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Fish-Oil Supplementation and Maternal Mental Health: A Triple-Blind, Randomized Controlled Trial

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Abstract

Objectives: The aim of this study was to evaluate the effect of fish oil supplementation on antenatal and postpartum depression score.

Methods: This was a randomized, triple-blind, placebo-controlled trial. We enrolled 150 eligible pregnant women with Edinburgh postnatal depression scale (EPDS) score of less than 20, aged 18 to 35 from Feburary 2014 to April 2015 in Tabriz, Iran. Participants were randomly assigned to receive either 1000 mg of fish oil supplements or placebo from 16 - 20 weeks of gestation to one month after giving birth. Participants completed the EPDS at baseline, 26 - 30 weeks, 35 - 37 weeks, and 30 - 45 days after birth. Primary outcome measures were the mean depression score at 26 - 30 weeks, 35-37 weeks, and postpartum period. The statistical analysis was intent-to-treat.

Results: A total of 150 females were included, and no one was lost to follow up. There were significant differences between the two groups in the mean score of depression only at 35 - 37 (adjusted mean difference = -1.4; [95% CI -2.6 to -0.25]). The mean score of depression during pregnancy and postpartum period significantly decreased within the fish oil group ($P < 0.05$). There were no significant differences between the two groups in terms of the baseline docosahexaenoic acid (DHA) and eicosapentaneoic acid (EPA) serum levels.

Conclusions: Fish oil supplements significantly decreased the mean score of EPDS at weeks 35 to 37. It seems that females may benefit from daily fish oil supplements during pregnancy especially in countries with low intake of fish yet further studies are needed to confirm these results.

Keywords: Fish Oil, Antenatal Depression, Postpartum Depression, Supplemantation

1. Background

Any mental disorder in pregnancy is closely associated with the growth of fetus and newborn and influences the relationship between mothers and their infants (1). Antenatal depression is a mood disorder that not only affects the mother and her baby but also increases the risk of developing postpartum depression (2, 3).

In a meta-analysis of 21 articles in the Cochrane database, the prevalence of antenatal depression was reported as 10.7% that varied from 7.4% in the first trimester to 12.8% in the second trimester of pregnancy (4, 5). Other researchers reported its rate up to 30% (6). A study that was conducted in Iran-Isfahan showed that 16% of pregnant females suffered from depression (7). The prevalence of antenatal depression was reported as 30.5% in Tabriz city of Iran (8).

Postpartum depression is a non-psychotic depression that occurs during the first six weeks after birth and its symptoms are similar to depression at other times. Studies in different cultures have shown that the prevalence of the postpartum depression is 10% to 15% (9). The prevalence of postpartum depression has been reported in different studies from 4.5% to 28% (10).

Postpartum depression is characterized by depressed mood, loss of interest in activities, change in appetite, fatigue, sleep problems, difficulty with child care, guilt, low self-esteem, difficulty concentrating, restlessness and thinking about suicide (11). Depressed mothers are less likely to carry out protective measures for their children. This behavior can have a negative effect on child development, so that these children have lower social and emotional growth, more dependence due to the lack of security and delayed mental development (12).

In dealing with antenatal and postnatal depression, there are a variety of approaches. Antidepressants are important medications for depression, but physicians and pregnant women are worried about their possible side effects during pregnancy and lactation (13). Antidepressants aren't the only treatment, and non-pharmacological methods have sufficient effectiveness in the prevention and treatment of antenatal and postnatal depression (14). Polyunsaturated fatty acids decrease the production of pro-inflammatory cytokines, which increase in depressed patients (15). Omega-3 fatty acids are polyunsaturated fatty acids that are essential nutrients for good health and development (16). Omega-3 fatty acids as non-pharmacological methods can be effective both in preventing and treatment of depression (14). These fatty acids are transported from the mother to the fetus during pregnancy and so maternal reserves are depleted. Because most mothers refuse to receive antidepressants during pregnancy and lactation, it is postulated that increased omega-3 fatty acids from the diet and supplements theoretically has a useful and protective effect (17). The use of fish oil supplements during pregnancy has been studied as a potential strategy for the prevention of postpartum depression (18-20). However, information about the effects of omega-3 fatty acids on perinatal depression is inconsistent (21).

Coletta et al., concluded that randomized, controlled trials have failed to demonstrate an obvious benefit for omega-3 fatty acid supplementation during pregnancy and postpartum to prevent depressive symptoms (19). Hibbeln in a systematic review of observational studies on postpartum depression found that a higher concentration of docosahexaenoic acid (DHA) in breast milk and so a higher consumption of seafood predicts lower prevalence of postpartum depression in simple and logarithmic models (22). Mozurkewich et al., in their review study concluded that current evidence does not support the omega-3 fatty acids supplementation for the prevention or treatment of perinatal depression (23).

In addition, it is possible that the amounts of fish consumption and the baseline maternal DHA and eicosapentaenoic acid (EPA) serum levels in different populations may have a role on the effectiveness of fish oil supplements.

Related articles, found in the following databases Medline, PubMed and Web of Science, recommended conducting more research to confirm the relationship between the consumption of seafood containing omega-3 fatty acids and depression (24). Most of the randomized clinical trials of prenatal fish oil supplementation have been done in high-income countries, and so the findings may not be generalizable to populations with low intake of fish (19).

2. Objectives

The current study aimed to evaluate the effect of fish oil supplementation on prenatal and postpartum depression.

3. Methods

3.1. Study Type and Subjects

This was a randomized, triple blind, placebo-controlled clinical trial with parallel design conducted from February 2014 to April 2015 in Tabriz, Iran. The inclusion criteria consisted of, age of 18 to 35 years old for mothers, first to fifth pregnancy, having health care record in health centers, willingness to participate in the study, having literacy and being able to answer the questions, an Edinburgh postnatal depression scale (EPDS) score less than 20, singleton pregnancy, a gestational age of 16 - 20 weeks. The exclusion criteria were history of underlying diseases such as cardiovascular and renal diseases, major depressive disorder and other known mental disorders, bleeding disorders, taking antidepressant or anticoagulant medications, any history of allergy to fish or fish products and gelatin, eating more than two servings of fish per week. Primary outcome measures were the mean depression score at third trimester of gestation and postpartum period.

Sample size, considering mean score of third trimester [$\alpha = 0.05$, $\beta = 0.1$, Power = 0.9, $M_1 = 14.06$, $M_2 = 11.95$, $SD_1 = SD_2 = 3.12$, n = 71] and postnatal depression [$\alpha = 0.05$, $\beta = 0.1$, power = 0.9, $M_1 = 13.29$, $M_2 = 11.3$ and $SD_1 = SD_2 = 4.08$, n = 39] based on EPDS in Tabriz (8), was calculated as 71 for each group and considering the possible drop-out, seventy-five subjects were allocated to each group.

3.2. Sampling

After permission from the ethics committee of research and technology vice chancellor of Tabriz University of Medical Sciences (No. 92141) and registration in the Iranian registry of clinical trials website (IRCT2013100914957N1), governmental primary health care centers in Tabriz with the highest number of referred women were selected. Health centers were selected from areas with different socio-cultural standings. After explaining the study, including objectives, probable risks, the benefits of participating in the study, and also stating the voluntary nature of participation in the study, informed consent was obtained and the EPDS was administered. Social-demographic and obstetric information were completed using health care records and interviews. The checklists of daily consumption of capsules and possible events were given to pregnant women. EPDS was

completed by participants three times during pregnancy and once after birth. Information about the mother and baby were collected by questionnaire. Content validity was used to determine the validity of the socio-demographic and obstetric information questionnaires.

Edinburgh postnatal depression scale is a valid 10-item self-report questionnaire that measures postnatal depression and assesses feelings of the mothers in the last week. Each question has four response options, and is rated on a four-point scale from 0 to 3, giving a total score between 0 and 30 (25). It can also be applied for depression screening during pregnancy (26). Although a high score in the EPDS depression cannot confirm the diagnosis, a score more than 12 is widely used to indicate the probable depressive disorder (14). Score of 10 to 12 represents a cross-border situation and a score of 0 to 9 indicates the absence of post-partum depression (23). This questionnaire has been frequently used to assess depression in Iran and has been standardized in this regard (27, 28). It was qualified as a reliable test for screening of postpartum depression in Tabriz with validity coefficient of 0.69, and reliability of 0.83, which had sensitivity of 0.63 and specificity of 0.85 (15).

In this study, 652 females were assessed in terms of eligibility criteria yet 502 were excluded because 192 didn't meet the eligibility criteria and 310 declined to participate in the study. Finally, 150 women participated in this study and were randomly allocated to fish oil or placebo groups.

3.3. Randomization and Intervention

Pregnant women were randomly divided to two groups using a computer-generated randomization scheme with a block size of 4 and 6 in two groups (the group receiving fish oil capsule supplements and the group receiving placebo) with an allocation ratio of 1:1. The dose of fish oil capsule supplementation was 1000 mg/day (containing 120 mg of DHA, 180 mg of EPA, and 400 mg of ALA). The placebo capsules had the same shape, size and weight and contained 1000 mg of liquid paraffin. Both supplements were produced by Zahravi pharmaceutical company, Tabriz, Iran. One capsule was consumed per day starting from the end of the 20 th week of pregnancy until one month after birth with duration of about 24 weeks (168 capsules). The capsules were placed inside opaque and identical containers. Two containers were prepared for each participant: one containing 70 capsules for a ten-week use, and the other one contained 98 capsules for a 14-week use. The two containers were placed in a big opaque pack numbered sequentially. The sequence generation and preparations were done by a person not involved in the study to conceal allocation and maintain blinding. Researchers, who were care providers enrolled participants at 16 - 20 weeks of gestation and assigned them to the study groups after obtaining an inform consent. The first container was delivered at the second pregnancy care period (weeks 16 - 20), whereas the second container was delivered at the third pregnancy care period (weeks 26 - 30) after making sure that the previous medication was consumed and collecting the first envelope, consumed medication packages and daily drug record checklist.

To ensure acceptance and medication use, the remaining consumed medication packages were also collected at the end of the intervention. The first pack was given to the first participant, and the process continued until the completion of the sample size. Participants were taught about the medication use, and it was emphasized that the medications were not forgotten. In order to ensure about the proper consumption of medication, follow-ups were conducted via phone contact during weeks 24 and 34. Stratified sampling was carried out in terms of number of pregnancies (first, second or more pregnancies). Numbers 1 to 75 were assigned to the nulliparous, while numbers 76 to 150 were assigned to the multiparous women 30 sequenced envelopes; 15 for nulliparus women and 15 for multiparous women, from the five health centers. For example, sequenced envelopes numbered 1 to 15 and 76 to 90 were allocated to health center 1 and the process continued for other health centers. Training and implementation of the protocol was standardized across health care centers through the establishment of training sessions attended by all researchers before the intervention. The head researcher as a trainer and coordinator monitored the whole process of randomized controlled trial (RCT) under supervision of the research deputy of Tabriz University of Medical Sciences and collected the data. Participants, health care providers, and those assessing outcomes were blind to the study after assignment to interventions.

3.4. Assessment of Study Variables

Antenatal and postnatal depressions were evaluated using the EPDS at three time points during pregnancy; the first time was before the intervention at 16 - 20 weeks, the second time at 26 - 28 weeks and third time at 35 - 37 weeks and once 30 - 45 days after delivery. Three milliliters of fasting blood was drawn from the subjects at the beginning of the study (week 16 to 20). The samples were immediately centrifuged (Hettich, Universal 320, Germany) at 3500 rpm for ten minutes to remove serum. The samples were sent to the biochemical laboratory at the medical school of Tabriz University of Medical Sciences for phospholipids assessment. Results were stated as percentage of total fatty acids. To determine the reliability of the laboratory tests, two separate samples were prepared from five

participants with two different names and then the results' correlation was determined by Pearson correlation coefficient. A correlation rate of 0.92 was accepted.

Mercury-free fish oil supplements were obtained from a pharmaceutical company. The cold vapor atomic absorption spectrometry measurement (CV-ASS) method was used to reassure lack of mercury in the oil. No mercury was found in the oils after three measurements from three different samples.

3.5. Statistical Analysis

The normal distributions of continuous variables were confirmed by Kolmogorov-Smirnov test among groups. The analyses were done based on intention-to-treat approach. Descriptive statistics including frequency, mean and standard deviation, and inferential statistics included chi-square, Fisher's exact test, Independent t-test, paired t-test, ANOVA with repeated measures, analysis of covariance (ANCOVA) were used for data analysis. P values of < 0.05 were considered statistically significant. All statistical analyses were done using the statistical package for social science version 21

4. Results

The participants were recruited from February to November 2014 and followed-up until May 2015. Only one participant in the placebo group discontinued taking capsules due to nausea but since the analysis was based on intention-to-treat, all 150 females (75 in each group) were included in the final analysis (Figure 1). Irregular use of capsules was reported in two subjects (2.6%) in either group. According to the psychiatrist examination, none of the participants received antidepressant intervention during the study.

In terms of socio-demographic characteristics, both groups were similar ($P > 0.05$). The mean (SD) age of the participants was 26 (4.7). About half of the participants' education level (48%) was high school. Almost all women (99%) were housewives. About two-third (63%) had relatively sufficient income. A little more than half of the participants (55%) had normal Body mass index (BMI) (18.5 to 24.9). The majority of them had wanted pregnancy. The mean (SD) serum levels of DHA and EPA fatty acids at baseline were 0.19 (0.08) and 0.16 (0.06), respectively (Table 1). Half of the participants in both groups were primiparous. About two-thirds of the participants in both groups (65% fish oil and 73% placebo group) consumed fish less than once a week and there was no significant difference between the two groups.

The mean (SD) score of baseline depression at 16 - 20 weeks of pregnancy in the fish oil group was 10.9 (4.9) and in the placebo group was 11.3 (4.7). There was no significant difference between the two groups ($P = 0.60$). The mean (SD) score of depression after the intervention at 26-30 weeks of pregnancy was 10.6 (5.2) in the fish oil group and 11.6 (4.9) in the placebo group (adjusted MD = -0.7; [95% CI -1.8 to 0.4]). Despite a decrease in the mean score of depression in the fish oil group at this stage, and no reduction in the placebo group, the difference between the two groups considering the pre-intervention score as a covariate using Analysis of Covariance (ANCOVA) was not significant ($P = 0.19$). The mean (SD) score of depression after intervention at 35 - 37 weeks of pregnancy in the fish oil group was 9.7 (4.6) and in the control group was 11.5 (4.8) (adjusted MD = -1.4; [95% CI -2.6 to -0.25]). Taking the pre-intervention scores into account using ANCOVA test, there were significant differences between the two groups ($p=0.02$). One-Way Analysis of Variance (ANOVA) with repeated measures showed that the mean score of depression significantly decreased in the fish oil group ($P = 0.02$) but it was not significant in the placebo group ($P = 0.87$). The mean difference between pre-intervention (16 - 20 weeks) and 35-37 weeks of pregnancy in the fish oil group was also significant ($P = 0.01$) (Table 2, Figure 2).

Analysis of data on the postpartum depression indicated that the mean (SD) score of depression at 30 - 45 days after birth in the fish oil group was 9.6 (5.3) and in the placebo group was 10.9 (5.1) (adjusted MD = -1.1; [95 % CI -2.5 to 0.47]). There were no significant differences between the two groups using ANCOVA ($P = 0.17$) with the pre-intervention score as a covariate. The paired t-test showed that the mean difference of depression score in the fish oil group between pre-intervention and 30 - 45 days after birth was significant ($P = 0.04$), yet there was no significant difference in the placebo group ($P = 0.33$) (Table 3, Figure 2).

No participant in the groups had blood pressure equal to 140/90 mmHg or more during pregnancy. One (1.4%) case in the fish oil group and three (4%) cases in the placebo group based on patient record had high hemorrhage at birth that required no blood transfusions. There was only one (1.4%) neonatal death in the placebo group. None of the newborns in the fish oil group versus two (2.6%) in the control group had Apgar scores below seven at the first minute. Only one (1.3%) newborn in the control group had an Apgar score equal to seventh in fifth minute and the rest of the infants in both groups had higher Apgar.

Nausea in seven (9.3%) participants in the fish oil group and ten (13.3%) participants in the placebo group, unpleasant taste in six (8%) subjects of the intervention group and ten (13.3%) subjects of the control group, vomiting and mild diarrhea in one (1.33%) case in the fish oil group and stomach pain in one (1.33%) in the placebo group were reported. There were no significant differences between the

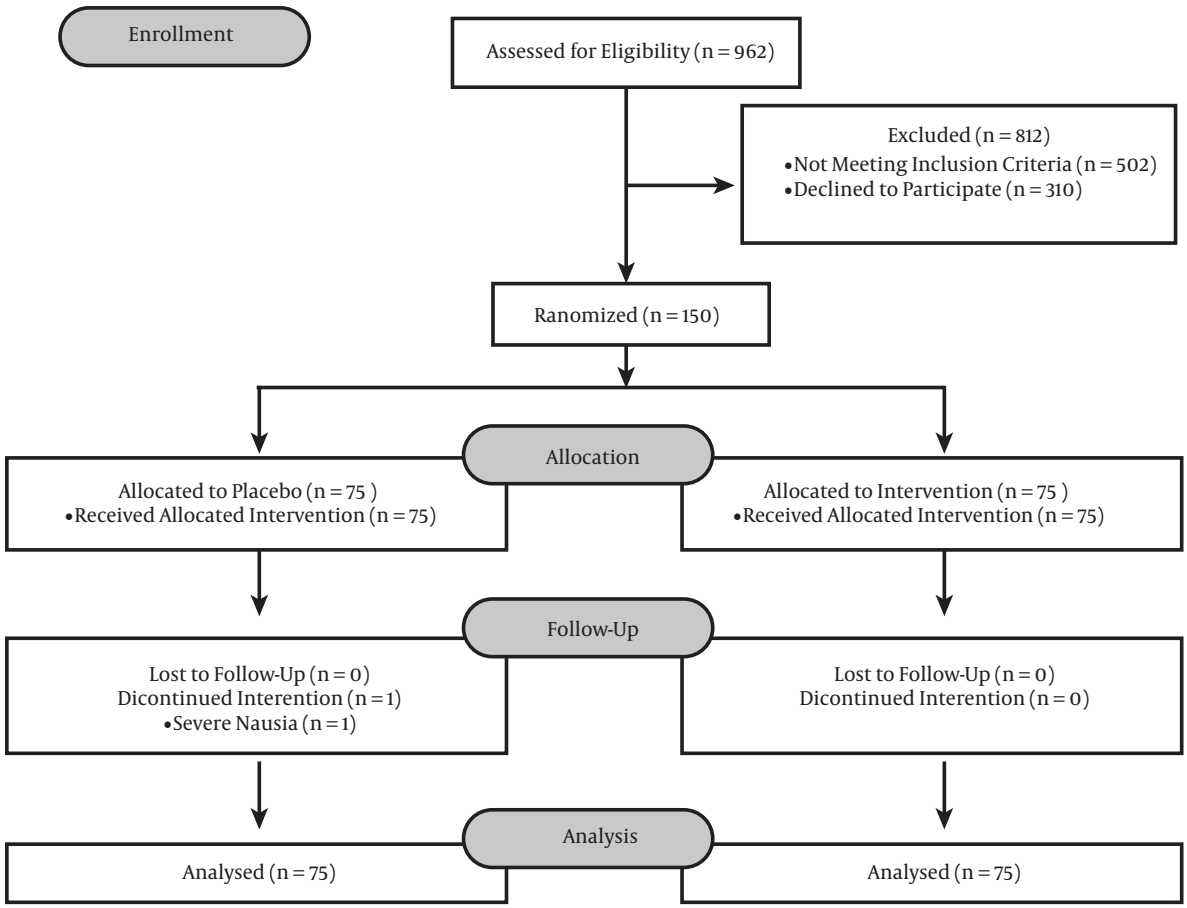

Figure 1. Summary of Patient Flow Diagram

two groups considering side effects (Table 4). These occurred mostly in the early use that did not prevent taking capsules.

5. Discussion

In this study, fish oil capsules 1000 mg (containing 120 mg of DHA and 180 mg EPA and 400 mg ALA) one per day were used from the end of the 20th week of pregnancy until one month after delivery. This RCT was the first research in Iran that evaluated the long-term effects of fish oil on both antenatal and post-partum depression with a large sample size, according to our search. Since, the consumption of fish and seafood is very low in Iran (29) as confirmed through baseline serum levels of DHA and EPA, the results of this study seem be useful in promotion of mothers health.

Fish oil supplementation could significantly decrease the mean (SD) score of depression after intervention at 37-35 weeks of pregnancy, so that the differences between groups were statistically significant. Although fish oil supplements decreased the mean (SD) score of depression at 26 to 30 weeks and 30-45 days after giving birth in the fish oil group but differences between the two groups were not statistically significant.

The mean score of depression during pregnancy within the fish oil group decreased significantly but it was not significant within the placebo group. Furthermore, difference between the mean score of depression between baseline and 30-45 days after giving birth was significant within the fish oil group but it was not significant within the placebo group.

Epidemiological data indicate that low intake of seafood during pregnancy is associated with higher levels of depressive symptoms (29). However, reviews of the literature demonstrate inconsistent results.

Hibbeln in a systematic review of observational studies indicated that a higher consumption of seafood predicts

Table 1. Baseline and Background Characteristics of Participants Among Fish Oil and Placebo Groups[a]

General Characteristics	Placebo Group, n = 75	Fish Oil Group, n = 75	P
Age, y[b]	26.9 (4.5)	25.9 (4.8)	0.19[c]
18 - 24	25 (33.3)	29 (38.7)	
25 - 29	29 (38.7)	28 (37.3)	0.76[d]
30 - 35	21 (28)	18 (24)	
Education			
Primary School	15 (20)	14 (18.7)	
Secondary school	14 (18.7)	23 (30.7)	0.44[e]
High school	39 (52)	33 (44)	
University	7 (9.3)	5 (6.7)	
Occupation			
Housewife	74 (98.7)	74 (98.7)	1.00[f]
Husband's education			
Primary School	20 (26.7)	16 (21.7)	
Secondary school	23 (30.7)	21 (28.4)	0.43[e]
High school	28 (37.4)	27 (36.5)	
University	4 (5.3)	10 (13.5)	
Income			
Adequate	13 (17.3)	15 (20)	
Relatively adequate	50 (66.7)	44 (58.7)	0.58[e]
Non adequate	12 (16)	16 (21.3)	
Weight, kg[b]	60.41 (10.4)	60.42 (9.3)	0.99[c]
Height, cm[b]	158.5 (5.2)	159.5 (5.8)	0.28[c]
BMI, kg/m^2[b]	23.9 (3.7)	23.7 (3.5)	0.84[c]
< 18.5	37 (49.3)	38 (50.7)	
18.5 - 24.9	27 (36)	28 (37.3)	0.96[d]
25 - 29.9	11 (14.7)	9 (12)	
Wanted pregnancy	66 (88)	59 (81.9)	0.36[f]
DHA[b]	0.193 (0.01)	0.189 (0.01)	0.88[c]
EPA[b]	0.163 (0.01)	0.159 (0.01)	0.41[c]

Abbreviations: DHA, docosahexaenoic acid, EPA, eicosapentaenoic acid that was expressed as percentage of total fatty acids.
[a]Values are expressed as No. (%) unless otherwise indicated.
[b]Mean (SD).
[c]Independent t.
[d]Chi-square.
[e]Trend χ^2.
[f]Fisher's exact test.

lower prevalence of postpartum depression (22).

Results of RCTs that evaluated the effect of omega-3 fatty acids on antenatal and postpartum depressions are contradictory. Dennis et al. in a review study aimed to assess the effects of omega-3 fatty acids in the treatment of antenatal depression in two clinical trials. In one trial, women who received omega-3 had significantly lower mean score of depression after eight weeks of intervention than those, who received the placebo (MD-4.70, 95% CI -7.82 to -1.58). In another trial with a smaller size, significant difference in mean depression scores was not observed between females who received omega-3 or placebo (MD 0.36, 95% CI -0.17 to 0.89) (5).

Mozurkewich et al. (23), in a controlled trial assessed

Table 2. Comparing the Mean (SD) Score of Antenatal Depression Between and Within the Fish Oil and Placebo Groups

Depression (0 - 30)	Before Intervention	After Intervention					
Group	16 - 20 wk	26 - 30 wk	35 - 37 wk	p[a]	P (1 × 2)	P (1 × 3)	P (2 × 3)
Fish oil, n = 75	10.9 (4.9)	10.6 (5.2)	9.7 (4.6)	0.02	0.31	0.01	0.06
Placebo, n = 75	11.3 (4.7)	11.6 (4.9)	11.5 (4.8)	0.87	0.61	0.81	0.83
Adjusted MD (95% CI)[b]	-0.4 (-1.9 to 1.1)	-0.7 (-1.8 to 0.4)	-1.4 (-2.6 to -0.25)				
Percent of changes	-	-6.03	-12.17				
p	0.60[c]	0.19[d]	0.02[d]				

[a] ANOVA with repeated measures (Sphericity Assumed, Greenhouse-Geisser).
[b] Adjusted mean difference (95% confidence interval).
[c] Independent t-test.
[d] ANCOVA adjusted for baseline depression score, recruitment center, parity.

Table 3. Comparing the Mean (SD) Score of Post-Partum Depression Between and Within Fish Oil and Placebo Groups

	Fish Oil, n = 75		Placebo, n = 75				
	Baseline Mean (SD)	Post-Partum Mean (SD)	Baseline Mean (SD)	Post-Partum Mean (SD)	Adjusted MD (95% CI)[a]	Percent of Changes	P[b]
Depression score (0 - 30)	10.9 (4.9)	9.6 (5.3)	11.3 (4.7)	10.9 (5.1)	-1.1 (-2.5 to 0.47)	-10.09	0.17
P value[c]	0.04		0.33				
	Fish oil, n = 75		Placebo, n = 75				
	Baseline Mean (SD)	Post-partum Mean (SD)	Baseline Mean (SD)	Post-partum Mean (SD)	P value[b]	Adjusted MD (95% CI)[a]	
Depression score (0 - 30)	10.9 (4.9)	9.6 (5.3)	11.3 (4.7)	10.9 (5.1)	0.17	-1.1 (-2.5 to 0.47)	
P value[c]	0.04		0.33				

[a] Adjusted mean difference.
[b] P value, compare two groups at postpatum using ANCOVA adjusted for baseline depression score, recruitment center, parity.
[c] Paired t-test, Baseline (16 - 20 weeks).

Table 4. Frequency of Reported Side Effects among Fish Oil and Placebo Groups

Side Effects	Fish Oil Group, No (%)	Placebo Group, No (%)	P Value[a]
Nausia	7 (9.3)	10 (13.3)	0.67
Vomiting	1 (1.3)	0	1
Unpleasant taste	6 (8)	10 (13.3)	0.58
Mild diarrhea	1 (1.3)	0	1
Stomach pain	0	1 (1.3)	1

[a] Fisher's exact test.

the supplementation of omega-3 fatty acid for the prevention of prenatal and postpartum depression. Participants received EPA-rich fish oil supplement or DHA-rich fish oil supplement or placebo. Significant difference in BDI scores from the baseline to 34 - 36 weeks of pregnancy and 6 - 8 weeks postpartum between the groups was not observed (30). Females at risk of depression were studied in the referred study.

Makrides et al., in an RCT in Australia evaluated the effect of taking DHA-rich fish oil capsules (providing 800 mg /d of DHA) during the second half of pregnancy on reducing depressive symptoms (EPDS score more than 12) at six weeks or six months after the birth. They indicated there was no difference between the DHA and control groups (vegetables oil) in the percentage of females with high levels of depressive symptoms during the first six months after birth (14). This study was consistent with our results but antenatal depression was evaluated.

Another study in an RCT conducted in Iran examined the effectiveness of omega-3 fatty acids in the treatment of mild to moderate postpartum depression. Mean depression score decreased significantly in the omega-3 group, but the decrement was not significant in the placebo

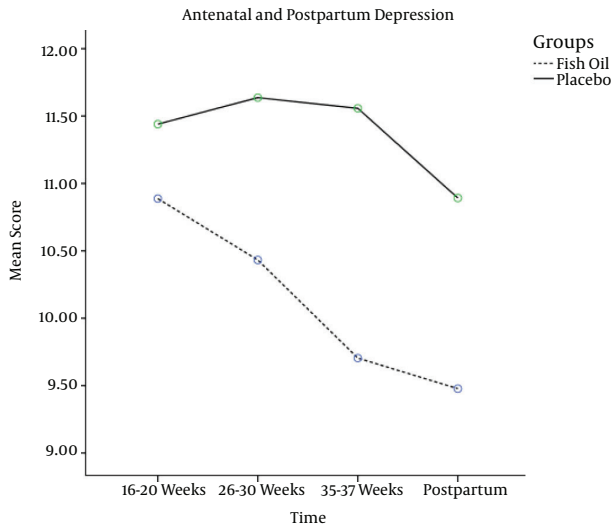

Figure 2. Mean Score of Antenatal and Postpartum Depression in the two Groups

group. Depression scores were significantly different between groups after treatment ($P < 0.001$) (31). The results of this study in terms of postpartum depression are consistent with our study in terms of within-group analysis, but it is inconsistent by considering between-group analysis. However, it has only been done in the postpartum period on depressive women.

Studies indicated that supplementation with omega-3 fatty acids during pregnancy increase maternal DHA and EPA (30, 32, 33). The major mechanism of the effect of omega-3 on the nervous system is through affecting phospholipids of nervous cells' walls and appropriate functioning of nerve cells and proper secretion of neurotransmitters. Researches have indicated the effect of omega-3 on serotonin of cerebrospinal fluid and a correlation between decrement of its level in the plasma and cellular membrane of depressed patients (34). Omega-3 fatty acids decrease the production of pro-inflammatory cytokines, which increase in depressed patients (5). These mechanisms could be the leading causes of reduction in mean score of depression in our study because the consumption of fish and seafood is very low in our population. However, various factors such as sample size, study population with or without depression at baseline, nutritional status, the amount of fish intake and so baseline serum DHA and EPA, and dose of supplements can be important in effectiveness of intervention.

One difficulty in relation to RCTs, especially in depression studies, was that the control group often has lower than expected rates of depressive symptoms. This may be due to the Hawthorn effect (19).

It was considerable that the mean score of antenatal depression at 35-37 weeks and also the mean score of postpartum depression in the fish oil group reached below 10. According to the classification of EPDS, scores below 10 were in the non-depressed category.

5.1. Strengths and Limitations

Participants were given the required information about the study before intervention for several times in this study. The necessity of regular intake of supplements was emphasized and enough opportunity to decide was provided for them. Participants were provided with 24-hour contact phone number, and necessary consultation was provided in case of complications. Follow-ups were conducted regarding capsules use. Used medication packages and daily intake checklist were collected twice. Nulliparous and multiparous participants were equally allocated to the two groups using the stratification method. Random allocation, allocation concealment and triple blinding were implemented in this study. Serum levels of DHA and EPA were examined before the intervention so that they could be adjusted if they were different. To ensure the safety of the medications, the mercury levels of fish oil supplements were reevaluated. Limitations of the present study were not using the Beck Depression Inventory along with EPDS, the impossibility to evaluate the umbilical DHA and EPA fatty acids, and the relatively low doses of omega-3, which was the only available dose. Therefore, it is recommended to conduct a study with different and higher doses of supplements. The umbilical fatty acid levels and their relationship with the antenatal and postpartum depression can also be studied.

5.2. Conclusion

According to the findings of our study in relation to the impact of fish oil supplementation on reduction of the mean depression score during pregnancy in the fish oil group as well as with regards to the significant difference between groups at 35 - 37 weeks of pregnancy, it seems that women, especially in countries with low per capita consumption of fish, may benefit from daily fish oil supplements during pregnancy. Further studies, especially on populations with low consumption of fish are necessary to confirm these results.

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