

# Long-Chain Omega-3 Fatty Acids and Women's Mental Health in the Perinatal Period and Beyond

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Recent research has shown that depression and a range of physical illnesses, including heart disease, metabolic syndrome, and type 2 diabetes, have an inflammatory etiology. The long-chain omega-3 fatty acids (omega-3s) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in fish and fish-oil products, may protect against these illnesses, in part because they lower inflammation. This article reviews the recent research on omega-3s and women's mental health, with a particular focus on the perinatal period. These studies include population studies examining fish consumption and studies testing the efficacy of EPA and DHA as treatments for depression. Although the findings are mixed, the majority of studies indicate that EPA has efficacy in treating depression either alone or in combination with DHA and/or antidepressant medications. The role of DHA alone in mental health is less clear, but it is generally combined with EPA and appears to have a beneficial effect. In moderate doses, EPA and DHA appear safe for pregnant and postpartum women, and they are well tolerated by patients. *J Midwifery Womens Health* 2010;55:561–567 © 2010 by the American College of Nurse-Midwives.

**keywords:** docosahexaenoic acid, eicosapentaenoic acid, inflammation, omega-3s, postpartum depression

## INTRODUCTION

Over the past two decades, researchers have discovered that inflammation has a causal role in the pathogenesis of depression and a wide range of physical diseases, including cardiovascular disease, metabolic syndrome, diabetes, and cancer.<sup>1–3</sup> Perinatal depression also has an inflammatory etiology.<sup>4,5</sup> Maes et al.<sup>6</sup> first documented that women with postpartum depression had higher plasma levels of proinflammatory cytokines than mothers who were not depressed. These data are consistent with what researchers have found with regard to depression in general. A key concept in this research is that stress triggers the inflammatory response, which increases the risk of depression.<sup>7,8</sup>

The immune system is one component of the stress response. It responds to stress by releasing proinflammatory cytokines, which are molecules that increase inflammation. Proinflammatory cytokines have the adaptive purpose of helping the body heal wounds and fight infection. However, when they are abnormally or chronically elevated, they increase the risk of depression and other inflammatory diseases, such as heart disease and diabetes. The proinflammatory cytokines that researchers identified most consistently as being elevated in depression are interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ .<sup>3,7</sup>

Puerperal women are especially vulnerable to depression because inflammation levels normally rise during the last trimester of pregnancy, a time when they are at highest risk for depression.<sup>5</sup> By itself, this normal elevation does not increase women's risk for depression. How-

ever, when the normal elevation is coupled with stresses that new mothers often experience, such as sleep deprivation, pain, and psychological trauma, it dramatically increases women's risk for depression.<sup>4,5</sup>

## Search Method

The studies cited in this review were assembled from a wide variety of sources as part of an ongoing project. Literature searches on PubMed and PsycINFO were conducted on depression; postpartum/postnatal depression; depression and inflammation; omega-3 fatty acids and depression; and omega-3 fatty acids in pregnant and postpartum women.

## OMEGA-3 FATTY ACIDS AND WOMEN'S HEALTH

Omega-3 fatty acids (omega-3s) lower levels of proinflammatory cytokines.<sup>2–4</sup> This characteristic helps them prevent and treat depression, cardiovascular disease, and other inflammatory conditions.<sup>3,9</sup> With regard to inflammatory disorders, it is the long-chain omega-3s that are of interest: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Humans do not efficiently synthesize these fatty acids and need to consume them directly.<sup>3</sup> Alpha-linolenic acid (ALA) is the parent omega-3 fatty acid, and is found in plant sources (Figure 1). ALA is metabolically too far removed from EPA and DHA to be sufficiently antiinflammatory. This means that omega-3s found in flax seed, walnuts, and other plant sources cannot be used to prevent or treat depression.<sup>10</sup> Fish and fish-oil products continue to be the only source of EPA and a good source of DHA; vegetarian DHA products are also available. Unfortunately, in many Western cultures, women tend to consume small amounts of omega-3 fatty acids in their diets and consume too many omega-6s.

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Omega-6s and omega-3s are both polyunsaturated fatty acids (PUFAs; Figure 1). Omega-6s are proinflammatory and are found in vegetable oils, such as corn and safflower oils. Omega-6s are necessary for good nutrition, but they become harmful when they are too abundant in the diet.<sup>9</sup> Kiecolt-Glaser et al.<sup>7</sup> noted that the hunter/gatherer diet had an estimated ratio of omega-6s to omega-3s of 2:1 or 3:1. In contrast, the typical ratio in the North American diet is approximately 17:1. This dramatic shift has had a negative effect on both physical and mental health, and chronic deficiencies of EPA and DHA increase the risk for disease.<sup>3,7</sup>

The pattern of consumption in North America and other industrialized countries means that many women are deficient in EPA and DHA throughout their lives. This is of particular concern during pregnancy and the postpartum period. Because infants specifically need DHA for brain and vision development, women's bodies will preferentially divert it to their fetuses. With each subsequent pregnancy, women are further depleted.<sup>11</sup>

### Stress, Inflammation, and Omega-3s

EPA lowers inflammation by competing for the same metabolic pathways as proinflammatory arachidonic acid. This action halts the arachidonic cascade, which leads to the synthesis of prostaglandins, leukotrienes, and eicosanoids.<sup>3</sup> A recent review found that people with major depression had significantly higher ratios of arachidonic acid to EPA in both serum cholesteryl esters and phospholipids.<sup>12</sup> In a large population study, high levels of omega-3s (ALA, EPA, and DHA) in participants' plasma were related to lower levels of the proinflammatory cytokines interleukin-1 $\alpha$ , interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ . For people with low levels of omega-3s, the opposite was true.<sup>13</sup>

EPA and DHA also appear to downregulate the stress response.<sup>4</sup> In a study of college students, those deficient in EPA/DHA had a heightened inflammatory response to lab-induced stressors. In contrast, students with higher levels of EPA/DHA were more resilient to stress and had a lower inflammatory response to stress.<sup>14</sup> Similarly, Kiecolt-Glaser et al.,<sup>7</sup> in their study of 43 older adults, noted that previous episodes of stress and depression appeared to "prime" the inflammatory response, making individuals more susceptible to subsequent stress. Even modest supplementation with EPA and DHA, however, lowered levels of norepinephrine, indicating an attenuated stress response.

A study from Japan had similar findings.<sup>15</sup> In a double-blind trial, 21 young adults took either a placebo or 762 mg

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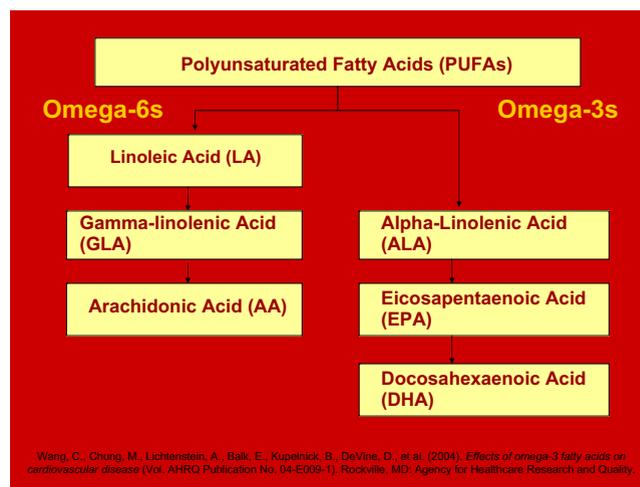


Figure 1. Polyunsaturated fatty acids: Omega-6s and omega-3s.

of EPA/DHA for 2 months. The researchers noted that EPA concentrations increased in the red blood cell membranes of the supplemented group. The EPA/DHA group also had significantly decreased levels of plasma norepinephrine.

### Omega-3s and Depression in Population Studies

Researchers first documented the mental health effects of EPA/DHA via population studies. Specifically, researchers compared national rates of fish consumption with national rates of depression and other affective disorders across different countries.<sup>7,16</sup> Several recent studies have found that populations that eat more fatty, coldwater fish have higher levels of EPA and DHA and lower rates of affective disorders. Summarizing these studies, Parker et al.<sup>12</sup> noted a surprisingly low incidence of seasonal depression in places where researchers would expect to find it (e.g., Iceland, Finland, and Japan). These findings were likely related to the high amounts of fish consumed. Kiecolt-Glaser et al.<sup>7</sup> also noted that depression is 10 times more common in countries where people do not eat fish or eat a small amount of it. Populations with high rates of fish consumption also have lower rates of heart disease and other diseases.<sup>3</sup>

In a study of 3204 adults from Finland, researchers assessed depression via the Beck Depression Inventory and the frequency of fish consumption via questionnaire.<sup>17</sup> The authors found that depressive symptoms were more likely in participants who ate smaller amounts of fish. Even after controlling for possible confounding variables, such as smoking, infrequent exercise, and unemployment, the likelihood of being depressed was 31% higher among individuals who did not eat high amounts of seafood.

Noaghiul and Hibbeln<sup>18</sup> noted that rates of bipolar disorders were lower in countries where people ate a lot of fish. In their study, they merged mental health data from the 10-nation Cross-National Collaborative Group with

national fish consumption data from the World Health Organization. Using logarithmic regression models, they found that greater fish consumption predicted lower rates of bipolar I disorder, bipolar II disorder, and bipolar spectrum disorder. People with bipolar I disorder have episodes of sustained mania and often have depressive episodes. People with bipolar II have major depressive episodes with less severe mania; they experience hypomania, a less intense mood involving increased energy, racing thoughts, and a reduced need for sleep. Bipolar spectrum disorder is a milder form of bipolar II. Noaghiul and Hibbeln<sup>18</sup> noted that the strongest findings were for bipolar II disorder, which has prominent depressive symptoms. The authors concluded that while they could not establish a causal relationship, their findings were consistent with deficiencies in omega-3s being related to higher risk for mental disorders.

Omega-3 status has also been related to suicide attempts. In this study, 33 patients who were depressed but not on medications were monitored for suicide attempts over a 2-year period.<sup>19</sup> The researchers assessed plasma PUFA levels at the beginning of follow-up. Seven patients attempted suicide over the study period, and two fatty acid levels predicted attempts: low DHA and a high ratio of omega-6s to omega-3s. Neither arachidonic acid nor EPA levels predicted suicide attempts.

Fish consumption has a similar effect on postpartum depression. Rees et al.<sup>11</sup> observed that the rates for postpartum depression in North America and Europe are 10 times those in Taiwan, Japan, Hong Kong, and some regions of China. In a large cross-national ecologic analysis of 41 published studies with more than 14,532 women from 22 countries,<sup>20</sup> Hibbeln noted that postpartum depression was up to 50 times more common in countries with low fish consumption. For example, the rate of postpartum depression in Singapore was 0.5%, where the national rate of seafood consumption was 81.1 pounds per person per year. In South Africa, it was 24.5%, where the national rate of seafood consumption was 8.6 pounds per person per year. Hibbeln also analyzed published reports of DHA, EPA, and arachidonic acid levels in mothers' milk from these sample studies. Greater national seafood consumption predicted higher levels of DHA in the milk. Mothers who ate high amounts of seafood during pregnancy and who had high levels of DHA in their milk postpartum had lower rates of postpartum depression. Rates of postpartum depression were not related to levels of EPA or arachidonic acid.

Not all researchers have found that lower rates of depression correspond to fish consumption. In a study of 865 pregnant Japanese women, investigators failed to find lower rates of depression in women who ate more fish.<sup>21</sup> Specifically, they found no dose-response effect of fish intake, EPA, DHA, omega-6s, or ratio of omega 6s to omega 3s on postpartum depression. There are, however, some limitations of these findings. First, fatty acid levels were

not assessed directly but were instead estimated from a dietary questionnaire administered during pregnancy. Second, the population they assessed has one of the highest fish-consumption rates in the world. It is possible that the researchers encountered a ceiling effect because none of the women were deficient—and it therefore may have been difficult to observe differences between the groups. In addition, depression was assessed anywhere between 2 and 9 months postpartum. That wide range could have influenced the findings, because rates of depression vary by when they are collected in the postpartum period.

In summary, eating fish appears to have a beneficial effect on mental health. Noaghiul and Hibbeln<sup>18</sup> noted that countries where people ate less than 50 lbs of seafood a year (1–1.5 pounds per person per week) had the highest rates of affective disorders. This finding provides some guidance about how much people need to eat to avoid being deficient. Pregnant women in particular may need to limit how much fatty fish they eat because of possible contaminants, and may need to obtain sufficient omega-3s through supplements.<sup>22</sup>

### **Treatment of Mood Disorders With Eicosapentaenoic Acid and Docosahexaenoic Acid**

EPA and DHA can also be used to treat depression.<sup>23</sup> A 2005 review<sup>24</sup> indicated that the use of EPA for treatment of depression demonstrated efficacy in four of the six studies reviewed. The authors determined that 1 g of EPA per day was the effective treatment dose. Two grams had the same effect as 1 g without adding any benefit, and doses higher than 2 g seemed to have the reverse effect.<sup>24</sup> Similarly, a metaanalysis by Lin and Su<sup>25</sup> of 10 studies (N = 329) found a significant antidepressant effect of EPA/DHA. They found that EPA (1, 2, or 4 g per day), was superior to the placebo in three out of six studies, that DHA alone was not more efficacious than the placebo in one study, and that EPA alone or with DHA was superior to the placebo in three out of three studies for bipolar disorder (all patients with bipolar disorder were also taking mood-stabilizing medications).

A recent trial randomized 120 middle-aged women with moderate to severe psychological distress to receive EPA (1.05 g) and DHA (0.15 g) or a placebo for 8 weeks.<sup>26</sup> Twenty-four percent of these women met the criteria for major depression. After 8 weeks, for women with distress but not major depression, symptoms significantly improved with EPA versus a placebo. For women with major depression, however, the difference between the EPA and placebo groups was not significant.

EPA was also studied in the treatment of depression in subjects with bipolar disorder. In a 12-week double-blind trial,<sup>27</sup> researchers randomly assigned 75 patients to one of three conditions in addition to their medications: placebo, 1 g ethyl-EPA, or 2 g ethyl-EPA. Both EPA groups showed substantial improvement in depressive symptoms

after 12 weeks compared to the placebo group. A dose of 1 g was as effective as 2 g, and there was no advantage to 2 g over 1 g. Summarizing their findings, the authors noted that EPA was well tolerated and safe, that it lowered depression, and that patients may prefer EPA to antidepressants.

EPA and DHA supplementation was also helpful in treating patients with recurrent self-harm.<sup>28</sup> In this study, researchers randomized 49 patients with repeated acts of self-harm to receive a placebo or 1.2 g EPA and 900 mg DHA per day. After 12 weeks, patients who had received EPA and DHA had significantly improved in two symptoms that the authors described as markers for suicidality: depressive symptoms and daily stresses. The authors concluded that EPA and DHA had lowered the risk of suicidality in these high-risk patients.

A recent study of 36 pregnant women with major depression randomized women to receive either a placebo or EPA (1.2 g) and DHA (2.2 g).<sup>29</sup> The EPA/DHA group had significantly lower depression scores on the Hamilton Rating Scale for Depression at 6 and 8 weeks of follow-up as compared to the placebo group, and had a higher (though nonsignificant) remission rate. There were no adverse effects for either mother or infant, and EPA and DHA were both well tolerated. The authors theorized that this treatment was likely effective because it halted the arachidonic acid cascade, which is theorized to promote depression and other inflammatory conditions.<sup>12</sup>

Not all studies have found that EPA and DHA are effective treatments for depression or improving mental health. Two recent randomized trials found no significant difference between EPA/DHA supplementation and a placebo. The first trial included 302 nondepressed men and women over 65 years of age. The outcome measured was mental well-being, which included scores on four measures: the Center for Epidemiology Studies-Depression Scale, the Montgomery-Asberg Depression Rating Scale (MADRS), the Geriatric Depression Rating Scale-15, and a subscale of the Hospital Anxiety and Depression Scale. Participants received low-dose EPA/DHA (400 mg), high-dose EPA/DHA (1800 mg), or placebo. At the end of the 26-week trial, there were no significant differences among the groups.<sup>30</sup> In other words, EPA and DHA did not further improve the mental well-being of people who were not depressed.

In the second study, 190 adults with mild to moderate depression were randomly assigned to receive EPA plus DHA (1.5 g) or a placebo for 12 weeks.<sup>31</sup> At the end of the trial, there were no differences in mood or cognitive performance for the EPA/DHA and placebo groups. The low amount of EPA (630 mg) may have influenced the findings; this amount was lower than the dosage (1 g) that was found to be effective in previous studies.

An open-label trial with pregnant women who had had previous episodes of postpartum depression found that fish oil supplements did not prevent depression from recurring

after the most recent pregnancy.<sup>32</sup> The women were treated from 34 to 36 weeks' gestation through 12 weeks postpartum. The dosages were of 1730 mg EPA and 1230 mg DHA. Recruitment for the study ceased when four of the seven women became depressed during the treatment phase. The authors speculated that their findings might be related to an inadequate dose of EPA or DHA, although the level of EPA was above the 1-g recommended dose. They also speculated that the treatment may have been too late in the pregnancy to prevent depression, and that the wrong ratio of EPA to DHA was used. They indicated that even though their study failed to find the results that they had hoped for, results from other studies support continued investigation of EPA and DHA in the treatment of postpartum mood disorders.<sup>32</sup>

More recently, in a study of 59 postpartum women with major depression, women received either 1.9 g EPA and DHA per day or a corn oil placebo.<sup>33</sup> Women in both groups also received supportive psychotherapy. At the end of the 8 weeks, both groups had significantly lower depression scores, but there was no difference between the treatment and placebo groups, possibly because the psychotherapy that both groups received may have obscured the effects of the omega-3s.

Despite these conflicting findings, the American Psychiatric Association's Omega-3 Fatty Acids Subcommittee has stated that EPA and DHA provided a significant benefit in unipolar and bipolar depression, but the results were inconclusive for other psychiatric disorders.<sup>10</sup> They also noted that a preponderance of evidence points to a protective effect of EPA and DHA in mood disorders. Furthermore, the subcommittee suggested that supplementation with omega-3s could help counter some of the metabolic and obesity side effects of psychotropic medications.

### **Additional Effects of Docosahexaenoic Acid in the Perinatal Period**

The role of DHA alone (rather than combined with EPA) in the prevention or treatment of depression is less clear, but there is some evidence that it may help prevent depression. In the Adelaide Mothers' and Babies' Iron Trial, a randomized trial of supplementing 430 pregnant women with iron, the authors found that DHA levels were more predictive of depression than iron levels. A 1% increase in plasma DHA was related to a 59% decrease in risk of depressive symptoms postpartum.<sup>11</sup> Unfortunately, as described earlier, pregnant women's diets are often deficient in DHA, which is unfortunate given fetuses' high need for it. As Rees et al.<sup>11</sup> noted, during the last trimester of pregnancy, fetuses accumulate an average of 67 mg per day of DHA. The average intake for Australian mothers is 15 mg per day. Because DHA is essential for fetal development, if mothers consume less than fetuses need, the mothers' bodies will preferentially divert DHA from maternal stores to their fetuses. This means that

mothers who are deficient during pregnancy will come into the postpartum period even more deficient, increasing their risk for depression. The amount of DHA mothers consume varies tremendously between countries, as noted earlier. For example, DHA consumption among Japanese, Koreans, and Norwegians is about 1000 mg per day. These populations also have notably lower rates of postpartum depression.<sup>11</sup>

Not every study has found that DHA prevents depression. One hundred thirty-eight mothers were randomly assigned to receive 200 mg DHA or a placebo for the first 4 months postpartum.<sup>34</sup> The outcome variables studied were plasma phospholipid DHA content, self-reported and syndromal depression, and maternal information processing. They found that while phospholipid DHA was 50% higher in the supplemented group at 4 months, DHA did not prevent depression. The dosage that they used may have been too low, as will be discussed in the next section. They found no adverse effects of DHA supplementation for either mother or infant.

The current recommended intake of DHA is 200 to 400 mg per day, but this may be too low a dose to prevent depression. According to McNamara,<sup>35</sup> recent research indicates that 7% erythrocyte DHA is the appropriate target amount needed to prevent affective disorders. In order to achieve that level, the dosage for children should be 400 to 700 mg DHA per day, and for adults 700 to 1000 mg per day. These amounts are consistent with the levels of DHA consumption in the populations that consume large amounts of fish cited above. Future longitudinal studies will be necessary to confirm the efficacy and safety of these higher dosages, but the population data are reassuring that these dosages appear to pose no threat to either mother or infant.

### Safety During Pregnancy and Lactation

EPA and DHA supplements are generally considered safe for pregnant and lactating women.<sup>34,35</sup> A few studies have found very mild negative effects at high-dose levels. In most studies, however, there are no adverse effects.<sup>22</sup> The findings for pregnancy and the postpartum period are summarized below.

### Studies During Pregnancy

Most studies on the effects of EPA/DHA on pregnant women are population studies examining fish or fish oil consumption.<sup>36</sup> There have been no adverse effects noted with even very high rates of fish consumption, such as in a study of pregnant women in the Faroe Islands, where average daily fish consumption was 72 g of fish, 12 g of whale muscle, and 7 g of blubber per day.<sup>37</sup> Another study examined the effect of fish consumption during pregnancy and whether it protected offspring from allergic disease in 462 pregnant women.<sup>38</sup> There were no adverse effects noted for either mother or infant.

A study of 488 pregnant women in Iceland examined the impact of cod liver oil on hypertension in pregnancy.<sup>39</sup> The researchers found that cod liver oil substantially increases the risk of hypertension (odds ratio = 4.7). There are some issues to consider, however, in the interpretation of these findings. First, cod liver oil contains not only EPA and DHA but three fat-soluble vitamins (A, D, and E) that can be potentially toxic in large doses. Second, consumption of cod liver oil was estimated from questionnaire data—not directly measured in participant serum. Third, when data were divided into centiles, the authors noted a U-shaped curve, with the odds ratios of hypertension being the lowest for those with a modest supplementation, similar to findings of other studies. Their findings suggest that modest amounts of cod liver oil (0.1–0.9 g) appear safe with no increased risk to the mother or infant. Because many pregnant women are also deficient in vitamin D, supplementing with cod liver oil may be helpful in preventing depression and other problems related to vitamin D deficiency.

Szajewska et al.'s<sup>40</sup> metaanalysis of EPA and DHA supplements during pregnancy found that only a few mothers experienced mild adverse effects (e.g., fish burps). Overall, neonates across studies did not differ in rates of adverse effects from neonates whose mothers were not supplemented.

### Impact on Breastfeeding

EPA and DHA supplementation of mothers appears to have no negative impact on breastfeeding infants, even at high dosages. Freeman et al.<sup>41</sup> conducted a small, randomized trial using three different dosages of EPA/DHA with 16 breastfeeding mothers with postpartum major depression (300 mg EPA/200 mg DHA; 840 mg EPA/560 mg DHA; or 1680 mg EPA/1120 mg DHA). Depression significantly decreased in all three groups. The study was severely limited by a small sample and no control group, but there were no adverse effects noted for either mother or infant at any dosage level.

At very high dosages, EPA and DHA slightly altered breast milk fatty acid composition for 83 mothers who were supplemented from 20 weeks' gestation to birth. These changes appeared to be beneficial.<sup>42,43</sup> Higher levels of EPA/DHA were related to increased levels of immunoglobulin A and sCD14 in the milk. The supplementation dosage used in this study was very high (2.2 g DHA, 1.5 g EPA)—which is 11 times the current recommended minimum of DHA. The authors did express some caution, but the potential risks associated with the changes in fatty acid composition that they noted were hypothetical, not observed.

### Sources of Eicosapentaenoic Acid and Docosaheptaenoic Acid

As the previously cited studies indicate, women are often deficient in long-chain omega-3 fatty acids during the

perinatal period. However, pregnant or breastfeeding women may need to limit the amount of fish they eat, the prime source of EPA and DHA, because of possible contaminants in seafood (although fish lower on the food chain generally have lower levels of contaminants). Fish oil supplements are another good source of EPA and DHA. The US Pharmacopeia Web site lists specific brands that are tested for contaminants and are USP verified. Several of these brands are inexpensive and widely available ([www.USP.org](http://www.USP.org)).

Fish oil capsules were found to be tolerable for pregnant and postpartum women.<sup>44</sup> In a recent study of 59 pregnant and postpartum women with major depression, participants received four capsules daily with either 1.84 g EPA and DHA or corn oil. Thirteen women reported side effects; the most common were unpleasant breath or heartburn/reflux. Six women reported side effects in the omega-3 group and seven in the placebo group. No participant dropped out of the study because of the tolerability of side effects from fish oil supplements.

## SUMMARY

Increasing evidence suggests that EPA and DHA can help prevent and treat depression in new mothers, either as a monotherapy or as an adjunctive therapy with medications.<sup>10</sup> A review in the *British Journal of Psychiatry* summarized these findings as follows:

“There is good evidence that psychiatric illness is associated with the depletion of EFAs [essential fatty acids] and, crucially, that supplementation can result in clinical amelioration....The clinical trial data may herald a simple, safe, and effective adjunct to our standard treatments.”<sup>45</sup>

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