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Maternal omega-3 fatty acid supplementation and risk for perinatal maternal depression

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Abstract

Objective—A systematic review was conducted to assess the possible association between omega-3 polyunsaturated fatty acid (PUFA) supplementation and intake in the perinatal period and the risk of maternal perinatal depression.

Methods—Two PubMed searches and a BIOSIS Preview, a Web of Science and a PsychInfo search were conducted with the search terms ‘DHA, pregnancy and depression’ and ‘omega-3 fatty acids, pregnancy and depression’.

Results—Ten articles – three longitudinal cohort studies, five randomized controlled trials and two pilot trials– that met selection criteria were reviewed. Six found no association, two found mixed results, and two found a positive association between omega-3 PUFAs and reduced incidence of maternal perinatal depression. The heterogeneity of results can be explained by dissimilar study designs, including differences in study duration, time period of measurement and number of participants, and in varied dosages and types of supplemental PUFAs. Some of the larger studies and those that found a positive effect were more likely to be using higher doses, close to 2 g of docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA), and began the supplementation earlier in pregnancy.

Conclusions—Future RCTs to investigate the role of PUFA supplementation and risk for maternal perinatal depression should begin supplementation early in pregnancy and use a dosage closer to 2 g of DHA + EPA. Depression should also be measured using a diagnostic interview schedule in addition to a screener.

Keywords

Omega-3; DHA; perinatal depression

Background

Omega-3 polyunsaturated fatty acids (PUFAs), in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are important factors in fetal and infant neuronal and retinal membrane development during the latter part of pregnancy and early postnatal life [1]. DHA and EPA are obtained from exogenous sources through breast milk and foods. Children and adults can also synthesize significant amounts from less saturated omega-3 fatty acids (specifically plant-based alpha-linolenic acid (ALA)). During pregnancy, women can become depleted of omega-3 PUFAs if intake is not sufficient to counteract demands due to fetal diversion, expanded maternal cell mass, and the requirements of the placenta [2].

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Omega-3 PUFAs are hypothesized to affect receptors and neurotransmitters that have been implicated in depression [3]. Therefore, pre-pregnancy DHA and EPA levels and DHA and EPA intake may play a role in risk for maternal psychological depression during pregnancy and the post-partum period. Additionally, DHA and EPA may have anti-inflammatory consequences via cytokines and eicosanoids that are linked to depression via the HPA axis [2].

Omega-3 PUFA supplementation could play a role in the treatment and prevention of maternal prenatal and postnatal depression. Studies suggest that formulations containing either or both DHA and EPA may be effective to prevent or treat maternal perinatal depression. Ecological and cross-sectional studies have demonstrated lower maternal post-partum depression in countries with greater seafood consumption during pregnancy, in women with higher concentrations of DHA in mother's breast milk and in women at higher risk for depression such as single and unmarried women with greater intake of EPA + DHA [4,5]. There is evidence from animal studies as well that omega-3 intakes may prevent depression. Huang et al. found that brain levels of DHA and not EPA were negatively correlated to depression-like behaviors in a rat model of depression [6]. Clinical studies have found that EPA may be a promising adjunctive treatment in patients taking standard antidepressant medications [7,8]. The Institute of Medicine (IOM) has established acceptable macronutrient distribution ranges (AMDR) for omega-3 PUFAs (specifically ALA – the precursor for DHA and EPA) at 0.6–1.2% of dietary intake, and that up to 10% of AMDR (approximately 100mg of DHA + EPA) should be omega-3 fatty acids to be consumed as EPA and/or DHA (2006) [9]. Other countries have much higher recommendations, closer to 500 mg/day, and certain at-risk populations may benefit from even higher daily intakes. For example, the American Heart Association recommends 2–4 g per day for individuals with coronary heart disease [10]. However, specific recommendations have not been made for the prevention or treatment of maternal perinatal depression or concerning appropriate levels in pregnancy. Meanwhile, increasing levels of maternal perinatal exposure to omega-3 fatty acids have not been shown to have any potential risk but rather may offer neurodevelopmental advantages to infants [11,12].

This review synthesized the findings from a small number of randomized controlled trials (RCTs) and longitudinal studies that have been conducted to date to evaluate possible associations between DHA and EPA intake and risk for maternal perinatal depression.

Methods

A PubMed search (January 1966–August 2010) was performed using the following search terms: 'DHA, pregnancy and depression' and 'omega-3 fatty acids, pregnancy and depression' to retrieve studies that evaluated the relationship between DHA or omega-3 PUFA levels and risk for maternal perinatal psychological depression. Sixteen articles were retrieved for the first search and 53 articles from the second search. Articles were excluded that were not conducted with humans, were review articles, evaluated only the tolerability of DHA or omega-3 fatty acid supplementation, or did not have a study design that was either a RCT, other trials (open-label) or a longitudinal cohort. For the first search, one article was not included as it was evaluating the tolerability of DHA, five articles presented data on experiments conducted with rats, 4 articles were review articles, and four articles did not have the appropriate study design, netting two articles from the first search. For the second search, 14 articles were excluded that had been retrieved in the first search, 26 were excluded as reviews, 2 were not conducted with humans, and 3 were inappropriate study design, netting 8 articles. Using the combined 2 searches, 10 articles were reviewed for this study.

Additionally, we scanned the reviews that were excluded from our search to see if any additional articles could be retrieved, conducted a BIOSIS Previews (1926–2010) search, a Web of Science (1980–2010) and a PsychInfo (1960–2010) search using the same search terms described above. These additional searches did not net any new studies. Lastly, the results that we present in this systematic review do not include a statistical synthesis of results because of the heterogeneity in study design, predictors (amount of DHA or EPA supplemented or how omega 3 PUFA intake was assessed). We concluded that at this stage a statistical synthesis of results would be premature, and it would be more important to highlight the differences in study design and measurement that could account for heterogeneity in results.

Results

Six studies did not show any association between DHA or omega-3 fatty acid intake and risk of maternal perinatal depression in pregnancy or the postpartum period [3,13–17], 2 articles had mixed results [18,19], and 2 showed a positive association [20,21]. Of the 10 studies, 3 were prospective longitudinal cohorts [14,18,19], 5 were RCTs [3,15–17,20,21], and 2 were pilot trials [13,15]. Below, the specific factors that impact the results for each study are discussed including time period of observation (pregnancy, postpartum or both), number of subjects in the study, measurement and amount of omega-3 fatty acids, study design, and measurement of outcome/results. The mixed studies are also discussed more in detail because they provided contrasting results. These variables are summarized in Table I.

Time-period

The studies had significant heterogeneity in terms of time of study and follow-up period. Women enrolled in the longitudinal studies were followed from pregnancy to the postpartum period. Two longitudinal studies were retrospective, evaluating women at 6 and 8 months postpartum in relation to dietary behaviors in pregnancy [14,19]. Strom et al. followed a cohort prospectively from mid-pregnancy until 1 year postpartum [18].

For the RCTs, women were followed through pregnancy to the postpartum period in two studies [16,20]. Two other studies followed women only during the postpartum period [17,21], and one followed a group of women from the third trimester of pregnancy until 6 months postpartum [3]. The pilot trial by Freeman et al. followed women only during the postpartum period (2–14 weeks postpartum) [15]. Marangell et al. conducted a pilot trial following a group of pregnant women with a past history of depression until 12 weeks postpartum [13].

Number of subjects

Study sizes ranged in size from 54,202 and 9960 participants for two longitudinal cohorts [18,19] to 16 and 26 participants for two RCTs [3,21]. The smallest study, an open label pilot study, had only seven participants [13] (Table I).

Amount/measurement of omega-3 fatty acids

The longitudinal cohorts used food frequency questionnaire to evaluate fish and omega-3 consumption in the perinatal period [18,19]. The RCTs and other trials supplemented with different amounts and formulations of DHA and EPA. Llorente et al. [17] and Doornbos et al. [16] supplemented 200 mg/day DHA and 220 mg/day DHA (or 220 mg/day DHA + 220 arachidonic acid (AA) mg/day), respectively. The other RCTs ranged from testing between 2 and 4 g/day of DHA + EPA [3,15,20]. The ratio of EPA to DHA in the supplements ranged between 1.8:1 and 1.38:1 [15,20], although one study provided supplements with a much higher ratio of DHA to EPA (4: 1) [3]. The study by Freeman et al. [15] also assessed

fish intake at baseline. The pilot trial by Marangell et al. [13] provided 173 mg EPA + 123 mg DHA supplement (ratio 1.4 EPA/DHA) and the pilot study by Freeman et al. provided between 0.5 and 2.8 g/day [21].

In addition to measuring intake of omega-3's, four studies assessed the fatty acid content of red blood cells either during pregnancy or in the postpartum period or at both time points. Two of these studies assessed fatty acid levels in pregnancy at two time points [16,20] and two assessed levels in pregnancy and during the postpartum period [14,17]. For two of these studies fatty acid levels [16,17] served as the main predictor and for two it was an additional predictor with fish or omega-3 intake evaluated in relation to perinatal depression [14,20].

Results/outcome for maternal depression

Most studies assessed maternal perinatal depression by employing a screener questionnaire to evaluate depressive symptoms, such as the Edinburgh Postnatal Depression Screener (EPDS) [3,13–17,19–21], the Hamilton Rating Scale for Depression (HAM-D) [3,13,15,20,21], the Beck's Depression Inventory II [14,17,20], or the Clinical Global Impression [15,21]. However, one study assessed risk for hospital admissions due to depression and prescriptions of antidepressant medication in the postpartum period [18]. Five studies also used diagnostic interview schedules to get a clinical diagnosis of depression in addition to the depression screeners [3,14,15,17,21]. The studies by Llorente et al. [17] and Freeman et al. [15,21] used the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders – Clinician Version (SCID-CV) and the study by Browne et al. [14] used the Composite International Diagnostic Interview for major depression (CIDI), both which can be used as a diagnostic instrument and permits evaluation of current and past episodes of syndromes of depression. Similarly, the study by Rees et al. confirmed the results of the depression symptoms screeners with a diagnosis of major depression or dysthymia through the clinical assessment of a psychiatrist and the CIDI-structured interview [3].

Randomized controlled trials and other trials

All RCTs compared supplementation with omega-3 PUFAs to placebo except for Freeman et al. [15], who added supportive psychotherapy to both the treatment (omega 3's) and control arm. Three out of five RCTs were double blinded [3,15,20]. Four RCTs found no differences between groups, while the one that did find a difference used higher doses of supplemental DHA (3.4 grams/day – 2.2 g EPA + 1.2 g DHA) (Table I). The open label pilot study by Marangell et al. used 173 mg EPA + 123 mg DHA and did not find an effect [13] while the 8-week pilot trial by Freeman et al. [21] used up to 2.8 g of day of EPA + DHA and found a decrease in depression scores at 8 weeks.

Tolerability

All studies that provided supplementation with omega-3 PUFA's indicated that the regimens were well tolerated. None reported any adverse effects on the subjects or the newborns [3,13,15,17,20,21].

Mixed studies

Two large, longitudinal studies found mixed results. The longitudinal study of individuals in the Danish National Birth Cohort did not find any association between postpartum depression (PPD) admissions and intake of fish or PPD admissions or PPD prescriptions and intake of n-3 PUFAs. Furthermore, the authors concluded that there was little evidence to support an association between intake of fish or n-3 PUFAs and depression [18]. However, this same study did find that those women who consumed < 3 g fish/day were at higher risk

for PPD-prescription than those who consumed > 30 g/day (OR: 1.61; 95% CI: 1.26–2.06) [18] and those who ate the least amount of omega 3's neared statistical significance for filling more PPD prescriptions (OR 1.24, 95% CI: 0.96–1.61) [18]. Similarly, the study by Golding et al. using the Avon Longitudinal Study of Parents and Children (ALSPAC) had mixed results finding that that higher intakes of omega-3 PUFAs at 32 weeks gestation were associated with reduced risk for depressive symptoms (those consuming no omega 3's had an increased risk of OR 1.54 (95% CI: 1.25–1.89) in comparison with those who consumed > 1.5 g/week) [19]. However, the same study did not show any association between intake of PUFAs at 32 weeks and depressive symptoms at 2 months although there were weak associations at 8 months postpartum.

Discussion

Our review found mixed results of published studies, with a couple reporting a positive and most reporting a negative association of supplementation with DHA + EPA and/or consumption of fish and decreased risk for maternal perinatal depression. The heterogeneity of these studies regarding time period of study and supplementation (prenatal, postnatal or combined prenatal/postnatal) makes interpretation of results difficult. Two RCTs that found a negative result had combined study subjects in the prenatal with those in the postnatal periods and provided both groups with the same supplementation [3,15] while two studies supplemented only in the postpartum period with only one finding an effect [17,21]. It is possible that supplementation that begins in the postpartum period may be too late due to meet the metabolic demands and depletion of omega-3 PUFAs associated with pregnancy.

The amount of the supplementation also likely plays a role. Studies providing only 200–220 mg/day of DHA did not report any difference in depressive scores after treatment [16,17], whereas those that provided higher levels of supplementation (3.4 g/day [20] or between 0.5 and 2.8 g/day [21]) found an effect although the study by Rees et al. which used a high dose (2.14 g) found no effect [3].

All studies had different formulations of omega-3 PUFAs. Some investigators did not provide EPA, while one added AA in addition to DHA [16]. The optimal formulation including the ratio of DHA to EPA for the prevention and treatment of perinatal depression is unknown. Typically most fish, especially oily fish that are recommended for the high concentration of omega-3 PUFAs, have a ratio of DHA to EPA of approximately 2:1, whereas commercial fish oils will often have a ratio of 2:3 or lower [22]. The only study that had a higher ratio of DHA to EPA did not find any effect [2].

Other heterogeneity in the studies reviewed included different measures of the predictor(s) and outcome. For the predictor(s), some studies evaluated fish intake and/or omega-3 PUFA consumption. Only 4 [14,16,17,20] out of the 10 studies assessed blood fatty acid levels and of those that did only two assessed in the postpartum period [14,17]. Future studies should evaluate both dietary intake and blood fatty acid levels. For the measures of depression, half of the 10 of the studies [3,14,15,17,21] validated the depression symptoms through the use of a diagnostic interview schedule and these studies were able to assess for more severe depression and may have had more study subjects with diagnosed clinical depression. Only one of these studies showed any effect possibly indicating that severity of depression may also play a role in response to omega-3 PUFA supplementation.

Some of the RCTs and pilot trials reviewed had very small sample sizes (e.g. 16 [21] and 26 [2]). The trials with the larger sample size, and hence more power to find an effect, also tended to supplement with smaller amounts of omega 3's (200–220 mg/day of DHA) and had negative results [16,17], although the mid-size study by Freeman et al, [15] with 59

subjects supplemented with the higher levels of omega-3 PUFAs supplemented (up to 2.7 g/day) and did find decreased risk for depression in the supplemented group.

A limitation of the studies selected for our review is that none of these studies assessed omega-6 PUFA consumption. While omega-3 PUFAs are the precursors for the anti-inflammatory series of eicosanoids (signaling molecules), omega-6 PUFAs are precursors for pro-inflammatory eicosanoids, and a high ratio of omega-6 to omega-3 PUFAs may be associated with depression and autoimmune and inflammatory disorders [23,24]. Omega-3 and omega-6 PUFAs also compete for enzyme systems for transformation into longer-chain, physiologically active metabolites (eicosanoids). The type of eicosanoids made is directly related to the levels of omega-3 and omega-6 PUFAs in the body. Future studies should potentially measure the omega-6 PUFA intake in addition to omega-3 PUFAs. Also, as described below, as omega-3 supplementation results in a decrease in certain omega-6 fatty acids, and any supplementation of omega-3's should be combined with formulations of omega-6 as well.

Concern has been raised about the safety of increasing omega-3 fatty acids during pregnancy and lactation, specifically the risks associated with contaminants such as mercury in certain fish sources of omega-3 PUFAs. In addition to being aware of the possible benefits that may be accorded to supplementation with omega-3 PUFAs, women should choose sources of omega-3 PUFAs that have low mercury and other contaminants. Furthermore, as studies suggest that maternal DHA supplementation alone reduces maternal AA, dihomo-GLA (DGLA) and gamma-linolenic acid (GLA) plasma and erythrocyte levels resulting in similar decreases in the neonate, it is important that any omega-3 supplementation formulation should not compromise neonatal GLA and DGLA status and that any supplementation involves a mixture of n-6 and n-3 fatty acids [23]. Additionally, any studies to evaluate supplementation early in pregnancy, particularly of higher doses of DHA or DHA + EPA (> 2 g/day), should be carefully monitored as most toxicity studies have been with non-pregnant women, men, and children [24].

Lastly, none of the studies reviewed assessed brain or synaptic DHA content while few assessed plasma DHA levels. It has been hypothesized that omega-3 fatty acids effects synaptic function by impacting membrane structure and through cytokine-immunoneuroendocrine interactions [25]. However, another study suggests that ALA, the precursor to DHA is taken up by cerebral microvascular endothelial cells and converted to DHA by astrocytes for uptake by neurons, suggesting that a diet high in DHA + EPA may not necessarily impact brain DHA levels. Such a theory could explain the lack of association found in some of the studies reviewed here between omega-3 supplementation and prevention of perinatal depression.

Meanwhile, given the study design and measurement heterogeneity of existing studies reviewed and the impossibility of testing brain DHA content in future clinical studies, we have three recommendations for future studies, which preferably should be double-blinded RCTs. Firstly, future RCTs should begin supplementation early in pregnancy before DHA demands peak. Secondly, supplementation should ideally be closer to 2 g/day of EPA + DHA in combination with n-6 fatty acids. Lastly, investigators should use a diagnostic interview schedule to measure depressive episodes in addition to a depression screener so that investigators can differentiate between severity of clinical symptoms.

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List of Studies Reviewed and Study Particulars

Table 1

References	Study design	Time period of study; study population	Number of subjects	Amount/measurement of DHA/other omega-3s	Result (±)
Longitudinal Cohort Studies Browne et al. [14]	Retrospective cohort	Pregnancy to 6 months postpartum; first time mothers	80	Fish consumption in pregnancy using FFQ; dietary supplements containing omega-3 in perinatal period; blood levels of omega-3's within 6 months postpartum	No association between fish consumption in pregnancy or lipid levels postpartum and depression status postpartum as measured by EPDS, BDI-II and CIDI (–)
Golding et al. [19]	Retrospective cohort	Pregnancy at 32 weeks gestation; until 8 months postpartum; pregnant women	9960	Food frequency questionnaire based on fish consumption at 32 weeks	Weak association between depressive symptoms (as measured by EPDS) at 8 months postpartum and fish intake at 32 weeks. No association between depressive symptoms at 2 months and intake at 32 weeks. Association between lower maternal intake of Omega 3's at 32 weeks gestation and depressive symptoms (±)
Strom et al. [18]	Longitudinal cohort	Mid-pregnancy to 1 year postpartum; pregnant women	54,202	Food-frequency questionnaire to assess fish and n-3 PUFAs administered at approx. 25 weeks of gestation (assessed diet in previous month).	No association between fish intake and risk of PPD admission (OR 0.82, 0.42–1.64); higher risk of PPD prescription for lowest group of fish intake (OR 1.46, 1.12–1.90). Also no associations with intake of n-3 PUFAs. (±)
Randomized controlled trials (RCTs) Doornbos et al. [16]	Randomized placebo controlled trial (3 arm)	16 weeks (pregnancy) until 3 months postpartum; pregnant women (first time mothers)	119	3 arms: DHA (220 mg/day) or DHA (220mg/day) + AA (220 mg/day) or placebo. All groups completed food frequency questionnaire (week 16 and 36 pregnancy and 12th week postpartum); fatty acid analysis conducted in RBC at 16 and 36 weeks.	Scores on EPDS (depression screener) did not differ based on group status at 36 weeks and 6 weeks postpartum. (–)
Freeman et al. [15]	Randomized, double-blind, placebo controlled trial for 8 weeks	Pregnancy (after 12 weeks) and postpartum period (before 6 months); current major depressive disorder	59	1.9 g/day EPA and DHA (1.1 grams EPA and 0.8 g DHA) + both arms were given psychotherapy	No significant changes in depression scores based on whether control or intervention arm using the EPDS, HAM-D and the Clinical Global Impression (–)
Llorente et al. [17]	Randomized, placebo controlled trial for 4 months	Postpartum period until 4 months; pregnant women who planned to breast-feed exclusively until 4 months	138	200 mg/day DHA. Blood fatty acid levels were measured at baseline (37–38 weeks gestation) and 4 months postpartum.	No difference between groups in depression symptom scores at 4 months (BDI score) Study also used EPDS and SCID-CV. (–)
Rees et al. [3]	Randomized, double blind, placebo controlled trial for six weeks	Perinatal period (third trimester to 6 months postpartum); current episode of major depression or dysthymia; excluded those with high fish intake	26 women (12 antenatal; 14 postnatal)	6 g/day fish oil (27.3% DHA; 6.9% EPA) in intervention group	No difference in depression scores at week 6 as indicated by EPDS; Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Scale (–)
Su et al. [20]	Randomized, double-blind, placebo controlled trial for 8 weeks	Pregnancy (between 16 and 32 weeks); current major depressive disorder.	36	Omega-3 PUFAs (3.4g/day) (2.2 g EPA and 1.2 g DHA). Red blood cell fatty acid analysis at week 8.	Omega 3 group had lower depressive symptom scores at week 6 and 8 ($p = 0.001$; $p = 0.019$) as indicated by the HAM-D. EPDS and BDI were also used (+)

References	Study design	Time period of study; study population	Number of subjects	Amount/measurement of DHA/ other omega-3s	Result (±)
Pilot trials Freeman et al. [21]	Double-blind trial for 8 weeks (3 arm but no placebo group)	Postpartum period (2–14 weeks); participants met criteria for major depressive episode by 1 month postpartum	16	3 groups: 0.5 g/day; 1.4 g/day or 2.8 g/day of omega-3s (ratio EPA: DHA was 1.5:1)	Decrease on 2 depression measures (EPDS, HAM-D) at 8 weeks compared with baseline by 51.5% and 48.8% (+)
Marangell et al. [13]	Pilot trial	From 34 to 36 weeks in pregnancy to 12 weeks postpartum; prior history of postpartum depression	7	2960 mg/day fish oil with 173 mg EPA and 123 mg DHA (ratio EPA:DHA was 1:4)	4/7 had relapse of postnatal depression as measured by the HAM-D and the EPDS (–)