Omega-3 Fatty Acids for Major Depressive Disorder During Pregnancy: Results From a Randomized, Double-Blind, Placebo-Controlled Trial

Kuan-Pin Su, M.D.; Shih-Yi Huang, Ph.D.; Tsan-Hung Chiu, M.D., Ph.D.; Kuo-Cherh Huang, Dr.P.H., M.B.A.; Chieh-Liang Huang, M.D.; Hui-Chih Chang, M.S.; and Carmine M. Pariante, M.D., Ph.D.

Background: Perinatal depression is common, and treatment remains challenging. Depression has been reported to be associated with the abnormality of omega-3 polyunsaturated fatty acids (PUFAs). A profound decrease of omega-3 PUFAs in the mother during pregnancy is associated with the higher demand of fetal development and might precipitate the occurrence of depression. In this study, we examined the efficacy of omega-3 PUFA monotherapy for the treatment of depression during pregnancy.

Method: From June 2004 to June 2006, we conducted an 8-week, double-blind, placebo-controlled trial comparing omega-3 PUFAs (3.4 g/d) with placebo in pregnant women with major depressive disorder (DSM-IV criteria). No psychotropic agent was given 1 month prior to or during the study period. The Hamilton Rating Scale for Depression (HAM-D) was scored every other week as the primary measurement of efficacy, while the Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory (BDI) were secondary measures.

Results: Thirty-six subjects were randomly assigned to either omega-3 PUFAs or placebo, and 33 among them were evaluated in more than 2 visits. A total of 24 subjects completed the study. As compared to the placebo group, subjects in the omega-3 group had significantly lower HAM-D scores at weeks 6 ($p = .001$) and 8 ($p = .019$), a significantly higher response rate (62% vs. 27%, $p = .03$), and a higher remission rate, although the latter did not reach statistical significance (38% vs. 18%, $p = .28$). At the study end point, subjects in the omega-3 group also had significantly lower depressive symptom ratings on the EPDS and BDI. The omega-3 PUFAs were well tolerated and there were no adverse effects on the subjects and newborns.

Conclusions: Omega-3 PUFAs may have therapeutic benefits in depression during pregnancy. In regard to the safety issue and psychotherapeutic effect, as well as health promotion to mothers and their newborns, it is worthy to conduct replication studies in a larger sample with a broad regimen of omega-3 PUFAs in pregnant women with depression.

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Received Aug. 7, 2007; accepted Nov. 7, 2007. From the Department of Psychiatry and Mind-Body Interface Research Centre (Drs. Su and C-L Huang) and the Department of Obstetrics and Gynecology (Dr. Chiu), China Medical University Hospital, Taichung, Taiwan; the School of Nutrition and Health Sciences (Drs. Su and S-Y Huang) and the School of Health Care Administration (Drs. K-C Huang and Chang), Taipei Medical University, Taipei, Taiwan; and the Institute of Psychiatry, King's College London, United Kingdom (Drs. Su and Pariante and Ms. Chang).

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Corresponding authors and reprints: Kuan-Pin Su, M.D., Mind-Body Interface Research Centre, Department of General Psychiatry, China Medical University Hospital, No. 2, Yuh-Der Rd., Taichung 404, Taiwan (e-mail: cobolsu@gmail.com); and Shih-Yi Huang, Ph.D., School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan (e-mail: sihuang@tmu.edu.tw).

Women during pregnancy and after childbirth are more vulnerable to psychiatric disorders,[1] which can affect 5% to 20% of pregnant women.[2–8] Poor attendance to prenatal clinics, substance misuse, low birth weight, and premature delivery are observed in pregnant women with depressed mood.[9,10] Untreated depression during pregnancy also increases the risk of negative pregnancy outcomes,[1,11] and psychopathologic symptoms during pregnancy could have further physiologic consequences to the fetus.[12]

As is well known, pharmacotherapy for depression during pregnancy is a clinical dilemma. Although it has been suggested that the relapse rates for depression are high during pregnancy[13] and taking antidepressants does not increase the risk of malformation or miscarriage,[1] more recent data have raised the concern that taking selective serotonin reuptake inhibitor (SSRI) antidepressants during the third trimester may be associated with considerably increased risk of perinatal complications.[14,15] In addition, antidepressant use during pregnancy in women with a history of major depression is associated

with a higher risk of premature delivery and lower gestational age at birth compared with women who elected to discontinue medication during pregnancy, and the adverse effect of antidepressants remained after the analyses controlled for severity and duration of depressive symptoms during pregnancy.[16] To date, the U.S. Food and Drug Administration has not approved any antidepressant agents during pregnancy. Furthermore, most mothers are exceedingly anxious about accepting antidepressant medication, and despite moderate to severe depressive symptoms and impaired functioning, they tend to focus on the risks of in utero exposure to medication rather than on the risks of untreated depression.[17] Most mothers-to-be choose not to take medications, a problem that was highlighted in the lay press *U.S. News and World Report* article, "The Baby or the Drug? It's a Choice That Many Pregnant Women Often Face—But Shouldn't."[18] Considering the potential impact on mothers and newborns, the development of safe and effective management is critical for pregnant women with depression.

Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are nutritional compounds with widely established health benefits.[19–21] Since essential fatty acids cannot be synthesized by the human body, they are considered an indispensable dietary component.[22] Pregnancy is associated with a decrease in the biochemical PUFA status, and it returns to normal slowly after delivery.[23,24] Recently, a deficit of omega-3 PUFAs was hypothesized to be etiologically important in depression.[25] Societies in which a large amount of omega-3 PUFAs are consumed appear to have a lower prevalence of major depressive disorder.[26–28] Consistent with the above-mentioned fact, it is found that patients with major depressive disorder have lower levels of omega-3 PUFAs,[29–33] and the level of omega-3 PUFAs is significantly negatively correlated with the severity of depressive symptoms.[31,33] The abnormalities in PUFA composition on cell membranes can alter membrane microstructure, cause abnormal signal transduction and immunologic dysregulation, and possibly increase the risk of developing depression.[25,34] More importantly, 2 meta-analytic reviews[35,36] and several clinical trials[37–41] have reported an antidepressant effect of PUFAs. In addition, the use of omega-3 fatty acids in psychiatric patients during the perinatal stage was supported by case reports of pregnant women with depression[42] and schizophrenia[43] and by a small, open-label, flexible-dose trial in 15 pregnant depressed subjects.[44] Due to the advantage of lack of teratogenesis[45] and its essentiality for the central nervous system development,[46–48] omega-3 PUFAs might be a promising alternative treatment for pregnant women with depression.

In this study, we conducted an 8-week, double-blind, placebo-controlled trial. Our hypothesis is that omega-3 PUFAs are effective and safe in treating major depressive disorder in pregnant women.

METHOD

Subjects

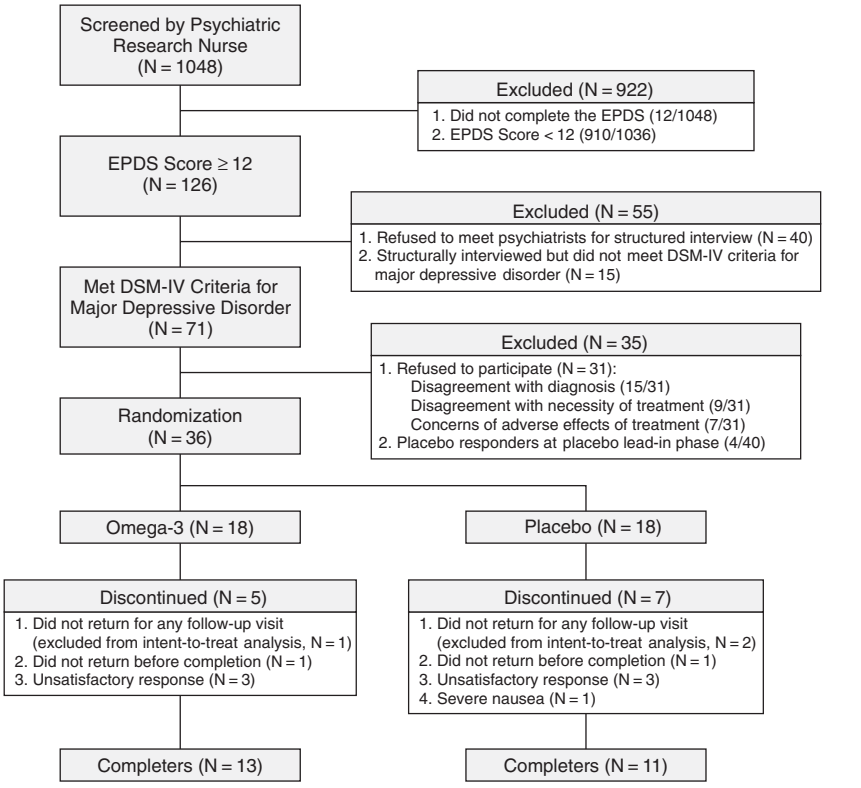
This 8-week, randomized, parallel-group, placebo-controlled, double-blind study was approved by the institutional review board and conducted at China Medical University Hospital, Taiwan. Eligible participants were pregnant women, aged 18 to 40 years, with DSM-IV major depressive disorder onset between their 16th week (second trimester) and 32nd week (third trimester) of gestation seen at the Department of Obstetrics during the 24-month study period (June 2004 to June 2006). They were screened with the Taiwanese version of the Edinburgh Postnatal Depression Scale (EPDS) by a psychiatric research nurse and then interviewed by experienced psychiatrists using the structured Mini-International Neuropsychiatric Interview (MINI).[49] The information on the translation, validation, and instruction of the Taiwanese version of the MINI can be accessed on the Web site of the Taiwanese Society of Psychiatry (http://www.sop.org.tw/dow_a.htm). The Taiwanese version of the EPDS has been validated in screening depression during pregnancy.[50]

Subjects were excluded if they had a DSM-IV diagnosis of bipolar disorder, psychotic disorder, or substance abuse/dependence or any Axis II diagnosis of borderline or antisocial personality disorder. Participants were required to be free from any psychotropic agents at least 1 month, to have a score of at least 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D) at screening phase, and to have good physical health as determined by medical history, physical examination, blood laboratory results, electrocardiogram, chest radiography, and urinalysis. The supply of open-label omega-3 fatty acids could be continued, and they were available upon subjects' requests even if the study were to end before the delivery. All participants were informed of other treatment options, including antidepressant medications and psychotherapy, and provided written consent before entering the study.

Study Design

At the baseline visit (week –1), the detailed psychiatric, obstetric, and medical histories were obtained, and the HAM-D, Taiwanese version of the EPDS, and 21-item Beck Depression Inventory (BDI) were used for assessment. Before random assignment, all the consenting participants received a single-blind placebo lead-in trial for 1 week. Those who showed a decrease of 20% or more in HAM-D scores (placebo responders) would not proceed to the randomization phase. After the placebo lead-in phase, participants were randomly assigned (at week 0) to receive 5 identical gelatin capsules per day containing either omega-3 fatty acids or placebo (olive oil ethyl esters) for 8 weeks. The capsules for the treatment group contained a total daily dosage of omega-3 fatty acid with 2.2

Figure 1. Flowchart of Subject Screening and Enrollment



Abbreviations: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EPDS = Edinburgh Postnatal Depression Scale.

g of EPA and 1.2 g of DHA, which were produced from menhaden fish body oil concentrate. The capsules (omega-3 fatty acid and placebo) were vacuum deodorized, amended by blending with orange flavor, and supplemented with tertiary butylhydroquinone, 0.2 mg/g, and tocopherols, 2 mg/g, as antioxidants.

We performed the HAM-D, EPDS, BDI, and a brief adverse-effect checklist at week –1 (placebo lead-in phase), week 0 (baseline), and weeks 2, 4, 6, and 8. Participants taking any antidepressants, antipsychotics, or mood stabilizers 1 month prior to the study were excluded, and no psychotropic agents were given during the study period. Blood samples were taken for omega-3 PUFA analysis at week –1 and week 8, with which each individual red blood cell fatty acid was analyzed with gas chromatography of methyl esters. The detailed step-by-step laboratory procedures were described elsewhere.[51]

Outcome Measures and Statistical Analysis

All participants after randomization were included in the analysis of illness characteristics and the incidence of treatment-emergent adverse events. The primary measurement of efficacy was the HAM-D, while the EPDS and BDI were the secondary measures, and statistical analyses were done between 2 groups. The intention-to-treat (ITT) population included all patients who had a baseline and at least 1 postbaseline observation, while the per-protocol population included all patients who completed 8 weeks of treatment. Biweekly changes in HAM-D total scores from baseline to endpoint were analyzed as the primary outcome. Treatment responders were characterized descriptively as those who improve at least 50% from baseline in HAM-D. Patients with remission were defined as those who had a HAM-D score of 7 or less. Categorical variables, such as the remission rate and response rate, were analyzed by using χ^2 tests.

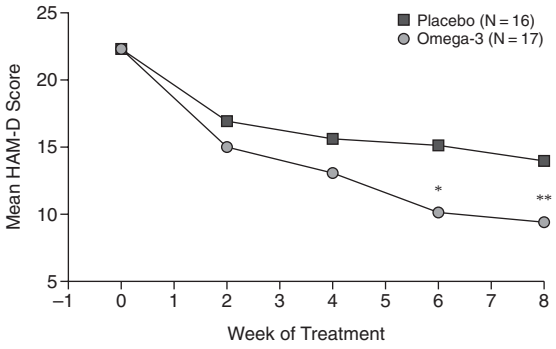
Differences of rating scores between placebo and omega-3 groups at each visit point were assessed by an independent-samples t test. The statistical model used to compare differences of outcome measurements at endpoint between groups was the analysis of covariance with treatment group as the main effect and the baseline score as the covariate. The effect of the omega-3 PUFAs was examined with repeated-measures analysis of variance using time as the repeated factor, treatment groups (placebo or omega-3 PUFA) as the independent factor, and clinical data (age, years of education, duration of current episode, number of previous depressive episodes, number of previ-

Table 1. Demographics, Clinical Characteristics, and Outcomes (HAM-D, erythrocyte EPA, and DHA) of Pregnant Women Before and After Treatment for Major Depressive Disorder

Variable	Omega-3[a] (N = 18)	Placebo[a] (N = 18)	p Value[b]
Age, y	30.9 ± 3.9	31.3 ± 5.7	.84
Gestational weeks	22.7 ± 4.2	24.5 ± 3.9	.20
No. of previous gestations	1.7 ± 1.1	1.8 ± 1.1	.76
No. of previous parturitions	0.4 ± 0.6	0.5 ± 0.7	.80
No. of previous abortions	0.2 ± 0.7	0.3 ± 0.7	.81
Duration of current episode, wk	7.3 ± 2.4	7.2 ± 2.6	.83
No. of previous depressive episodes	0.2 ± 0.4	0.3 ± 0.5	.84
HAM-D score			
Week 0	22.1 ± 5.0	21.8 ± 3.9	.88
Week 8	9.0 ± 4.0[c]	13.8 ± 5.3[d]	.02
EPA level, %			
Week 0	2.9 ± 0.4[e]	3.0 ± 0.4[f]	.62
Week 8	3.8 ± 1.2[d]	3.5 ± 1.5[g]	.85
DHA level, %			
Week 0	3.5 ± 0.5[e]	3.6 ± 0.7[f]	.51
Week 8	5.4 ± 1.5[d]	4.6 ± 1.2[g]	.03

[a]Mean ± SD; case numbers of both groups were 18 unless otherwise specified.
[b]Independent samples t test results.
[c]N = 13.
[d]N = 11.
[e]N = 15.
[f]N = 14.
[g]N = 10.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HAM-D = 21-item Hamilton Rating Scale for Depression.

Figure 2. Evolution of the 21-Item Hamilton Rating Scale for Depression (HAM-D) Scores in Pregnant Women With Depression Treated With Omega-3 PUFAs or Placebo During the Study Period[a]



[a]The significant differences were noted at week 6 (p = .001)* and week 8 (p = .019)** by independent-samples t test. All values represent the intent-to-treat population. Biweekly changes in HAM-D scores illustrate a significantly greater decline in the omega-3 group by the mixed-model analysis of variance approach (F = 7.467, p = .010).
*p = .001.
**p = .019.

ous instances of gestation and/or abortion, and baseline red blood cell omega-3 PUFA compositions) as covariates. A mixed-model analysis of variance approach was applied for repeated-measurement analysis. The missing values in the ITT population were handled by using the PROC MI procedure of the SAS statistical software to implement the expectation-maximization algorithms. Data were analyzed using SAS statistical software, version 8.02 (SAS Institute, Inc., Cary, N.C.). A value of p less than .05 is considered statistically significant.

RESULTS

Disposition and Demographics

One thousand forty-eight pregnant women were screened by a psychiatric research nurse; 86 of 126 women with EPDS score more than 12 agreed to be structurally interviewed by psychiatrists, and 71 met the DSM-IV diagnosis of major depressive disorder. Forty women consented to participate in the study initially. The reasons for refusal to participate were patients' disagreement with having a depressive disorder (15/31), disagreement with necessity of treatment (9/31), and concerns of adverse effects of treatment (7/31).

Figure 1 provides a detailed flow chart summarizing study recruitment. Four placebo responders (10%) were withdrawn by the investigators because of a greater than 20% decrease in the HAM-D score at placebo lead-in phase. The remaining 36 subjects were then randomly assigned to either the omega-3 group (N = 18) or the placebo group (N = 18). Among these, a total of 33 patients (N = 17 in the omega-3 group, N = 16 in the placebo group) who had been evaluated in more than 2 visits were included in the ITT analysis. With a dropout of 12 subjects, 24 patients (N = 13 in the omega-3 group, N = 11 in the placebo group) completed this 8-week study, and these data were used for per-protocol analysis. Five of the dropouts were from the omega-3 group (2 failed to return in follow-up and 3 withdrew consent for unsatisfactory response), while 7 were from the placebo group (3 failed to return, 3 withdrew consent for unsatisfactory response, and 1 withdrew consent for severe nausea). Nine of the omega-3 group and 6 of the placebo group were willing to take open-label omega-3 fatty acids after the study period (including early dropout) until the delivery. Table 1 shows no statistical differences in demographics, clinical characteristics, or omega-3 PUFA composition on red blood cells.

Therapeutic Outcomes

As shown in Figure 2, participants in the omega-3 group differed significantly from those in the placebo group in the mean HAM-D score at week 6 and week 8. We used the mixed-model analysis of variance approach for repeated-measurement analyses in the ITT population, and the results indicated that biweekly changes in the scores of HAM-D (F = 7.467, p = .010), EPDS (F = 4.976, p = .033), and BDI (F = 4.695, p = .038) in the

Table 2. Effects of Treatment on Total Scores of HAM-D, EPDS, and BDI

	Omega-3, Mean ± SD		Placebo, Mean ± SD		
Outcome Measure	Baseline	Week 8	Baseline	Week 8	p Value[a]
Intent-to-treat[b]					
HAM-D	22.3 ± 5.0	9.9 ± 4.3	22.3 ± 3.9	14.6 ± 4.8	.023
EPDS	16.8 ± 3.8	8.5 ± 5.5	17.5 ± 4.0	14.3 ± 6.3	.016
BDI	22.1 ± 9.7	10.8 ± 8.3	23.9 ± 9.3	19.8 ± 11.2	.015
Per protocol[c]					
HAM-D	22.1 ± 5.0	9.0 ± 4.0	21.8 ± 3.9	13.8 ± 5.3	.020
EPDS	16.7 ± 3.7	7.1 ± 4.3	17.0 ± 4.0	14.0 ± 7.6	.021
BDI	21.8 ± 9.5	8.8 ± 6.0	23.0 ± 9.2	19.7 ± 13.1	.004

[a]p Values are based on the pairwise comparisons from the analysis of covariance model with treatment as the main effect and baseline as the covariate.
[b]N = 17 for the omega-3 group; N = 16 for the placebo group.
[c]N = 13 for the omega-3 group; N = 11 for the placebo group.
Abbreviations: BDI = 21-item Beck Depression Inventory, EPDS = Edinburgh Postnatal Depression Scale, HAM-D = 21-item Hamilton Rating Scale for Depression.

Table 3. Response Rate and Remission Rate Defined by the Change of Hamilton Rating Scale for Depression Score

Variable	Week 0	Week 2	Week 4	Week 6	Week 8
Patients with 50% reduction, N/N (%)					
Omega-3	0/18 (0)	3/17 (18)	6/14 (43)	9/14 (64)	8/13 (62)
Placebo	0/18 (0)	3/16 (19)	2/14 (14)	2/12 (17)	3/11 (27)
p Value[a]	…	.94	.09	.01	.03
Patients with score ≤ 7, N/N (%)					
Omega-3	0/18 (0)	1/17 (6)	2/14 (14)	5/14 (36)	5/13 (38)
Placebo	0/18 (0)	1/16 (6)	1/14 (7)	2/12 (17)	2/11 (18)
p Value[a]	…	.97	.54	.28	.28

[a]χ^2 test results.
Symbol: … = not applicable.

omega-3 group showed significantly greater declines. On the other hand, the interactions between time and treatment assignment for those aforementioned outcome measurements were not significant.

In Table 2, primary and secondary outcome measures at the final study end point are shown with ITT and per-protocol analysis. Also, Table 3 presents a significantly higher response rate in the omega-3 group at weeks 6 and 8 (compared with placebo) and a higher remission rate for the omega-3 group at weeks 4, 6, and 8, but the differences in remission rate did not reach statistical significance.

Adverse Events

No participant was withdrawn because of adverse events by investigators' decision, and 12 of 18 in the placebo group and 10 of 18 in the omega-3 fatty acid group reported no adverse events. The events attributed to treatment were insomnia (2 in the placebo group and 3 in the omega-3 group), nausea (4 in the placebo group and 6 in the omega-3 group), and diarrhea (2 in the placebo group and 1 in the omega-3 group). Reported events were mostly mild and self-limited, except 1 occurrence of severe nausea in the placebo group that terminated the treatment. There was no effect found in any blood laboratory parameter, such as abnormal bleeding time or liver function. No obstetric complication was noted in any participant, and all the newborns were normal in general physical and neurobehavioral examination at birth.

DISCUSSION

This is the first double-blind placebo-controlled trial of omega-3 PUFAs in pregnant women with depression. This is also the first double-blind placebo-controlled trial to demonstrate omega-3 PUFAs' monotherapy effect on depression, as several other double-blind placebo-controlled trials were done as adjunct therapy.[37–41] We found that omega-3 PUFA monotherapy significantly improved depressive symptoms in pregnant women with major depressive disorder. The antidepressant effect of omega-3 PUFAs was significantly better than placebo after week 6, a result that appeared to show a delayed effectiveness of omega-3 PUFAs, compared to the results of 2 to 4 weeks in nonpregnant patients with major depression reported in previous studies.[37–39] The remission rate did not reach a significant difference between the omega-3 and placebo groups. Furthermore, the early dropout rate was high (8/36 for the first 4 weeks) in this study. One

possible explanation is that the antidepressant effect of omega-3 PUFAs was not as effective in pregnant women as in nonpregnant depressed patients. The other explanation is that the participants in this study were aware and expecting the continuous open-label omega-3 PUFA treatment when the study ended. We also observed that most participants expressed a high interest in the "nutrition therapy" option when entering this study, which might lead to a choice not to continue the trial eventually if they did not experience the improvement they expected and guessed they were in the placebo arm.

There are 2 potential mechanisms of omega-3 PUFAs' effect on depression during pregnancy. First, a profound decrease of omega-3 PUFAs in pregnant women due to the high demand of fetal development[23,24] might precipitate depression[43] because omega-3 PUFAs' deficit can induce serotonergic dysfunctions[52–54] and has been reported extensively in patients with major depressive disorder.[29–33] Another possible mechanism is that omega-3 PUFAs play an important role in mood stabilization by targeting parts of the "arachidonic acid cascade."[55] The arachidonic acid cascade hypothesis in mood disorders has been supported by other studies, including the higher levels of arachidonic acid and increased activity of phospholipase A_2, a major metabolic enzyme of arachidonic acid, in patients with mood disorders[32,33,51,56] and the inhibitory effect on phospholipase A_2 activity of mood stabilizers.[57–60]

The treatment was well tolerated with few adverse events. The only patient who withdrew from the study did so due to severe nausea and was in the placebo group. This finding is consistent with the finding in the Freeman et al.[44] open-label trial that no dropout occurred due to omega-3 PUFAs' side effects in 15 pregnant depressed patients. Also, there was no obstetric or newborn complication noted, which is very important because the adverse effects of medication to the fetus are the major concern for women when considering pharmacotherapy during pregnancy.[61,62] In the light of an ideal treatment for perinatal depression, which should be harmless for both mothers and newborns, in uterus and even during breastfeeding,[63] omega-3 fatty acids have established their safety and benefits during pregnancy[45,64] and thus deserve further attention of clinical study and application as a treatment modality for perinatal depression.

There are matters needing further attention when applying the findings of this study to clinical practice. First, the optimal composition and the dosage of EPA and DHA for treatment of depression during pregnancy require further exploration. It has been suggested that there is a possible dose-dependent relation of the antidepressant effect of EPA; however, heterogeneity in the severity of depression, difference in the body EPA and DHA composition, and dietary intake of fish should be taken into account.[36] Taiwan is a high fish-consuming country,[28] and pregnant women generally consume even more fish for a better source of nutrition as suggested.[65] When compared with previous clinical trials for nonpregnant depressed populations, the daily dose used in this study (3.4 g per day) was higher than the effective dose of clinical studies from the United Kingdom (1 to 2 g/day)[39] or Israel (2 g/day),[38] but lower than that of our previous study (6.6 g/day) in Taiwan.[37] Being aware of the relationship between depression and low fish intake in some epidemiologic studies, it will be of interest to know if pregnant depressed patients, who had a low content of bodily omega-3 PUFAs, will respond to a lower dose than nonpregnant depressed patients with normal contents. Second, the supplement of omega-3 PUFAs in this study induced a significant increase in the DHA level, but not the EPA level. This could result from the small sample size; however, it might imply that DHA level had a stronger relationship with depression than EPA did. The correlations of omega-3 fatty acid concentrations and behavioral parameters in the rat model of depression have been examined, and it was found that the level of brain DHA, not EPA, was negatively correlated to depression-like behaviors.[66] Furthermore, the changes of EPA and DHA levels in this study might not reach a steady state because that is expected to take more than 12 weeks.[67] Finally, caution should be taken because the high discontinuation rate (33%) and the lack of information about compliance might bias our results.

To date, no psychotropic drugs have been approved to be safe during pregnancy and breast-feeding, which challenges psychiatrists with the difficult task of recommending pharmacotherapy to pregnant patients.[68] Knowledge of risks of psychotropic medications to the fetus of prenatal exposure is still limited, and it is neither feasible nor ethical to conduct prospective, case-control studies for the benefits and risks of antidepressant agents during pregnancy. Thus, the appropriate data from alternative, nondrug treatments are important. In regard to the safety issue and psychotherapeutic effect, as well as health promotion to mothers and newborns, omega-3 PUFAs are a promising agent for patients with major depressive disorder during pregnancy. Replicated studies in a larger sample with a broad regimen of dose and composition of omega-3 PUFAs in pregnant depression are needed before we could suggest omega-3 PUFAs as the first-line treatment for depressive disorders during pregnancy.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.