

## Brief Report

# OMEGA-3 FATTY ACIDS FOR THE PREVENTION OF POSTPARTUM DEPRESSION: NEGATIVE DATA FROM A PRELIMINARY, OPEN-LABEL PILOT STUDY

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*Based on the putative relationship between depleted omega-3 fatty acids and postpartum depression, we initiated an open-label pilot study of omega-3 fatty acid supplementation with the aim of preventing postpartum depression. Euthymic pregnant females with a past history of depression in the postpartum period were started on 2,960 mg of fish oil (1.4:1 eicosapentaenoic acid:docosahexaenoic acid) per day between the 34th to 36th week of pregnancy and assessed through 12 weeks postpartum. Four of seven participants had a depressive episode during the study period. No participants withdrew from the study due to adverse events. This preliminary, small, open-label pilot study failed to show promising results for the use of omega-3 fatty acid monotherapy beginning at 34 to 36 weeks gestation for the prevention of postpartum depression in patients with a prior postpartum depression history. Controlled studies are lacking. Depression and Anxiety 19:20–23, 2004.*

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**Key words:** *omega-3 fatty acids; eicosapentaenoic acid; docosahexaenoic acid; postpartum depression; fish oil*

## INTRODUCTION

Women with a prior history of postpartum depression have an estimated 25–50% risk for recurrence in subsequent pregnancies [Cooper and Murray, 1995; Davidson and Robertson, 1985; Garvey et al., 1983; Wisner and Wheeler, 1994; Wisner et al., 2001]. Several investigators have suggested a relationship between depleted omega-3 fatty acids and affective disorders [Edwards et al., 1998; Hibbeln and Salem, 1995; Maes et al., 1996; Peet et al., 1998]. Data pooled from numerous studies demonstrated a significant negative correlation between the point prevalence of postpartum depression in 19 countries and the apparent fish consumption in those countries [Hibbeln, 1999]. Interestingly, maternal docosahexaenoic acid (DHA, an omega-3 fatty acid) status has been reported to decline during normal pregnancy [Al et al., 1995]. Results from a cross-sectional study in pregnant primigravida and multigravida women demonstrated a significant negative correlation between gravida num-

ber and maternal DHA plasma levels, suggesting that maternal DHA status may decrease further with each subsequent pregnancy [Al et al., 1997]. However, recently published data did not show a relationship between DHA status and parity in nonpregnant women at least 1 year after their last pregnancy, suggesting an

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Received for publication 15 February 2003; Accepted 29 September 2003

DOI 10.1002/da.10148

Published online in Wiley InterScience (www.interscience.wiley.com).

eventual normalization of DHA status after pregnancy [van den Ham et al., 2001]. Eicosapentaenoic acid (EPA, an omega-3 fatty acid) has recently been found to be a promising adjunctive treatment for patients with unipolar depression taking standard antidepressant medications [Nemets et al., 2002; Peet and Horrobin, 2002]. Fish oil supplementation, a natural source of EPA and DHA, appears to be safe during pregnancy and lactation. We report the results of a preliminary, small, open-label trial of fish oil in the prophylaxis of postpartum depression.

## SUBJECTS AND METHODS

This study was approved by the Institutional Review Board at Baylor College of Medicine. All participants provided written informed consent prior to study participation. Pregnant adult women 18 years of age or older with a past history of a depressive episode in the postpartum period who were not suffering from a current depressive episode were considered for entry into the study. Candidates were excluded if they were currently depressed at the time of clinical interview, were taking psychotropic medications within 2 weeks of baseline, had a history of nonresponse to two or more antidepressants, had serious comorbid medical or psychiatric illnesses, or posed a significant risk of dangerousness to self or others. All participants were aware of conventional treatment options available, and none were instructed to discontinue psychotropic medications or decline available treatments for the purpose of study participation.

Following a clinical diagnostic assessment, consenting subjects were instructed to take 10 study capsules per day, each containing 173 mg of EPA and 123 mg of DHA obtained from arctic deep-sea fish oil (total daily dose 2,960 mg). The capsules were manufactured and provided by Nordic Naturals (Aptos, CA). The baseline visit and initiation of treatment began between the 34th and 36th week of pregnancy. Participants returned for study visits 2 weeks after the baseline visit, and then at weeks 2, 4, 8, and 12 postpartum. Assessments included vital signs, the 28-item Hamilton Rating Scale for Depression (HAM-D), the Edinburgh Postnatal Depression Scale (EPDS), an adverse experiences log, a daily mood diary, and a dietary questionnaire to assess the dietary intake of omega-3 fatty acids [Cox et al., 1987; Hamilton, 1967]. Study endpoints included completion of the study at 12 weeks postpartum or the onset of a depressive episode prior to study completion.

## RESULTS

Seven candidates met study criteria and were enrolled in the study. The participants ranged in age from 31 to 42 years. There was one married, Hispanic woman. All other participants were married, Caucasian

women. No participants were taking antidepressant medications or mood stabilizers.

The past history of postpartum depressive episodes and study outcomes for each participant are shown in Table 1. Exit HAM-D and EPDS scores are not available for two participants who informed us about the onset of a depressive episode by phone. One of these participants returned for a study exit visit, but formal assessments for depressive symptoms were not completed because she had already started open-label treatment with a conventional antidepressant prescribed by her obstetrician. The other participant did not return to the clinic for a final study visit. Attempts were made to have this participant return to clinic for final study assessments and further care or referral.

Adverse events reported during the study were mild in nature, including a "fishy" aftertaste ( $n=4$ ), mild dyspepsia ( $n=1$ ), and increased stool frequency with loose stools ( $n=1$ ). No participants withdrew from the study due to adverse effects.

## DISCUSSION

This open trial of fish oil in the prophylaxis of postpartum depression did not yield promising results. The expected relapse rate of postpartum depression in untreated individuals is approximately 50%. The study was designed to enroll 20 participants, with the one-sided 95% lower confidence interval for a 50% relapse rate of slightly over 30% of the study population, or six subjects. Fewer than six relapses in a sample size of 20 participants would be significantly lower than the expected rate and would warrant further investigation. However, given the high relapse rate observed after enrolling only seven participants in a study with an open-label design, we made the ethical decision to terminate the study and cease further enrollment. Although no clear standard of care for the prophylactic treatment of postpartum depression currently exists and fish oil does not cause known adverse events, we feel that the level of recurrence risk and the lack of promising results after enrolling seven participants justified early study termination.

Several limitations warrant discussion. First, the findings are difficult to interpret given the small sample size. Given the preliminary nature of this study and the open-label design, we felt that a small sample size was appropriate to look for results that might suggest the potential benefits of this treatment strategy and lead to a larger, controlled study. Second, the lack of a control group limits our ability to determine whether the rate of depression seen in this study population would have been different had participants taken a conventional antidepressant or a placebo. Third, the dose of fish oil chosen was based on its reported safety in pregnant females when used in other disorders. However, the optimal dose of omega-3 fatty acids in the treatment or prophylaxis of major depression is not known. Similarly, while omega-3

**TABLE 1. Past postpartum depression history and study outcome for participants**

Participant/episode	Postpartum depression history			Study assessment				Study outcome
	Onset (days)	Duration (days)	Treatment	HAM-D		EPDS		
				Base	Exit	Base	Exit	
Subject 1								
1	90	180	Maprotiline	4	4	2	4	No relapse
Subject 2								
1	2	21	None	9	0	8	2	No relapse
2	2	21	None					
3	2	21	None					
Subject 3 <sup>a</sup>								
1	7	90	None	7	9	10	13	Relapse 7 days PP
2	7	90	None					
Subject 4								
1	21	180	None	4	22	12	20	Relapse 61 days PP
2	21	N/A	Sertraline					
Subject 5								
1	2	90	None	3	35	9	21	Relapse 3 days PP
2	2	42	None					
3	2	42	Progesterone					
4	2	42	Sertraline					
Subject 6								
1	2	14	None	1	4	10	2	No relapse
Subject 7								
1	4	90	None	4	4	N/A	N/A	Relapse

<sup>a</sup>Final HAM-D and EPDS scores shown for this participant were done 10 days prior to actual study exit date (via phone contact); participant did not return for five exit assessments.

Onset = number of days postpartum that depression began; HAM-D = 28-item Hamilton Depression Rating Scale; EPDS = Edinburgh Postnatal Depression Scale; Base = baseline assessment prior to beginning study medication; PP = postpartum; N/A = data not available.

fatty acid deficiency is hypothesized in this population, the degree of deficiency is not known. It is conceivable that the use of a different dosing strategy or different fish oil preparation (e.g., a formulation with a different ratio of EPA to DHA or a formulation containing only EPA or only DHA) may have yielded more promising results. Similarly, the duration of treatment with omega-3 fatty acids in this study may have been inadequate to prevent postpartum depression in a cohort of patients with a prior history of postpartum depression. Perhaps a longer trial of omega-3 fatty acids initiated earlier in pregnancy is indicated. Fourth, most of the participants were referred from a birthing center where they were under the care of a midwife. This group of participants may not be representative of the target population. Finally, socioeconomic stressors, marital discord, and other psychosocial stressors that may increase the risk of postpartum depression were not assessed during the study.

We caution the reader to consider the preliminary nature of our data when interpreting these results. Although this study failed to suggest the potential efficacy of our treatment strategy employing the use of an omega-3 fatty acid preparation containing both EPA and DHA in a 1.4:1 ratio prescribed in daily doses of 2,960 mg beginning at months 34–36 of pregnancy in a population at increased risk for postpartum depression,

current scientific literature supports the continued investigation of omega-3 fatty acids in the treatment of mood disorders.

**Acknowledgments.** Fish oil capsules were donated by Nordic Naturals (Aptos, CA). No other commercial support was received in relation to this study.

## REFERENCES

- Al MD, van Houwelingen AC, Kester AD, Hasaart TH, de Jong AE, Hornstra G. 1995. Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. *Br J Nutr* 74:55–68.
- Al MD, van Houwelingen AC, Hornstra G. 1997. Relation between birth order and the maternal and neonatal docosahexaenoic acid status. *Eur J Clin Nutr* 51:548–553.
- Cooper PJ, Murray L. 1995. Course and recurrence of postnatal depression: Evidence for the specificity of the diagnostic concept. *Br J Psychiatry* 166:191–195.
- Cox JL, Holden JM, Sagovsky R. 1987. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 150:782–786.
- Davidson J, Robertson E. 1985. A follow-up study of post partum illness, 1946–1978. *Acta Psychiatr Scand* 71:451–457.
- Edwards R, Peet M, Shay J, Horrobin D. 1998. Depletion of docosahexaenoic acid in red blood cell membranes of depressive patients. *Biochem Soc Trans* 26:S142.

- Garvey MJ, Tuason VB, Lumry AE, Hoffmann NG. 1983. Occurrence of depression in the postpartum state. *J Affect Disord* 5:97-101.
- Hamilton M. 1967. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278-296.
- Hibbeln JR, Salem N, Jr. 1995. Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy. *Am J Clin Nutr* 62:1-9.
- Hibbeln JR. 1999. Membrane lipids in relation to depression. In: Peet M, Glen I, Horrobin DF, editors. *Phospholipid spectrum disorder in psychiatry*. Carnforth, UK: Marius Press. p 202-203.
- Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. 1996. Fatty acid composition in major depression: Decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 38:35-46.
- Nemets B, Stahl Z, Belmaker RH. 2002. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 159:477-479.
- Peet M, Murphy B, Shay J, Horrobin D. 1998. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 43:315-319.
- Peet M, Horrobin DF. 2002. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 59:913-919.
- van den Ham EC, van Houwelingen AC, Hornstra G. 2001. Evaluation of the relation between n-3 and n-6 fatty acid status and parity in nonpregnant women from the Netherlands. *Am J Clin Nutr* 73:622-627.
- Wisner KL, Wheeler SB. 1994. Prevention of recurrent postpartum major depression. *Hosp Community Psychiatry* 45:1191-1196.
- Wisner KL, Perel JM, Peindl KS, Hanusa BH, Findling RL, Rapport D. 2001. Prevention of postpartum depression: A randomized clinical trial. *J Clin Psychiatry* 62:82-86.

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