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Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression

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Objective: Postpartum depression (PPD) affects 10–15% of mothers. Omega-3 fatty acids are an intriguing potential treatment for PPD.
Method: The efficacy of omega-3 fatty acids for PPD was assessed in an 8-week dose-ranging trial. Subjects were randomized to 0.5 g/day ($n = 6$), 1.4 g/day ($n = 3$), or 2.8 g/day ($n = 7$).
Results: Across groups, pretreatment Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD) mean scores were 18.1 and 19.1 respectively; post-treatment mean scores were 9.3 and 10.0. Percent decreases on the EPDS and HRSD were 51.5% and 48.8%, respectively; changes from baseline were significant within each group and when combining groups. Groups did not significantly differ in pre- or post-test scores, or change in scores. The treatment was well tolerated.
Conclusion: This study was limited by small sample size and lack of placebo group. However, these results support further study of omega-3 fatty acids as a treatment for PPD.

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Key words: postpartum period, depression, omega-3 fatty acids

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Significant Outcomes

- Omega-3 fatty acids, specifically a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), appeared beneficial and well tolerated for women with postpartum depression.
- Depressive symptoms significantly improved in all three dosage groups from baseline.
- There were no significant differences in treatment response between dosage groups.

Limitations

- The major limitations to this pilot study include small sample and lack of placebo group.
- A randomized, placebo-controlled trial is warranted to determine the efficacy of omega-3 fatty acids in PPD.

Introduction

Postpartum depression (PPD) affects 10–15% of women after childbirth and is defined in the DSM-IV as a major depressive episode that begins within 1 month of delivery (1, 2). PPD has broad, long-lasting consequences for a woman and her infant. Children of affected mothers may experience impaired attachment, and PPD may adversely affect behavioral and cognitive development (3–6). Despite its prevalence and serious effects, few studies have been published that inform the evidence-based treatment of PPD.

Omega-3 fatty acids are polyunsaturated essential fatty acids associated with health benefits in humans. For example, the American Heart Association recently provided guidelines for adult intake for the prophylaxis and treatment of cardiovascular disease, recommending regular fish intake for the general population and the use of omega-3 fatty acid supplements for those with coronary artery disease and hypertriglyceridemia (7). The long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in fish. Omega-3 fatty acids are necessary for optimal neurodevelopment *in utero* and in infants, among other benefits for pregnancy and infant health outcomes (8). Because of the developing baby's high demand for omega-3 fatty acids *in utero*, maternal essential fatty acid stores of essential fatty acids progressively decrease during pregnancy (9–11). Omega-3 fatty acid supplementation may confer benefits for the pregnancy outcome. For example, in a randomized, placebo-controlled trial, preterm deliveries were demonstrated to be lower in the group that received omega-3 fatty acids (2.8 g/day) compared with controls (12).

In regard to mood disorders, Hibbeln reported in cross-national studies that higher prevalence rates of both major depression in general and also specifically PPD are associated with lower per capita seafood consumption (13, 14). Most of the treatment studies conducted to date have utilized omega-3 fatty acids as an adjunctive treatment for major depression. Three randomized, placebo-controlled trials in which omega-3 fatty acids were assessed as an add-on treatment for treatment-refractory major depression demonstrated significant benefit of EPA or the combination of EPA and DHA in doses ranging from 1 to 9.6 g/day (15–17). Silvers et al. (18) did not find a combination of EPA and DHA more efficacious than placebo as an adjunctive treatment for major depression at a dose of 8 g/day. Also, Marangell et al. (19) did not find efficacy of DHA monotherapy (2 g/day) in depression. Additionally, this group also reported a small negative study of PPD prophylaxis ($n = 7$) with EPA and DHA supplementation in the third trimester, in women at high risk for PPD (20).

Aims of the study

Omega-3 fatty acids are intriguing as a treatment option for PPD. Because of the demands placed on the mother's supply of omega-3 fatty acids during pregnancy and lactation, PPD may be particularly responsive to treatment with DHA and EPA. Minimal data are available regarding standard antidepressant efficacy for the treatment of PPD. Some women refuse medications during pregnancy and/or breastfeeding, because long-term effects of antidepressants on the infant are unknown. Omega-3 fatty acid supplementation is associated with health benefits and is an attractive potential treatment. Thus, we conducted a randomized, dose-finding pilot trial of omega-3 fatty acids for PPD.

Material and methods

The study was an 8-week dose-finding interventional trial of a combination of EPA and DHA in 16 women with PPD. This study was approved by the Investigational Review Board at the University of Arizona. Twenty-one women were initially consented, although five patients decided not to participate after consenting for the study.

Participants were assessed with the Structured Clinical Interview for DSM-IV and baseline mood rating scales, including the Edinburgh Postnatal Depression Scale (EPDS) (our primary outcome measure), The Clinical Global Impressions Scale (CGI), and the Hamilton Rating Scale for Depression (24 items) (HRSD).

Participants were randomly assigned to a dosage of omega-3 fatty acids (EPAX 5500; Pronova, Lysker, Norway; ratio of EPA : DHA was 1.5 : 1): 0.5, 1.4, or 2.8 g. The doses were selected based on available data in major depression and safety/tolerability considerations. Placebo capsules (corn oil plus 1% fish oil) were provided so that total capsules per day equaled six for each treatment group. A small amount of fish oil was included in placebo capsules to maintain the blind. A placebo-only group was not included because of ethical concerns and the exploratory purposes of this study.

Inclusion criteria were: i) women aged 15–45 years, ii) participants met criteria for a major depressive episode with onset within 1 month of live childbirth, and iii) score of ≥15 on the HRSD or ≥9 on the EPDS, and iv) participants were able to provide written informed consent.

Exclusion criteria were: i) previous intolerance/allergy to omega-3 fatty acids, ii) current use of an antidepressant medication, iii) psychotic symptoms, iv) history of mania/hypomania, and v) active suicidal ideation.

Medical screening and history were obtained at study intake. Participants received laboratory screening prior to study participation that included a complete blood count and thyroid-stimulating hormone, to rule out anemia and thyroid abnormalities. Blood samples were collected pre- and post-treatment for later analyses.

Participants were assessed at intake visits at baseline, and then at weeks 1, 2, 4, 6, and 8. The HRSD and EPDS were administered at each visit. Compliance was assessed by asking subjects about the number of missed doses each week and pill counts. Patients were asked at each of the assessment sessions whether they had experienced any side effects since the last visit. They were asked specifically about whether they had any medical problems, seen a healthcare provider for any reason, or taken any prescription or over-the-counter medications for any reason.

Results

For all participants who returned for at least one visit after starting omega-3 fatty acids ($n = 16$), the mean age of mothers was 31 (range 20–42). Eleven were Caucasian (69%), and five were Hispanic (31%). Thirteen were married, one was separated, one divorced, and one single. Eleven had past histories of major depressive episodes, while this episode was the first for five of the mothers. Eleven experienced vaginal deliveries; three had cesarean sections. None had undergone infertility treatment prior to the pregnancy. Eleven were full term, and three babies were premature by approximately 3 weeks. At the time of study enrollment, all of the mothers were between 2 and 14 weeks postpartum (the mean was 8 weeks). In two cases the type of delivery and gestational age at delivery was not obtained. Nine mothers were multiparous; seven were primiparous. Twelve mothers (75%) were breastfeeding their babies (Table 1).

Mean scores of the EPDS and HRSD at study entry were 18.1 and 19.1 respectively; end scores were 9.3 and 10.0 respectively. Mean percent decreases in EPDS and HRSD scores were 51.5% and 48.8%, respectively. There were no serious adverse events, and omega-3 fatty acids were well tolerated.

We did not offer a controlled diet in this study. Baseline fish consumption was low in this sample. The mothers' mean fish intake was 0.25 servings of fish per week (range 0–1 serving per week of fish). Mothers were asked not to alter their fish consumption from their baseline intake assessment.

Between-group analyses

Subjects were randomly assigned to a daily dose of 0.5 g ($n = 6$), 1.4 g ($n = 3$), or 2.8 g ($n = 7$). We compared pretest scores across dose groups to see if there was a significant difference in baseline level of depression as measured by the EPDS and the HRSD. We also compared post-test scores across dose groups to see if there was a significant difference in the final measure of depression. As these groups were independent, we used analysis of variance (ANOVA) to test the differences between groups.

Small sample size was addressed by the re-sampling technique bootstrapping (21), a procedure in which random sub-samples are generated from the actual sample. The sub-samples are used to estimate parameters such as mean and standard deviations. We generated 1000 sub-samples from within each dose group. Each permutation yields a desired parameter, such as a mean or standard deviation. The bootstrap procedure does not yield more 'valid' estimates, but rather estimates that are more reliable. As small samples will tend to yield unstable estimates, we used the bootstrapped standard deviations in our calculations. We used the standard deviation summary statistic from the bootstrap procedure with the observed mean values and degrees of freedom to perform ANOVAs to test for significant differences in mean depression score between each dose group [see the following references for similar usage of these procedures (22–25)]. Each significance test was tested at the 0.05 level and ANOVAs were calculated for both the EPDS and the HRSD.

Table 1. Pre- and Post-treatment Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD) scores

Dosage group	Subjects per group	Mean pretreatment EPDS score	Mean Post-treatment EPDS score	Mean Pretreatment HRSD score	Mean Post-treatment HRSD score
0.5 g/day	6	18.5	8.5	18.0	9.3
1.4 g/day	3	15.3	5.0	19.0	7.0
2.8 g/day	7	19.0	11.9	20.3	11.9
All groups	16	18.1	9.3	19.1	10.0

There were no significant differences between groups for pretest depression scores: EPDS (F2, 13 = 1.86, $P > 0.05$) and HRSD (F2, 13 = 1, $P > 0.05$). In addition, there were do significant differences between groups for post-test depression scores: EPDS (F2, 13 = 2.27, $P > 0.05$) and HRSD (F2, 13 = 1.03, $P > 0.05$).

Within-group analyses

We also did an intention-to-treat analysis to test for significant differences between pre- and post-test depression scores within each dose group. As comparing within-group pre- and post-test scores yields comparisons between dependent groups, we used paired *t*-tests to calculate differences between pre- and post-test scores. Only observed data were used in the analyses. There were significant differences between pre- and post-test EPDS scores within each group: dose of 0.5 g ($t = 4.44$, d.f. = 5, $P < 0.05$), dose of 1.4 g ($t = 4.72$, d.f. = 2, $P < 0.05$), and dose of 2.8 g ($t = 4.67$, d.f. = 6, $P < 0.05$). There was also a significant difference between pre- and post-test EPDS scores when all dose levels were combined ($t = 8.47$, d.f. = 15, $P < 0.05$). There were significant differences between pre- and post-test HRSD scores within each group: dose of 0.5 g ($t = 3.67$, d.f. = 5, $P < 0.05$), dose of 1.4 g ($t = 8$, d.f. = 2, $P < 0.05$), and dose of 2.8 g ($t = 3.56$, d.f. = 6, $P < 0.05$). There was also a significant difference between pre- and post-test for HRSD scores when all dose levels were combined ($t = 6.76$, d.f. = 15, $P < 0.05$).

Discussion

In this pilot trial for PPD, we found that women experienced a significant improvement in depressive symptoms while receiving an intervention of a nutritional supplement with broad health advantages. We did not find an advantage of the higher doses over the lowest dose of 0.5 g/day. The interpretation of our findings is limited by small sample size and lack of a placebo-control group, but the improvements observed among all treatment groups suggest omega-3 fatty acids may have efficacy as a treatment for PPD. Another limitation in this study is that our randomization did not yield equal numbers in each group.

Additionally, this report does not include biochemical measures. Biological measures, including pre- and post-treatment assessments of plasma levels of essential fatty acids, may help to determine which patients may be most likely to benefit most from omega-3 fatty acid supplementation. As a result of these study limitations, we cannot rule out the possibility that subjects improved because of non-specific effects of study participation. However, we find these findings especially compelling, considering that omega-3 fatty acids offer health benefits to the mother, and also to her infant if she is breastfeeding.

While the treatment considerations regarding depression during pregnancy and PPD do not completely overlap, the high recurrence rate of PPD after subsequent deliveries supports that an ideal treatment is one that can be safely utilized during pregnancy. Also, many women diagnosed with PPD report the onset of depression during pregnancy (26). At this time, the issue of antidepressant medication use during pregnancy is increasingly controversial, due to a growing number of reports of a neonatal withdrawal or toxicity syndromes in neonates after *in utero* exposure to antidepressants (27, 28). Concurrently, patients are often interested in complementary and alternative treatments (29). Further study of omega-3 fatty acids for depression during pregnancy may also be warranted.

In summary, in this study we observed that regardless of dose, women improved significantly from baseline during the course of the study. These results support the inclusion of omega-3 fatty acid supplements among treatments that deserve further study for PPD. Clinical use for PPD is attractive, as there are health benefits and low risks of modest doses of omega-3 fatty acids for perinatal women and their babies.

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