An open trial of Omega-3 fatty acids for depression in pregnancy*

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Objective: In this flexible-dose, open-label trial, we examined the efficacy of omega-3 fatty acids for the treatment of depression during pregnancy.

Methods: Fifteen pregnant women with major depressive episodes participated. Subjects initially received two capsules per day [0.93 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)]; the dose could be increased by one capsule per day every 2 weeks to a maximal dose of 2.8 g. Subjects were assessed with the Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD).

Results: Average duration of participation in this treatment trial was 8.3 weeks (SD ± 7.1). Average final dose of EPA + DHA in this flexible dose trial was 1.9 g per day (±0.5). The mean reduction in EPDS scores was 40.9% (SD ± 21.9); the mean decrease in HRSD score was 34.1% (SD ± 27.1).

Conclusions: This open trial provides data to support the need for randomized controlled dose-finding trials of omega-3 fatty acids in major depressive episodes during pregnancy.

Introduction

Depression during pregnancy is common. In a prospective study, Evans et al. (2001) (1) found that 13.5% of women (n = 14,541) experienced serious depressive symptoms at 32 weeks of pregnancy. In that study, women were actually more likely to experience substantial depressive symptoms between 18 and 32 weeks of pregnancy than in the postpartum. Depression in pregnancy and postpartum has a negative impact on the development and health of the baby. Maternal stress in humans is associated with lower birth weight and gestational age at birth, and it has been associated with fetal hypoxia, low birth weight, and miscarriage in animals (2,3). Although the risks of antidepressants in pregnancy must be balanced against the risks of untreated maternal depression, some adverse effects may occur from antidepressant use in pregnancy. Possible selective serotonin reuptake inhibitor withdrawal syndromes and/or toxic reactions in neonates have been reported (4–6). A high rate of admission of neonates to special care nursery after late pregnancy exposure to fluoxetine has been reported (7). Therefore, many women and their physicians may prefer an option to standard antidepressant medication during pregnancy. To our knowledge, there are no published data for antidepressant medication efficacy during pregnancy.

*Preliminary results from this study were presented by Dr Freeman at the American Psychiatric Association Research Colloquium for Junior Investigators; (Abstract: Freeman MP, Wisner KL, Gelenberg AJ, Hibbeln JR. Omega-3 Fatty Acids for Depression in Pregnancy. American Psychiatric Association Research Colloquium for Junior Investigators, San Francisco, CA, May 18, 2003).
In contrast to the concerns regarding infant exposure to antidepressant medications, omega-3 fatty acids are required for optimal growth and development in utero and in infants. Maternal omega-3 fatty acid stores are diminished, as they are selectively transferred to the developing fetus during pregnancy for brain and retinal development (8,9,10). Intake of omega-3 fatty acids during pregnancy and lactation in the United States is inadequate, reaching only approximately 20–60% of amounts recommended by a National Institutes of Health workshop (11). Omega-3 fatty acid supplementation protects against preterm delivery (12,13). Dietary data also suggest omega-3 fatty acids protect against pre-eclampsia and cerebral palsy (14,15). Maternal omega-3 fatty acid supplementation offers benefit for the infant postpartum, who relies on breastmilk or formula for essential fatty acids as a nutritional requirement. Data suggest infant formulas should be supplemented with omega-3 fatty acids, especially in cases of prematurity (16,17). Several international organizations advocated for the addition of omega-3 fatty acids to infant formulas (18–21). Omega-3 fatty acids have been identified as a promising treatment for depression during pregnancy. In countries in which intakes of omega-3 fatty acids are low, prevalence rates of postpartum depression are 50-fold greater compared with countries with the highest intakes (22). Women with postpartum depression have higher ratios of omega-6 to omega-3 fatty acids in phospholipids compared with controls (23). Three recent double-blind, placebo-controlled trials demonstrated that adjunctive omega-3 fatty acids were effective for antidepressant-refractory depression in non-pregnant patients. Two of those studies utilized eicosapentaenoic acid (EPA) (24,25); the other utilized a combination of EPA + docosahexaenoic acid (DHA) (26). However, a trial of DHA alone as monotherapy was not found to be effective for unipolar depression in a double-blind trial (27). A case study of the successful use of omega-3 fatty acids for the treatment of depression during pregnancy has been published (28).

Methods
We conducted an open-label trial of omega-3 fatty acids, EPA and DHA, for major depression during pregnancy. The study was approved by the Institutional Review Board at the University of Arizona. Informed consent was obtained after the study had been fully explained. Due to the high incidence of morning sickness in early pregnancy, we limited participation to women who were ≥16 weeks gestation.

Study participation was offered to pregnant women who met criteria for major depressive episodes and declined treatment with antidepressants. A major depressive episode was verified using the structured clinical interview for DSM-IV. Eligibility criteria included (1) pregnant women ages 18- to 45-years-old, (2) regular attendance at outpatient prenatal care appointments, (3) a minimum score of 9 on the Edinburgh Postnatal Depression Scale (EPDS) or 15 on the 24-item Hamilton Rating Scale for Depression (HRSD), (4) outpatient status, and (5) ability to provide written informed consent. Exclusion criteria included (1) previous intolerance or allergy to omega-3 fatty acids or fish oil, (2) current use of antidepressant medication, (3) psychotic symptoms, (4) history of mania/hypomania, and (5) active suicidal ideation.

Pronova Biocare provided the study oils. Subjects initially received two capsules per day (0.93 g of EPA/DHA). The dose could be increased by one capsule per day every 2 weeks to a maximal dose of 2.8 g (1.7 of EPA and 1.1 g of DHA). The decision to increase dose was based on the investigator's clinical assessment and patient preference. Each capsule contained 0.467 g EPA + DHA (0.28 g EPA, 0.18 g DHA). The U.S. Food and Drug Administration (FDA) recognizes up to 3 g/d of a combination of EPA and DHA in the category of Generally Recognized As Safe, which was the primary consideration in selection of the maximal dose. Subjects were assessed with the EPDS and HRSD at 2-week intervals. Subjects were allowed to continue participation until delivery of their baby.

Results
Fifteen women enrolled in the trial. Of subjects screened for study participation, three were excluded. One was excluded for heparin treatment, one for active substance abuse, and one opted for treatment with standard antidepressant medication. We excluded subjects receiving heparin treatment as a safety measure. In several published studies, omega-3 fatty acid supplementation does not appear to increase the risk of adverse events of bleeding, even with concomitant anticoagulation therapy (29,30). However, a case was reported in which a patient treated with warfarin experienced significant changes in
coagulation studies after an increase in dose of concomitant fish oil (31).

Average duration of participation in this treatment trial was 8.3 weeks (SD ± 7.1). Average final dose of EPA + DHA in this flexible dose trial was 1.9 g per day (±0.5). The mean reduction in EPDS scores was 40.9% (SD ± 21.9); the mean decrease in HRSD score was 34.1% (SD ± 27.1).

The EPDS and HRSD changes are summarized in Table 1. Side-effects were limited to a mild increase in burping after ingestion of capsules. No drop-outs occurred due to side-effects.

**Discussion**

This was a small, flexible-dose, open trial of omega-3 fatty acids for major depressive episodes during pregnancy. The purpose of this study was to gather pilot data regarding the tolerability and efficacy of omega-3 fatty acids for depression during pregnancy and to inform further study.

At intake, participants in this study were informed of other treatment options, including antidepressant medications and psychotherapy. As the case with the general public (32), the patients in this study expressed strong interest in a ‘natural’ treatment option. We suspect that fears about medication exposure to the fetus prevent many women from seeking treatment for depression during pregnancy.

The optimal dose of omega-3 fatty acids for depression is unclear at this time. In our small sample, the majority of the strongest responses were seen with 1.9 g per day of omega-3 fatty acids. In this preliminary trial, we utilized a slow upward titration of dose due to consideration of morning sickness. As many participants were treated for only 4–6 weeks, it is possible that a therapeutic dose was not reached for many subjects.

There is a paucity of data to inform clinicians about the safety and efficacy of the use of pharmacologic treatments for depression during pregnancy. To our knowledge, this is the first study of omega-3 fatty acids for depression during pregnancy. The risk/benefit analysis is different when the patient is pregnant, and both maternal depression and antidepressants pose risks to the baby. Omega-3 fatty acids have established safety and health benefits in pregnancy and deserve further study as a treatment modality for depression during pregnancy. Omega-3 fatty acids are an exciting potential treatment alternative for the pregnant or breastfeeding mother with depression, with promising benefits for her child.

As this trial was limited by the lack of a control group, a placebo effect cannot be ruled out as a contributing factor to the substantial reduction in depressive symptoms observed. The tolerability, participant acceptance, and magnitude of response suggest that omega-3 fatty acids may be an effective treatment for major depressive episodes during pregnancy. Randomized, placebo-controlled trials of omega-3 fatty acids for depression during pregnancy are urgently needed to further evaluate efficacy, time-course of response, and optimal dosing.

**Table 1. Omega-3 fatty acid supplementation for depression during pregnancy**

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<tr>
<th>Subject</th>
<th>Initial EPDS</th>
<th>Final EPDS</th>
<th>Initial HRSD</th>
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EPDS, Edinburgh Postnatal Depression Scale; HRSD, Hamilton Rating Scale for Depression.
Acknowledgements
This work was supported by a K23 award from the National Institutes of Mental Health (1 K23 MH66265-01), Pronova Biocare (provision of materials) and Wyeth Nutritionals (grant-in-aid).

References

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