Women and Omega-3 Fatty Acids

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Omega-3 fatty acids (omega-3 FA) are constituents of the membranes of all cells in the body and are precursors of locally produced hormones, eicosanoids, which are important in the prevention and treatment of various diseases, especially in women. Omega-3 FA are of interest in some of the most common conditions afflicting women. One mechanism underlying dysmenorrhea is a disturbed balance between anti-inflammatory, vasodilatory eicosanoids derived from omega-3 FA and pro-inflammatory, vasoconstrictor eicosanoids derived from omega-6 FA. Increased intake of omega-3 FA can reverse the imbalance in this condition by decreasing the amounts of omega-6 FA in cell membranes. An increased prostacyclins/prostacoxane ratio induced by omega-3 FA can facilitate pregnancy in women with infertility problems by increasing uterine blood flow. Supplemental EPA with omega-7 FA during pregnancy lowers the risk of premature birth and can increase the length of pre-laborary and birth weight by altering the balance of eicosanoids involved in labor and promote fetal growth by improving placental blood flow. Intake of omega-3 FA during pregnancy and breast feeding may facilitate the child's brain development. There is also some evidence that supplementation with omega-3 FA might help to prevent preclampsia, postpartum depression, menopausal problems, postmenopausal osteoporosis, and breast cancer. Furthermore, increased levels of triglycerides are associated with cardiovascular disease, especially in women, and become omega-6 FA have powerful effects on triglycerides, women in particular gain from an increased intake of these fatty acids. This is especially important in women receiving hormone therapy, which can increase triglyceride levels. The quality of the omega-3 FA preparation is important. It should have an appropriate antioxidant content not to induce lipid peroxidation, and its content of dioxin and polychlorinated biphenyls (PCBs) should be well below the established safe limit.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to describe the function and actions of omega-3 and omega-6 fatty acids; to outline the potential advantages of omega-3 fatty acid supplementation, and to list the potential sources of omega-3 fatty acids.  

Omega-3 fatty acids (omega-3 FA) are incorporated in the membranes of all cells in the body and are of great importance for health. When released from the cell membranes, these fatty acids become precursors of the locally produced hormones, eicosanoids, which are important in the defense against, and treatment of, various diseases.

An insufficiency of fish and fish products in the Western diet has led to a decrease in our intake of omega-3 FA by 80% during the last century and a deficiency of omega-3 FA in the cells is common today (1). The average daily intake of the 2 most important omega-3 fatty acids, eicosapentanenoic acid (EPA) and docosahexaenoic acid (DHA), has to be increased 5-fold from 0.25 to 1.25 mg daily to counteract this deficiency. Omega-3 FA are of special importance in women and in some of the most common conditions that women face.

DIYSMENORRHEA

Dysmenorrhea is the most common gynecologic complaint and the leading cause of recurrent short-
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term school absenteeism among female adolescents. It affects more than 50% of women. During the luteal menstrual phase, omega-6 FA are released from phospholipids in the cell membranes and proinflamatory, prostanoid or eicosanoid derivatives such as thromboxane A2 (TXA2), prostaglandin E2 (PGE2), and leukotriene B4 (LTB4) are produced (1) (Fig. 1). These induce painful cramps as well as systemic symptoms such as nausea, vomiting, and headache. In the uterus, vasodilatation and myometrial contractions occur, leading to ischemia and pain. As EPA competes with the omega-6 FA arachidonic acid in the cell membranes at the eicosanoid synthesis level, an increased dietary intake of omega-3 FA, in particular EPA, will reverse the omega-6 FA-induced symptoms (1).

The concentration of omega-6 FA-derived eicosanoids such as PGE2 are elevated in the blood and urine of dysmenorrheic women during menstruation. Menstrual pain and menstrual discomfort have been found to be correlated with a low dietary intake of omega-3 FA and low dietary ratios of omega-3/omega-6 FA (2) as well as with a low intake of vitamin B6. Omega-3 FA intake has been shown to be valuable in the management of dysmenorrhea. In a study, supplementation with 1.04 g omega-3 FA daily for 3 to 4 months reduced menstrual discomfort (3). Supplementation with 7.5 μg of vitamin B6 daily potentiated the effect of the omega-3 FA. In another study (4), supplementation with 6 g of natural (3F% omega-3) fish oil daily significantly relieved menstrual pain in adolescents.

Daily intake of 5 to 10 mL natural fish oil with high stability (5) (as a result of an appropriate antioxidant content) in women with dysmenorrhea, with or without the addition of nonsteroidal antiinflammatory drugs (NSAIDs) is often used in Sweden. The gastric mucosal irritation induced by NSAIDs is re- duced by the intake of fish oil. The mechanism of this action is probably that omega-3 FA inhibit the NSAID-induced decrease of prostacyclin in the stomach. Also, with simultaneous intake of omega-3 FA, the dose of NSAIDs, eg, aspirin, can be reduced. The increase in LTB4 induced by aspirin and other NSAIDs can lead to inflammatory reactions, including bronchial asthma. This increase in LTB4 is inhibited by intake of fish oil with high stability (6).

FERTILITY-INFERTILITY

Whereas 50 years ago women often focused on efforts not to become pregnant, today the problem is often the reverse, the inability to have a child. One reason for infertility is a delay in childbearing. Another reason may be that a change in diet has decreased the levels of omega-3 FA with a resulting imbalance in the eicosanoids. High carbohydrate intake resulting in increased levels of insulin in the blood can decrease fertility, whereas an elevated prostacyclin/thromboxane ratio resulting from, for example, omega-3 FA intake can lead to an increase in fertility. RoNtstein and colleagues studied 298 infertile patients undergoing in vitro fertilization (IVF) in a prospective, randomized, double-blind, placebo-controlled study (7). In addition to ovarian stimulation, 50% of the women received a daily dose of 100 mg aspirin and the rest placebo. The low-dose aspirin treatment increased the pregnancy rate from 26% to 45% and doubled the implantation rate. Aspirin as well as fish oil decreases thromboxane production by endometrial cells, improving implantation. IVF patients with low uterine blood flow, the pregnancy rate is reduced. It is possible that the reduced pregnancy rate in women with a thin endom- etrium can be improved by increasing the uterine blood flow. This increase can be achieved by substances such as aspirin or fish oil, which decrease the thromboxane production and improve the prostacycl/ thromboxane ratio (6,7).

Pregnant women have lower arterial flow resistance than infertile women. A decrease in peripheral resistance in the uterine vascular bed is a consequence of increased blood flow and tissue perfusion, which may improve uterine receptivity. RoNtstein et al also showed that methylprednisolone can improve
the pregnancy and implantation rates in IVF patients (8), probably by inhibiting phospholipase A2 and thus preventing the release of arachidonic acid, the precursor of inflammation-producing eicosanoids such as TXA2 and PGE2, from the phospholipids in the cell membranes. Natural stable fish oil has no known side effects (1) and may be a new interesting way of increasing the pregnancy rate in IVF patients. We recommend a daily dose of 5 ml of highly stable natural fish oil in infertility cases.

One cause of female infertility is polycystic ovary syndrome (PCOS), which is linked to miscarriages. They are associated with imbalance of eicosanoids resulting from deficiency of omega-3 FA. Women with PCOS show signs of endocrinopathy, some with increased body weight, elevated levels of insulin and glucose, and a decreased level of HDL-cholesterol. PCOS is also associated with elevated serum levels of luteinizing hormone (LH) and an increased LH/follicle-stimulating hormone (FSH) ratio. Treatment with the antihyperglycemic agent metformin not only lowers the insulin level, but also reverses the endocrinopathy (9). In obese women with PCOS, calorie restriction has a similar effect. Kady et al., for example, found that calorie restriction for 6 to 7 months, resulting in moderate weight loss, led to an improvement in reproductive function (10). It is thus possible that fish oil treatment in infertility should be combined with calorie restriction, especially low intake of carbohydrates.

PREGNANCY

The mother’s intake of omega-3 FA during pregnancy influences the development of the child after birth. Intake of fish or fish oil containing omega-3 FA during pregnancy may thus be of importance. Unfortunately, fatty fish seldom contains environmental poisons, and supplementation with fish oil carefully purified from such contaminants is therefore often necessary.

Fish oil supplementation from the 30th week of gestation has been shown to lower the risk of premature birth by 40% to 50%, increase the length of pregnancy by 5 days, and result in babies with a 100-g higher birth weight (11). Premature birth poses a health risk to the infant. Omega-3 FA increase the level of prostacyclin, which relaxes the uterine muscles, resulting in delay of onset of labor. Prematurity birth occurs in 6% to 7% of pregnancies and is the most important cause of neonatal mortality and morbidity, long-term neurologic handicaps, and a low IQ. The risks of pre-eclampsia, infection, and hypertensive during pregnancy are also increased in premature birth.

It is suggested that fish oil delays delivery by altering the balance of the eicosanoids involved in labor and that it increases the fetal growth rate by improving placental blood flow. We expect little seafood early in pregnancy runs a greater risk of having a premature or low-birth-weight baby than those who eat more seafood. This was shown in a study examining the fish-eating habits of nearly 9000 pregnant women in Denmark (12). It was found that low consumption of seafood had a strong association with premature birth in young women, more often eating less than 0.15 mg omega-3 FA daily. Of the women who never ate fish, 7.1% gave birth prematurely, compared with 1.9% of those eating fish at least once a week. The results suggest that just 1 0.5-g capsule of natural fish oil daily could be enough to prevent premature birth, at least during the first part of the pregnancy (13-15).

Intake of fish oil can also prevent gestational dia betes by increasing insulin sensitivity (16). Diabetes and impaired glucose tolerance during pregnancy create potential problems in the mother and fetus, namely an increased risk of malformations in the fetus, preeclampsia, respiratory problems, and even death of the fetus. Many of these risks can be decreased by regulation of the blood glucose levels before and during pregnancy, but it is not certain whether this is enough to keep endothelial function intact. It is possible that offspring of mothers with diabetes are at increased risk of having disorders that develop later in life in disease. So, a possible strategy of changing the food intake during pregnancy, e.g., by increasing the intake of fish oil containing omega-3 FA to alter the prostaglandins production, may be important.

Fish oil supplementation during pregnancy is important for the development of the fetal brain, and the need for DHA, in particular, is greatest in the last trimester of pregnancy. After birth, the mother should continue with a high intake of omega-3 FA, especially if she is breast feeding, to support the development of the child’s rapidly growing brain and to decrease the risk of postpartum depression (17). In fetal growth restriction (small-for-gestational age babies), the prostacyclin/thromboxane ratio in the umbilical vein is reduced, indicating that fetal growth restriction might be associated with disturbed endothelial function in this vessel (17,18). In diabetics, the TXA2 production in the umbilical-placental vascular tree has been shown to be increased, resulting in a lower prostacyclin/thromboxane ratio (19,20).
central lesions in diabetes have been found to be associated with generally increased vascular TXA2 synthesis and/or a decreased prostacyclin/thromboxane synthesis ratio (21). Cord plasma TXA2 was higher in diabetes. Placental lesions have been shown to be more common in diabetes and to be associated with increased vascular synthesis of TXA2 and/or a lower prostacyclin/thromboxane synthesis ratio (22).

During and after pregnancy, the woman may have an inadequate amount of omega-3 FA in the diet, especially if she has a multiple birth, has a short interval between pregnancies, or is breast feeding. In one study, women were given three different doses of omega-3 FA, 300, 500, or 1000 mg daily, from the second trimester until delivery. Analysis of umbilical cord arterial and venous wall fatty acids showed that the lowest dose had no effect. The middle dose resulted in higher omega-3 FA values than the highest dose (23). Low birth weight has been related to mortality from coronary artery disease and development of hypertension and diabetes in adult life (24). An intake of omega-3 FA during pregnancy has been shown to increase birth weight, such intake by the mother may decrease the risk of the child getting cardiovascular disease, hypertension, and diabetes later in life.

PREECLAMPSIA

Preeclampsia is 1 of the more serious complications of pregnancy, occurring in approximately 6% of pregnant women. It usually develops in the third trimester and is characterized by high blood pressure, proteinuria, and edema. Clinical studies have shown that preeclampsia is the result of the vascular dysfunction that occurs in preeclampsia (25). Aspirin and caffeine have failed, possibly because an increase in TXA2 production is not the initial abnormality. Because omega-3 FA is known not only to decrease TXA2, but also to increase prostacyclin production, in contrast to aspirin (65), fish oil may be a better choice in prevention of preeclampsia. A combination of fish oil and evening primrose oil has been shown to decrease edema in pregnancy (26).

POSTPARTUM DEPRESSION

Many mothers who develop postpartum depression have a low intake of fish and have lower levels of DHA in the breast milk than mothers who do not suffer such depression (27). The DHA levels in the mothers can decrease to half during pregnancy and the values are not restored until 6 months after the birth of the child. Polysaturated fatty acids are important in the brain, where they not only act as structural components of nerve cells, but also appear to take part in the process of signal transmission by the neurons. Depression in the period after delivery affects 16% to 15% of all mothers. Omega-3 FA, especially DHA, are low in the breast milk and in red cells of women affected by depression after delivery. These reductions, in turn, are associated with a low intake of fatty fish (28).

MENOPAUSAL PROBLEMS

During menopause, the ovaries stop producing hormones, with a marked decrease in circulating estrogen as a result. This rapid decrease is combined with a disturbance in the eicosanoid balance, giving rise to hot flashes and other discomforts. Approximately 80% of women going through menopause experience hot flashes. An overproduction of PG2 occurs. The estrogen decrease leads to an increase in insulin production, resulting in an increased production of arachidonic acid. Japanese women, who consume large amounts of seafood, rarely suffer from hot flashes. Evening primrose oil has been found to have no effect on menopausal flushing (29).

Osteoporosis

Omega-3 fatty acids have been shown to be of importance in the prevention and treatment of postmenopausal osteoporosis. A low n-6/n-3 ratio has been found to be associated with a better bone mineral density (30). PG2 is a potent stimulator of bone resorption and the primary prostaglandin affecting bone metabolism. Leukotriene B4 (LTB4) is also known to increase bone resorption and the number of osteoclasts. PG2 and LTB4 are produced by arachidonic acid and this production is inhibited by EPA. On the other hand, it has been suggested that cod liver oil, because of its high content of vitamin A, increases the risk of osteoporosis and hip fractures (31).

BREAST CANCER

Omega-6 FA, especially linoleic acid, have been shown to promote tumor growth (32). Because omega-3 FA are known to inhibit the formation of omega-6 FA, it has been proposed that omega-3 FA may play a role in the prevention, and possibly also treatment, of cancer (34). In fact, a diet rich in omega-3 FA has been found to slow the growth of tumors in...
animals (35). A large epidemiologic study showed that people consuming a Mediterranean diet with high levels of omega-3 FA were 56% less likely to get cancer and 61% less likely to die from it (36).

Women who eat the most fish tend to have the lowest rates of breast cancer. This is surprising because fat in general, and animal fat in particular, have been supposed to increase the risk of breast cancer. It thus seems that although most fat—saturated fat, trans fatty acids, and omega-6 FA—increase the risk of breast cancer, omega-3 FA in fish oil is protective in this respect.

Cargill et al. (37) reported that consumption of fish and fish oil is associated with protection against breast cancer and female colorectal cancer. Siemsen et al. (38) found that higher ratios of omega-3/omega-6 in breast tissue were linked to lower rates of breast cancer. This was especially true for EPA and DHA. A metabolite of omega-6 FA, PGE2, is known to suppress the immune system, which may promote tumor growth. EPA inhibits delta 5-desaturase, an enzyme that helps to produce arachidonic acid. More research is needed to shed further light on the role of omega-3 FA in cancer.

CARDIOVASCULAR DISEASE AND TRIGLYCERIDES

Several studies have shown that an elevated triglyceride (TG) blood level is an important risk factor for cardiovascular disease (CVD), especially in women, and particularly in older women (39-41). In a meta-analysis of 90,000 subjects, a 1-mmol/L increase in TG was associated with a 32% increase in CVD in men and a 76% increase in women (39). In women, plasma TG levels $>$0.94 mmol/L are associated with an increased risk of death from CVD (42).

The TG/HDL ratio has been shown to be a stronger predictor of myocardial infarction than the total cholesterol/high-density lipoprotein (HDL) ratio or the low-density lipoprotein (LDL)/HDL ratio (40). A high TG/HDL ratio has been found to be 16 times more dangerous than a low ratio and is associated with small, dense LDL particles (B type) (Fig. 2) with an increased ability to induce atherosclerosis. Because omega-3 FA have powerful effects on TG, women in particular gain from an increased intake of fish oil, which also increases HDL cholesterol and turns the LDL cholesterol particles into more innocent, large, fluffy ones (A type) (Fig. 2) (43).

We have seen a good effect of daily intake of 5 mL of natural (34% omega-3 FA) fish oil with high stability (containing 1.65 g omega-3 FA and a mixture of different antioxidants) on TG in women with moderately increased TG levels. Women with markedly increased TG levels sometimes need 10 mL daily, especially during the initial phase. Based on a study of more than 80,000 female nurses, it was concluded that among women, higher consumption of omega-3 FA is associated with a lower risk of CVD (44).

HORMONE THERAPY

One group of special interest is women receiving hormone therapy (HT) with estrogen and progesterin. Women receiving HT usually show a decrease in the circulating level of LDL cholesterol and an increase in HDL cholesterol during treatment. This should in theory be accompanied by a decreased risk for CVD, but unfortunately this is not the case. In fact, most investigations have shown unchanged, or even an increased, risk. This may be the result of the increased TG induced by HT and an increase in a special marker of inflammation, C-reactive protein (CRP) (45,46). Both the increase in TG (5) and that in CRP (47) is inhibited by omega-3 FA.

Intake of estrogen + progesterin in 1 study resulted in an 21% lower LDL cholesterol level and a 16% higher level of HDL cholesterol (45). However, coronary heart events were more common in the HT group than in the placebo group after 1 year, and there was an increase in the rate of thrombotic events. Such events may be prevented by natural stable fish oil containing omega-3 FA (48).

Waters reported a study of 423 postmenopausal women who were given HT, antioxidants (800 IU vitamin E as alpha-tocopherol and 1 g vitamin C daily), or placebo for 3 years (49). Quantitative radiologic assessment of the degree of atherosclerosis in the coronary arteries was performed. Neither HT nor antioxidant vitamin supplements provided cardiovascular benefit. On the contrary, a potential for harm was suggested with each treatment. Simular
observations were made in 2 other recent studies (30,51). For many years, we have regularly pre-
scribed 5 ml of natural stable fish oil daily to women receiving HT for prevention of risk factors for car-
diovascular disease with a good effect. Our findings are supported by the results of a recent study by Stark
et al. (52), who showed improved TG levels and TG/HDL ratios in women using HT after intake of fish
oil.

IMPORTANT OF THE QUALITY OF OMEGA-3 PREPARATIONS

As pointed out here, fish oil containing omega-3
FA has several important beneficial effects in
women. Reports on adverse effects are few, and most
fish oil preparations can be regarded as safe. The
adverse effects reported have been seen primarily
with concentrated fish oil preparations (>38% omega-
3 FA) with low stability and given in high doses
and are the result of lipid peroxidation. The increased
lipid peroxidation can induce LDL oxidation and a
proinflammatory state with aggravation of angina
pectoris instead of an expected improvement (53–
56).

The stability of fish oils in vitro has been shown to
be inversely correlated to lipid peroxidation in vivo
(57,58). The in vitro stability of different commercial-
cially available fish oil preparations varies markedly
(58) (Table 1). As shown in the table, the stability of
14 different fish oil preparations varies between 1
and 200 days. Highly concentrated fish oils usually
have markedly lower stability than natural fish
oils. As seen, most fish oil products available today have
low stability, i.e., they become rancid when exposed to
air, and after intake they can induce consumption of
antioxidants such as vitamin E. This will lead to
formation of free radicals, which can cause cellular
injury. There is no direct association, however, be-
tween the content of vitamin E in the fish oils and
their stability (Table 1). As shown, even fish oil
preparations containing large amounts of vitamin E
can have low stability in vitro.

The problem with the instability of fish oils was
not widely known until recently. Oily fish and crude
fish oil preparations contain toxic contaminants such
as pesticides and mercury. These have to be re-
moved, and during this process, the antioxidants in
the fish oils are lost and have to be restored to keep
the fish oil stable. The effects observed after intake of
an unstable fish oil are the net effects of the positive
actions of the omega-3 FA and the negative results of
the formation of free radicals. It has been shown (53)
that intake of highly concentrated omega-3 FA prep-
arations can have adverse effects. In 1 study, for
instance, intake of such preparations for 6 months
almost doubled the frequency of angina pectoris (55).
The adverse effects were ascribed to increased lipid
peroxidation in these patients. It was also pointed out
that highly concentrated omega-3 FA preparations
induce oxidation for more easily than natural fish oil.

Hau et al. (54) and Stalenhoef et al. (55) showed
that concentrated fish oil preparations increased the
solubility of LDL to oxidation. Similar effects were
found by Lussier-Cacan et al. (56). Highly stable fish
oils seem to have more beneficial effects on the
inflammatory process than fish oils with lower
stability. Thus, intake of a fish oil with high stability
had a better effect on joint stiffness (59) than a fish
oil with the same fatty acid composition but a lower
in vitro stability and was more effective in decreasing
plasma fibrinogen (60). Intake of several different
fish oil products has been found to increase blood
glucose, probably as a result of increased lipid per-
oxidation in the pancreas, with decreased production
of insulin. After intake of a natural fish oil with high
stability, no such increase in blood glucose is seen
(61).

Recently, there has been greater awareness of dan-
gers posed by dioxins and polychlorinated biphenyls

<table>
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<th>TABLE 1 Stability of different fish oils (The Royal Society of Chemistry, Cambridge, UK, 1998)</th>
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<td><strong>Stability (days)</strong></td>
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<tr>
<th>Stability (days)</th>
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<td>Fish oil 14</td>
<td>200</td>
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Stability = time to rancidity (peroxide value 20) after exposure of the oil to air at room temperature.
* Chemistry modified fish oils. Other fish oils are natural.

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Effects on plasma non-HDL cholesterol and lipoprotein(a) levels after treatment with fish oil.