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Polyunsaturated Fatty Acids in Perinatal Depression: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: Omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) are promising antidepressant treatments for perinatal depression (PND) because of supporting evidence from clinical trials, the advantage in safety, and their anti-inflammatory and neuroplastic effects. Although several observational studies have shown n-3 PUFA deficits in women with PND, the results of individual PUFAs from different studies were inconsistent.

METHODS: This systematic review and meta-analysis aims to compare the levels of PUFA indices, including eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid, total n-3, total n-6, and the n-6/n-3 ratio between women with PND and healthy control subjects. The meta-analysis included 12 eligible studies available as of December 2016. The effect sizes were synthesized by using a random effects model. In addition, we performed subgroup analysis for the PUFA levels in patients with prenatal and postnatal depression, both of which were compared with healthy control subjects.

RESULTS: There were significantly lower levels of total n-3 PUFAs and docosahexaenoic acid and significantly increased n-6/n-3 ratios in PND patients. In the subgroup analyses, there were significantly lower levels of n-3 PUFAs, eicosapentaenoic acid, and docosahexaenoic acid in women with prenatal depression. The n-6/n-3 ratio was significantly increased in both prenatal and postnatal depression subgroups.

CONCLUSIONS: Our meta-analysis consolidates the important role of n-3 PUFAs in PND. Nutritional medicine is an important strategy to improve the effectiveness of treatment for depression, and our findings provide the strong rationale to conduct clinical trials to test the therapeutic and prophylactic effects of n-3 PUFAs in PND.

Keywords: Arachidonic acid, Docosahexaenoic acid, Eicosapentaenoic acid, Omega-3, Perinatal depression, Polyunsaturated fatty acids

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Perinatal depression (PND) refers to major and minor depressive episodes during pregnancy (prenatal) and after delivery (postnatal) (1). The prevalence of clinical depression ranges from 6.5% to 12.9% at different trimesters of pregnancy and months in the first postpartum year (2). The consequences of PND include difficulty to perform usual activities, failure to seek perinatal care, inadequate diet, the abuse of tobacco, alcohol, and other harmful substances, the risk of self-harm or suicide, and adverse effects on fetal growth, infant temperament, and later behaviors in childhood (3–7). However, the etiology of PND remains unclear. Although PND is often explained by psychosocial dysfunction or endocrine alternation, its underpinning biochemical deficits, including nutritional risk factors, have been recently explored (8–10).

Omega-3 polyunsaturated fatty acids (omega-3 or n-3 PUFAs) are essential nutrients for maintaining perinatal physiological function of mothers and infants (11–15). In addition, omega-3 PUFA deficits have been hypothesized to be etiologically important in depression (16–18). For example, societies in which a large amount of n-3 PUFAs are consumed appear to have a lower prevalence of major depressive disorder (19). Patients with major depressive disorder have lower levels of omega-3 PUFAs (20). More importantly, several independent meta-analyses (21–25), if not all (26,27), have reported antidepressant effects of omega-3 PUFAs from data of published randomized controlled trials. During pregnancy and the postpartum breastfeeding period, omega-3 PUFAs are in high demand for fetal and infant development, and a functional decrease of omega-3 PUFA levels has been considered a risk factor for PND (28–30). In 2002, Hibbeln (31) reported in a cross-national ecological study that higher concentrations of docosahexaenoic acid (DHA) in breast milk and greater seafood consumption (rich in DHA) are associated with lower prevalence rates of postpartum depression. However, clinical trials showed inconsistent antidepressant effects of omega-3 PUFAs in PND (12,32–34), mainly because of the heterogeneity of study participants, the methodology of trial designs, composition and dosage of PUFA supplements, and uncontrolled baseline differences in dietary intakes and blood concentrations of omega-3 PUFAs.

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It is believed that depletion of PUFAs reserves throughout pregnancy and a lack of recovery postpartum may increase a woman's risk for depression. Several observational studies examined the omega-3 PUFA levels in PND but had inconsistent findings. For example, De Vriese *et al.* found that the levels of DHA and total n-3 PUFAs were significantly lower and the ratio of n-6/n-3 was significantly higher in women with postpartum depression (28). However, Otto *et al.* (35) and Browne *et al.* (36) could not replicate De Vriese *et al.*'s results. Although lower n-3 PUFAs were also reported to be associated with prenatal depression in some studies (37–40), others did not reveal similar findings (41,42). In addition, Sallis *et al.* found a weak "positive" rather than the hypothesized "inverse" association between n-3 PUFAs and perinatal-onset depression (41).

To understand this discrepancy, we performed a systematic review and meta-analysis to examine the levels of individual n-3 and n-6 PUFA compositions in women with PND compared with control subjects by pooling the results from all available observational studies. In addition, through subgroup analysis, we examined the difference of these PUFA levels in both prenatal and postnatal depression. We hypothesized that the levels of eicosapentaenoic acid (EPA), DHA, and total n-3 PUFAs were lower in women with PND than control subjects.

METHODS AND MATERIALS

Literature Search

To identify eligible studies in the systematic review and meta-analysis, two independent reviewers (P-YL and C-HC) searched for studies available as of December 2016 in the electronic databases of PubMed at the National Library of Medicine, Scopus, and Google Scholar. The search was performed by using the search terms: (omega-3 OR n-3) AND (perinatal OR postpartum OR pregnancy) AND depression, without special limitation in language. The titles and abstracts of studies found by the search strategy were screened to determine whether the studies were potentially eligible for inclusion in this meta-analysis. Studies that were apparently noneligible were excluded, such as review articles, nonhuman studies, case reports or series, and comments on other studies. In addition, the reference lists of relevant articles and review articles were examined for citations not indexed in above databases. In case of disagreement in eligibility, we reached agreement through consensus.

Selection Criteria for Studies in the Systematic Review and Meta-analysis

The included studies fulfilling the initial screening were examined based on the inclusion criteria used in this review, including studies that 1) included women in pregnancy or within 1 year after delivery; 2) examined depressive symptoms or diagnosis of depression; 3) used blood sample to measure any of the following PUFA indices: EPA, DHA, arachidonic acid (AA), total n-3, total omega-6 (n-6), and n-6/n-3 ratio; and 4) had a dataset that did not overlap with other studies. There was no limitation about the type of diagnostic criteria of depression, if it clearly described cases and noncases in the manuscript. When datasets from two studies overlapped, we included only the study with the larger sample size between them.

Meta-analytic Methods

The first purpose of the current meta-analysis was to compare the levels of PUFA indices, including EPA, DHA, AA, n-3, n-6, and n-6/n-3, between women with PND and control subjects. Second, we examined these levels between prenatal depression, postnatal depression, and relevant control subjects using subgroup analysis.

The case definition of depression was based on criteria provided in individual studies, through formal psychiatric diagnosis or assessment by rating scale. For each identified study, the effect sizes (ESs) expressing the difference in the level of PUFA index between patients with PND and control subjects were described as standardized mean differences based on Hedges' adjusted g, where values >0 indicated that the level of PUFA index was longer in patients. The means and standard deviations of the level of PUFA index of both patients and control subjects were used to derive the ES from each included study. When these data were not available from these articles, we contacted the authors to acquire the data or derived the ES from other statistical parameters, such as the t value, correlation, or p value. The ESs of individual studies were synthesized using the random effects model (43). The significance of the pooled ES was determined with the z test. Sensitivity analyses were performed in the analysis resulting in significant difference to determine if any individual study was responsible for the significant result. Each study was individually removed and the significance was retested.

Heterogeneity was examined to determine whether the group of ESs came from a homogeneous source and assessed by Q statistic, their related p value, and the I^2 statistic, which is the percentage of the variability in the estimate of effects that is caused by heterogeneity rather than random error. A rejection of homogeneity suggests that there may be systematic differences existing among included studies. In addition, we examined the existence of publication bias by using Egger's regression method, followed by a t test (44). Duval and Tweedie's trim and fill method (45) was used to correct any possible publication bias when it was identified. When publication bias was present, we performed additional sensitivity analyses using a fixed effect model followed by Duval and Tweedie's method, given that the fixed effect model was less sensitive to publication bias (46). Also, the quality of each individual study was examined by the Newcastle–Ottawa Scale adapted for cross-sectional studies (range 0–10) (47). We examined whether the ES was modulated by the individual study quality by conducting unrestricted maximum likelihood metaregression. In addition, we performed a subgroup analysis for overall analysis for these PUFA indices based on study design (case control vs. prospective) and case definition of PND (formal psychiatric diagnosis vs. by rating scale).

Statistics in meta-analyses were assessed with Comprehensive Meta-Analysis software (version 2; Biostat, Englewood, NJ). Two-sided p values $< .05$ were considered statistically significant. We reported the methods and the results of meta-analyses by following the Meta-analysis Of Observational Studies in Epidemiology checklist (Supplemental Table S1) (48).