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Omega-3 Fatty Acids and Supportive Psychotherapy for Perinatal Depression: A Randomized Placebo-Controlled Study

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Abstract

Background—Perinatal major depressive disorder (MDD), including antenatal and postpartum depression, is common and has serious consequences. This study was designed to investigate the feasibility, safety, and efficacy of omega-3 fatty acids for perinatal depression in addition to supportive psychotherapy.

Methods—Perinatal women with MDD were randomized to eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), 1.9 g/day, or placebo for eight weeks. A manualized supportive psychotherapy was provided to all subjects. Symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D) and Edinburgh Postnatal Depression Scale (EPDS) biweekly.

Results—59 women enrolled; N=51 had two data collection points that allowed for evaluation of efficacy. Omega-3 fatty acids were well tolerated. Participants in both groups experienced significant decreases in EPDS and HAM-D scores ($p < .0001$) from baseline. We did not find a benefit of omega-3 fatty acids over placebo. Dietary omega-3 fatty acid intake was low among participants.

Limitations—The ability to detect an effect of omega-3 fatty acids may have been limited by sample size, study length, or dose. The benefits of supportive psychotherapy may have limited the ability to detect an effect of omega-3 fatty acids.

Conclusions—There was no significant difference between omega-3 fatty acids and placebo in this study in which all participants received supportive psychotherapy. The manualized supportive

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psychotherapy warrants further study. The low intake of dietary omega-3 fatty acids among participants is of concern, in consideration of the widely established health advantages in utero and in infants.

Keywords

Perinatal; depression; postpartum; pregnancy; omega-3; supportive psychotherapy

Perinatal Major Depressive Disorder (MDD), defined as occurring during pregnancy or postpartum, is common and presents distinct treatment challenges. MDD affects between 10–20% of perinatal women (Marcus et al., 2003; Evans et al., 2001). Untreated depression increases the risk of negative pregnancy outcomes (Wadhwa et al., 1993; Wisner et al., 2000; Istvan, 1986). Postpartum depression (PPD) negatively impacts child development, affecting attachment, cognitive development, and behavior (Newport et al., 2006). Successful treatment of maternal MDD improves mental health outcomes for children (Weissman et al., 2006). Relapse rates of MDD are high during pregnancy, especially if antidepressants are discontinued (Cohen et al., 2006). Generally, older data pertaining to use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) do not suggest antidepressants increase the risk of major malformations (Wisner et al., 2000), and overall risk of teratogenicity following first trimester exposure appears low, although some rare birth defects have been observed to occur at higher rates with use of specific SSRIs (Alwan et al., 2007; Louik et al., 2007). Chambers et al. (2006) demonstrated an association between late antenatal SSRI use and persistent pulmonary hypertension in the newborn, a rare but serious condition (Chambers et al., 2006). There is a growing literature regarding a neonatal syndrome and medical complications with late pregnancy antidepressant use (Moses-Kolko et al., 2005). Although the literature suggests low levels of antidepressant exposure through breastmilk, there have been case reports of suspected adverse events in breastfed babies and a lack of long-term safety data (Weissman et al., 2004).

There are generally few controlled trials for postpartum depression that assess medication treatment, and no controlled trials have been published that assess efficacy of antidepressants in pregnancy. In women with postpartum depression, there has been only one placebo-controlled antidepressant trial for PPD (using fluoxetine), and one randomized trial comparing sertraline to nortriptyline (Appleby et al., 1997; Wisner et al., 2006). There have been no published efficacy trials of antidepressants in pregnancy. Psychotherapies appear efficacious, but have not received a large amount of study (Stuart et al., 2003; Dennis, 2004). Studies of novel, safe, and accessible treatments are needed for perinatal depression.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential omega-3 fatty acids found in fish. Omega-3 fatty acids offer broad health benefits that are particularly established in the field of cardiology (Kris-Etherton et al., 2003). Meta-analyses of placebo-controlled treatment studies in affective disorders have demonstrated significant benefit of omega-3 fatty acids over placebo, although heterogeneity of study methodology complicates interpretation (Freeman et al., 2006a; Parker et al., 2006). The majority of positive placebo-controlled studies have utilized EPA or a combination of EPA and DHA as adjunctive treatments in MDD. Epidemiologic and biological data also support a role of omega-3 fatty

acids in MDD and PPD (Freeman et al., 2006a; Parker et al., 2006; Hibbeln, 2002; Otto et al., 1997).

Omega-3 fatty acids are particularly attractive for consideration in the treatment of perinatal MDD, as depletion of maternal omega-3 fatty acids occurs during pregnancy due to high demand for fetal central nervous system development (Otto et al., 1997; Min et al., 2000; Al et al., 2005). Perinatal omega-3 fatty acid intake has beneficial effects upon pregnancy outcome and infant development. Data support a protective effect of omega-3 fatty acids in pregnancy outcomes, including length of gestation, preeclampsia, and cerebral palsy (McGregor et al., 2001). Unlike in utero or neonatal antidepressant medication exposure, which is considered of potential risk, increasing perinatal exposure to omega-3 fatty acids offers neurodevelopmental advantages (Carlson, 2001; Dunstan et al., 2006; Oken et al., 2005; Hibbeln et al., 2007).

In animal models, maternal brain DHA levels decrease when omega-3 fatty acid intake is low during pregnancy (Levant et al., 2006). Despite the demand for omega-3 fatty acids during pregnancy, dietary intake of omega-3 fatty acids by pregnant and postpartum women in the U.S. fell short of recommended levels in 2000 (Benisek et al., 2000)). Since that time, the U.S. Food and Drug Administration (FDA) has issued mercury advisories recommending pregnant women avoid fish with the highest levels of mercury, and fish consumption has subsequently diminished among pregnant women (Oken et al., 2003; http://www.fda.gov/bbs/topics/news/2004/NEW01038.html). Importantly, fish oil capsules do not contain significant levels of mercury or other contaminants, due to the refining process (Foran et al., 2003).

Our group conducted an open study of omega-3 fatty acids in antenatal depression and a randomized dose-ranging study of omega-3 fatty acids in PPD (Freeman et al., 2006b; Freeman et al., 2006c). Both studies were limited by small sample size and lack of a placebo group but provided promising data for future studies in perinatal depression. To build upon findings in the previous studies, the objectives of this study were to assess the feasibility, safety, and efficacy of omega-3 fatty acids as a treatment in a randomized placebo-controlled trial for antenatal and postpartum MDD.

METHOD

Subjects

Fifty-nine women with perinatal MDD were enrolled in the study. Pregnant and postpartum women with MDD were included in the trial, as both groups were hypothesized to be especially responsive to omega-3 fatty acids, and there are known health benefits of omega-3 fatty acids to a baby in utero and in infancy. Inclusion of both pregnant and postpartum women was also intended to ascertain whether there would be differences in recruitment rates, tolerability, and efficacy between pregnant and postpartum women.

Initial target enrollment was N=50, but the investigators received approval to increase the number of subjects due a large number of referrals. Due to the high incidence of morning sickness in the first trimester, participation was limited to after 12 weeks gestation.

Eligibility criteria included: Women 18–45 years of age who were either pregnant (12–32 weeks gestation) or postpartum (within six months of childbirth) and met criteria for MDD, verified with the Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association , 1994) (postpartum women must have experienced onset of MDD by four weeks postpartum), scored ≥9 on the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987), outpatient status, and ability to provide written informed consent. Exclusion criteria included: previous intolerance to omega-3 fatty acids, current use of antidepressants or anticoagulants, psychosis, diagnosis of bipolar disorder, active substance abuse, or active suicidal ideation.

Treatment and Assessments

The protocol was approved by the Institutional Review Board at the University of Arizona. Patients randomly received either omega-3 fatty acids (EPA and DHA, 1.9 g per day) or matching placebo. Each subject received a manual-based supportive psychotherapy. The following symptom rating scales were completed at baseline and every two weeks: the EPDS, Hamilton Rating Scale for Depression (HAM-D), and Clinical Global Impression (CGI) (Guy, 1976). Dietary history was obtained regarding fish intake at baseline. Subjects agreed to continue their current dietary intake of fish and seafood. Laboratory assessments to screen for thyroid abnormalities and anemia were completed at baseline. Compliance was assessed by inquiry regarding missed doses and pill counts at each visit.

Omega-3 Fatty Acids—Subjects received 1.9 g per day (1.1 grams of EPA and 0.8 g of DHA) in a total of four capsules per day. The placebo was corn oil, selected as it minimally alters the fatty acid composition of the typical American diet. To preserve the double-blind status in the proposed study, a small amount of fish oil was added to the placebo (1%), and patients were informed that the placebo contained some fish oil.

Supportive Psychotherapy Intervention—We carefully considered the advantages and disadvantages of offering a placebo-only arm as part of this study, and provided the psychotherapy for ethical reasons and as a safety measure. The psychotherapy intervention included six thirty-minute individual supportive psychotherapy sessions during the trial. The manual was adapted for this population with permission from authors of the original manual (Brent and Kolko, 1989). Clinicians documented participation in sessions and missed sessions.

Statistical analyses

Generalized Estimating Equations (GEE) were used to investigate the effect of omega-3 fatty acids on MDD in the perinatal period. We used Proc GENMOD in SAS Version 9.1 to conduct the analyses. This approach was used in order to utilize multiple follow-up measures collected at various time points. The dependent variables were self-report (EPDS) and clinician-rated (HAM-D) scales of depressive symptoms. The generalized estimating equations were adjusted for: depression at baseline, number of previous medications for depression, perinatal status (pregnant vs. postpartum), fish intake at baseline (to control for dietary omega-3 fatty acids), and finally, treatment assignment to test the efficacy of omega-3 fatty acid treatment. Multivariate imputation was used to replace the few cases with

missing values. Subjects with one or more outcome visits were included in the outcomes analyses. A total of 51 women had follow-up assessments; 23 in the placebo group, and 28 in the treatment group.

RESULTS

Of the 59 participants enrolled, 7 dropped out after the baseline visit, and 1 was ineligible after hyperthyroidism was diagnosed after randomization, leaving 51 subjects who completed at least two assessments. The subjects were similar in the treatment and placebo groups on most baseline characteristics (see Table 1). There were no significant differences between the study groups regarding depression scores at baseline, and the groups were alike on most of the indicators. There were a few exceptions; women in the treatment group tended to be Caucasian (χ=5.41, $p < .10$). Pregnant women in the omega-3 group were more likely to present earlier in pregnancy than pregnant women in the control group ($t_{(1,23)} = 2.05$, $p = .05$). The mean fish intake was extremely low in study participants (below 0.5 servings per month).

Differences were observed between pregnant and postpartum women who presented to the study. Pregnant patients were significantly more likely to have unplanned pregnancies, a greater number of previous antidepressant trials, and a sibling with a diagnosis of depression. There was a trend for pregnant patients to have a mother with a history of depression. Pregnant women in the omega-3 fatty acid group were also significantly more likely than those in the placebo group to have a personal history of depression for which they received antidepressant treatment; the omega-3 group received 1.5 prior medications for depression, compared to 0.8 medications in the placebo group.

Table 2 includes the intake scale scores, final scores, and rate of change (slope) for the EPDS and HAM-D scales for the 51 women who had at least two assessments. Overall, pregnant and postpartum participants in both omega-3 fatty acid and control groups experienced significant decreases in EPDS and HAM-D scores ($p < .0001$) from baseline. We did not find a difference in efficacy outcomes between pregnant and postpartum women. However, compared to postpartum women and regardless of treatment group, pregnant women showed smaller decreases in their depression scores.

Treatment outcomes

The GEE analyses were limited to subjects who had at least one follow-up visit, and were adjusted for baseline test scores, previous medication history (an indicator of history and severity of MDD course), perinatal status, and fish intake at enrollment (to control for dietary factors).

There were no significant effects of study condition (omega-3 fatty acids vs. placebo) for either the EPDS (b=0.2, z=1.15, p=0.25) or HAM-D scores (b=0.06, z=0.34, p=0.73). The only significant predictor of change in the EPDS or HAM-D was number of previous medication trials for depression.

Tolerability

Of N=59, seven (12%) did not return after the baseline/consent visit. One subject was excluded after consenting to participate because she was found to have hyperthyroidism at baseline screening, and she was provided appropriate referrals for treatment. The dropout rates were similar in both groups, with 90% in the treatment group and 82% in the placebo group completing at least 2 visits with rating scale assessments. The women in the placebo group completed 3.6 visits (SD = 1.5), and women in the omega-3 group completed 3.9 visits (SD = 1.4). The number of visits did not significantly differ between groups (t = .079, p = .44).

Overall, 20 (34%) of the total participants did not complete the full 8-week study. Patients reported that reasons for drop-outs included difficulty with scheduling or transportation, perceived lack of efficacy or concern from the patient that she was not improving, or patient decision non-specified. Clinical impression of the investigators was that patients were often overwhelmed with demands of caring for young children and/or infants, and although they were welcome to bring infants to study visits, this was often difficult for some participants. Side effects were not cited by any participants as a reason for discontinuation. Thirteen (22%) reported side effects that were generally mild and transient. Six were in the omega-3 fatty acid group, and 7 were in the placebo group. Some of the subjects who reported side effects reported more than one side effect. Of those who received omega-3 fatty acids, side effects reported were: unpleasant breath/taste (N=4), burping (N=2), heartburn/reflux (N=3), and nausea (N=1). Side effects reported with placebo were: heartburn/reflux (N=2), dizziness, (N=1), diarrhea (N=1), burping (N=1), difficulty swallowing capsules (N=1), and fatigue (N=1). Six of the 23 pregnant patients experienced side effects, half of whom were randomized to omega-3-fatty acids. Seven of the 36 postpartum subjects experienced side effects, three who received omega-3-fatty acids and four who received placebo.

DISCUSSION

In this study, there was no significant difference on primary outcome measures of depression between omega-3 fatty acids and placebo in an 8-week study for women with perinatal MDD. There was a significant benefit of participation in the study, with significant improvement from baseline in both groups, which could be attributed to the supportive psychotherapy intervention or nonspecific effects of the study. Omega-3 fatty acids were well tolerated by pregnant and postpartum women in this study, and omega-3 fatty acids were well accepted in this population, as demonstrated by a higher than anticipated enrollment.

Fish intake among both the omega-3 and placebo groups was low, less than half of a serving per month. Committees from both the American Heart Association and American Psychiatric Association have recommended that adults consume at least two servings of fish per week for optimal health (Kris-Etherton et al., 2003; Freeman et al., 2006a), and in pregnancy and the postpartum, the baby’s needs and diversion of the mother’s supply to meet those needs necessitate higher maternal dietary omega-3 fatty acid intake. In consideration of the widely established health benefits for adults and babies, including

neurodevelopment in utero and in infants, the low intake of omega-3 fatty acids at baseline is a public health concern that affects the health of mothers and babies.

Strengths of the study include a placebo-controlled design for the assessment of omega-3 fatty acids, which have known health benefits for mothers and babies. It is possible that the psychotherapy intervention provided to all subjects diminished our ability to detect a difference between omega-3 fatty acids and placebo. As previously stated, advantages and disadvantages of offering a placebo-only arm as part of this study were carefully weighed, and supportive psychotherapy was provided for ethical reasons and as a safety measure. Limitations of the study include a small number of subjects, although in the area of perinatal depression it represents one of the largest randomized, placebo-controlled trials. In consideration of the differences that we observed between the pregnant and postpartum participants, it appears that antenatal and postpartum depression should be studied separately in treatment studies, and the numbers in this study are considerably smaller when separating pregnant vs. postpartum subjects. Another limitation was the use of a single fixed dose of EPA and DHA for an eight-week duration. It remains unclear whether a longer treatment trial or a higher dose might have resulted in different findings. Also, randomization did not equalize subjects according to number of previous trials of antidepressants, and participants who received omega-3 fatty acids had a significantly higher number of previous antidepressant trials, perhaps indicating a more recurrent course of MDD.

It is not possible to discern from these results whether omega-3 fatty acids have a modest antidepressant effect that was not observable due to the above mentioned limitations. The preponderance of the evidence in the published literature in this area supports further study of omega-3 fatty acids as a treatment in MDD, mostly as an adjunctive treatment (Freeman et al., 2006a; Parker et al., 2006). Considering the large relapse rate in pregnant women observed by Cohen and colleagues (2006), even among women who continued antidepressants, it is imperative to investigate strategies that promote remission from MDD (Cohen et al., 2006). As omega-3 fatty acids offer health benefits to the mother and baby, it is reasonable to study their use as an augmentation strategy. Also, based on epidemiologic data that demonstrate that higher omega-3 fatty acid intake is associated with a lower prevalence of postpartum depression (Hibbeln, 2002), omega-3 fatty acids may be considered in future studies as a prophylactic intervention for PPD.

In addition, this study provides pilot data regarding supportive psychotherapy for perinatal depression. The manualized psychotherapy was designed to be easy to implement, flexible to accommodate the schedules of women with infants and small children, cost-effective, and provide additional safety monitoring. Ideally, an effective intervention would be feasible for wide implemention in the community. It appears from this pilot study that a specifically adapted, manualized supportive psychotherapy was feasible in this population, and could be provided in a small number of brief sessions with good preliminary efficacy. There is an urgent public health need for safe, easy to deliver, and cost effective treatments for perinatal depression, in the context of growing concern about antidepressant exposure in pregnancy and an appreciation for the risks of untreated maternal depression. Future controlled studies should focus on whether a short course of supportive psychotherapy tailored to the perinatal population is efficacious for the treatment of perinatal MDD.

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Table 1

Demographic and clinical characteristics of subjects (N=59)

	Supportive Psychotherapy +	
Characteristic	**Placebo (N = 28)**	**Omega 3 (N = 31)**
	Mean (SD)	Mean (SD)
Age (years)	29.7 (6.2)	31.0 (5.8)
Education (years)	14.6 (2.2)	15.5 (2.1)
Weeks pregnant at enrollment	27.3 (4.2)	22.8 (6.4) *
Weeks postpartum	8.8 (3.6)	9.7 (4.5)
Fish intake at baseline (meals/month)	.43 (.42)	.33 (.50)
Previous antidepressant medication trials	0.68 (.67)	0.94 (1.12)
Depression measures at baseline		
EPDS	16.7 (4.1)	16.9 (3.8)
HAM-D	18.5 (3.7)	18.7 (3.3)
CGI	4.0 (0.3)	4.1 (0.4)
	N (%)	N (%)
Ethnicity		
Caucasian	15 (53.6)	24 (77.4)
Hispanic	11 (39.3)	4 (12.9)
Other	2 (7.1)	3 (9.7)
Married	21 (75.0)	24 (77.4)
Employment status (% employed)	17 (60.7)	19 (61.3)
First child (% primapara)	22 (78.6)	24 (77.4)
Planned pregnancy (% planned)	15 (53.6)	19 (61.3)
Previous psychiatric history	23 (82.1)	22 (71.0)
Family history of depression	16 (57.1)	17 (54.8)
Pregnant/Postpartum status	12 (42.9)	13 (41.9)

* $p < .05$

Table 2

Outcome measures for subjects with at least 1 follow-up (N = 51)

Variable and		Placebo				Omega-3		
		Initial Score	Final Score			Initial Score	Final Score	
Group	N	Mean (SD)	Mean (SD)	Slope	N	Mean (SD)	Mean (SD)	Slope
EPDS								
Pregnant	9	15.78 (4.71)	7.78 (4.15)	−1.07 (.61)	12	17.50 (3.48)	11.17 (6.78)	−1.10 (1.05)
Postpartum	14	15.86 (2.93)	8.29 (5.57)	−1.12 (.76)	16	16.81 (4.02)	10.81 (5.42)	−0.84 (.79)
EPDS Total	23	15.83 (3.63)	8.09 (4.96)	−1.10 (.69)	28	17.11 (3.75)	10.96 (5.92)	−0.95 (.90)
HAM-D								
Pregnant	9	16.22 (1.20)	10.22 (3.67)	−0.82 (.36)	12	18.00 (3.16)	14.17 (5.83)	−0.46 (.83)
Postpartum	14	18.21 (2.36)	9.71 (5.44)	−1.25 (1.04)	16	19.50 (3.58)	11.81 (5.17)	−1.14 (.53)
HAM-D Total	23	17.43 (2.19)	9.91 (4.74)	−1.08 (.86)	28	18.86 (3.43)	12.82 (5.48)	−0.85 (.75)

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Table 3

Predictors of reduction of depression for prenatal and postnatal women (N=51)

	Parameter Estimate	Z	*p*
EPDS			
EPDS at baseline	.00	−.02	ns
Medication history for depression	.31	4.57	<.001
Pregnancy status	−.24	1.31	ns
Fish	.00	.02	ns
Omega-3	**.20**	**1.15**	**ns**
HAM-D			
HAMD at baseline	−.03	−.74	ns
Medication history for depression	.27	4.42	<.001
Pregnancy status	.09	.57	ns
Fish	.06	.96	ns
Omega-3	**.06**	**.34**	**ns**

N=51