM dosage form is a soft dye-free gelatin capsule that contains 150 mg of omega-3 fatty acids and 50 mg of omega-3 and omega-6 precursor fatty acids, with vitamin $D_3$ (as cholecalciferol), 170 IU; vitamin E (dl-alpha-tocopheryl acetate), 30 IU; and calcium (as calcium carbonate), 150 mg. The evening (PM) dosage form is a film-coated tablet that contains the following: biotin, 35 µg; folic acid, USP, 1 mg; vitamin $B_1$/thiamine (as thiamine mononitrate, USP), 3 mg; vitamin $B_2$/riboflavin, USP, 3.4 mg; vitamin $B_3$/niacin (as niacinamide, USP), 20 mg; vitamin $B_6$/pyridoxine (as pryridoxine HCl, USP), 10 mg; vitamin $B_{12}$/cyanocobalamin, 12 µg; vitamin C (as *Ester-C*®), 100 mg; vitamin $D_3$ (as cholecalciferol), 230 IU; vitamin K, 90 µg; and pantothenic acid, 7 mg. The following minerals are included: Calcium (as Calcipure™ calcium carbonate), 250 mg; chromium, 45 µg; copper (as cupric oxide), 1.3 mg; iron (as MicroMask™ ferrous fumarate), 30 mg; molybdenum, 50 µg; selenium, 75 µg; and zinc (as zinc oxide, USP), 11 mg.

Note: *Ester-C*® (Inter-Cal Corp, Prescott, Ariz) is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate.

evening.* Such supplements can be continued into the postnatal period, during lactation, and during interconceptional periods throughout the child-bearing years.

Micronutrients essential to development of the central nervous system in infants include zinc, copper, selenium, folate, sodium, and iron. Deficiency of iron during pregnancy is found worldwide, and is associated with decreased cognitive function in the infant. All of these substances can be provided routinely in prenatal supplements.

**Make nutritional adjustments at follow-up.** For example, the individual who dislikes eating fish could eat DHA-enriched eggs, if available. A concurrent adjunctive strategy is to take a daily prenatal vitamin enriched with omega-3 fatty acids.

Besides the strong recommendations of several scientific groups that omega-3 intake be increased during pregnancy, the American Heart Association now recommends that men and women eat a variety of fish at least twice a week (**Table 3**). Patients with coronary heart disease should consume 1 g of EPA and DHA daily, preferably by eating oily fish. Results of large controlled clinical studies indicate that omega-3 fatty acid supplements be considered to provide the desired intake of EPA and DHA. Cardiac risk reduction with omega-3 supplementation has been reported in multiple clinical studies.

Unfortunately, fish consumption can pose health risks because of potential contamination with organic mercury compounds and PCBs that can produce neurologic and renal damage.[40] Offspring of mothers who consume large amounts of contaminated fish during pregnancy are at greater risk for adverse changes in the central nervous system, which can affect the child's ability to learn. The use of highly purified, pharmaceutical-grade supplements and the consumption of fish low in mercury and PCBs obviate this risk.

## Conclusion

Although the optimal daily doses of DHA and EPA to prevent preterm delivery in American women remain to be confirmed in randomized, controlled clinical trials, significant evidence exists that supplementation with EFAs is crucial in American mothers, whose diet is typically low in these vital substances.

The panelists agree that a regimen that includes a diet rich in omega-3 fatty acids, plus a prenatal supplement containing these substances, should be initiated early in pregnancy or, preferably, prior to conception, and then continued throughout lactation.

The panelists also agree that nutritional approaches can help prevent preterm birth while providing optimal nutrition to the mother and breastfeeding baby. Early-pregnancy nutrition is essential, as there is no way to catch up on a deficiency of omega-3 fatty acids later in fetal development. An unevaluated potential advantage of these substances is prevention of cardiovascular disease in both the baby and the mother. There is also the potential for the prevention of preeclampsia and the relief/prevention of postpartum depression. Ongoing research promises to expand our current understanding of these potentially invaluable health benefits of essential fatty acids.

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