Research Article

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The Effect of Perinatal Fish Oil Supplement on Perinatal Depression: A Systemic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Perinatal depression is a common complication of pregnancy and can have severe and long-term adverse effects on both mother and infant. Randomized controlled trials (RCT) assessing the effect of fish oil supplements on perinatal depression have shown mixed results.

Objectives: We performed a systematic review and meta-analysis to assess the effects of fish oil supplementation during pregnancy on perinatal depression.

Methods: A comprehensive search of MEDLINE (PubMed), EMBASE, and Cochrane Central Registry were conducted in adherence with the PRISMA guideline. Only RCTs published in English from January 2000 to date were included. The participants were pregnant women receiving fish oil supplementation or placebo. Summary effect measure of each study was converted to a common effect measure (log odds ratio) and its variance was calculated to estimate the pooled odds ratio and its 95% confidence Interval using random Effects model. Heterogeneity was assessed using restricted maximum likelihood method.

Results: Nine trials were included in our analysis (2,979 women). Prevention Cohort (n = 5): Fish oil supplementation during pregnancy was associated with reduced risk of developing perinatal depression (OR: 0.87; CI: 0.076 to 0.99; p = 0.03). Treatment Cohort (n = 4) Fish oil supplementation during pregnancy was associated with reduced risk of persistent perinatal depression during postpartum period but did not reach statistical significance.

Conclusion: In conclusion, a meta-analysis of included RCTs data shows a significant reduction in incidences of perinatal depression in women who received fish oil supplements during pregnancy. However, there was no evidence for a similar effect among women diagnosed with perinatal depression or women with major depressive disorder.

Keywords: Perinatal depression, Fish oil supplements, Meta-analysis, Pregnancy

Background and Rationale

While childbirth is typically a joyful moment in women lives, some might be affected by depression. This range from mild self-limiting depressive symptoms known as baby blues to major depression or even psychosis. Historically, the term '*perinatal depression*' has been used to describe the occurrence of at least one major depressive

episode during pregnancy and up to six months post-delivery [1,2]. Perinatal depression is an important obstetric complication with a significant detrimental effect not only on women but extends to affect the infant [3,4] and family [5]. Furthermore, prenatal depression is a significant predictor of offspring depression [5] and rarely may end with suicide [6-10] or even infanticide [8,11-13]. The exact prevalence of antenatal depression is

unknown [14,15], It is, however, estimated to fall between 10%-25% [1,14,16-18]. While several mechanisms have been proposed, the exact is not fully understood [15]. One possible mechanism is inappropriate activation of the inflammatory pathway [19]. This hypothesis has been supported by an increase in pro-inflammatory cytokines and CRP (inflammatory biomarkers) [20-22] observed in women diagnosed with perinatal depression [20]. Other possible mechanisms that have been proposed, includes activation of the hypothalamus-pituitary axis and dietary insufficiencies [15,20,23,24]. Moderate to high fish, specifically oily fish, consumption has been proposed as a possible intervention to prevent and halt the progression of perinatal depression [25-27]. This proposition draws upon the theoretical premise of the anti-inflammatory effect of omega-3 long-chain polyunsaturated fatty acid (n-3 LCPUFA) commonly referred to as fish oil [28,29]. Furthermore, epidemiologic studies have linked maternal fish intake during pregnancy to reductions in perinatal depression [25,30]. However, these findings have not been supported by randomized clinical trials [31-33], and to date, there has been little agreement on the effect of fish oil supplement on perinatal depression. Thus, we performed a systemic review and a meta-analysis of RCTs comparing fish oil supplementation and placebo starting from 12 weeks up to 6 months post-partum in women with no history of perinatal depression, and women with major depressive disorder. The aims of the current meta-analysis were, therefore, to investigate (1) whether fish oil supplement prevents prenatal depression (2) whether fish oil supplement is an effective treatment for perinatal depression.

Methods

Literature search

The systematic review and meta-analysis were done in compliance with preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [34]. A comprehensive search of MEDLINE (PubMed), EMBASE, and Cochrane Central Registry were carried out from first January 2000 till the first of July 2019 since the use of supplementary fish oil was not common before January 2000. Articles of interest were identified using search terms that combined the intervention terms like polyunsaturated fatty acids (PUFA), omega-3 fatty acids (O3FA), marine oil, fish oil, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) with outcome terms like perinatal, peripartum and postpartum depression. Reference list of primary articles was inspected to find additional studies that were not previously identified. Literature search was performed under the guidance of a

medical librarian (K.M).

Search strategy

Comprehensive search strategy involving MEDLINE (PubMed) EMBASE and Cochrane Central Registry is detailed table S1 in the supplementary materials.

Inclusion/Exclusion criteria

We only included RCTs published in English language, from first of January 2000 till the first of July 2019. We included studies on women with twin pregnancies and studies where intervention period was extended to the postpartum period. We excluded studies in women who had chronic medical problems and who were already on antidepressants, prenatal supplements containing either DHA or EPA. We also excluded studies that did not assess outcome using a validated depression screening tools (Edinburgh Postnatal Depression Scale (EPDS), Beck Depression Inventory (BDI)).

Study selection

Studies were selected in a two-stage process. In the first step, the electronic citations were reviewed for potential eligibility. In the second step, full copies of the eligible studies were obtained for detailed evaluation by two independent reviewers (S.H., R.B.B.) who reviewed the full text for inclusion and exclusion criteria. Any disagreements between the reviewers were resolved by discussion, and if needed by involving a third reviewer (T.N.).

Data extraction

Data were extracted by two independent reviewers using predesigned forms. (S.H., M.H.). Data on study author, year of publication, location, sample size, inclusion and exclusion criteria, risk status of the population, type, dose, and frequency of intervention, gestational age at commencement of intervention, and the timing and type of outcomes were extracted.

Study quality assessment

We assessed the quality of the included studies using Cochrane Collaboration tool. This tool is used to evaluate the risk of bias in RCTs and comprises of following six domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

Statistical analysis

All included studies were initially grouped into two major cohorts. Prevention cohort if the intervention was used to prevent perinatal depression in healthy pregnant women and treatment cohort if it was used to treat it. All statistical analyses mentioned below were performed in each individual cohort separately using R software version 3.3.2, and “metafor” package version 2.0-0 on Mac operating system x86_64-apple-darwin13.4.0 (64-bit) [35,36].

Though the included studies addressed a similar question, each study used a different summary effect measure (mean difference in EPDS or BDI scores in case of continuous outcome and odds ratio (OR) of perinatal depression for the binary outcome). Thus before pooling, summary effect measure of each study was converted to a common effect measure and it's variance was calculated using methods detailed by Borenstein M et al. [37]. OR was chosen as the common effect measure because relative effect measures like odds ratio and risk ratio are more stable across studies than risk difference, especially if the studies included had different follow-up intervals.

Due to the clinical and methodological heterogeneity between the studies, a random effects model was used to estimate the pooled effect size, and it's 95% confidence interval (CI) and restricted maximum likelihood (REML) estimation method to compute the between-study variance (τ^2). As OR has skewed distribution in typical sample sizes, effect estimates, standard errors and confidence intervals were calculated using the natural logarithm of OR and the final results were then back-transformed to the original scale for presentation.

Between-study variance (heterogeneity) was quantified using Higgins' and Thompson's I^2 statistic [38], and $I^2 > 50\%$ was considered significant. In the event of significant heterogeneity, we performed meta-regression to look at the effect of covariates (Study year) on the desired outcome. We also evaluated the possibility of reporting bias using funnel plot but no formal tests for funnel plot asymmetry were carried out as the number of studies in each cohort were less than 10 which decreases the power of the test and makes the results misleading.

Results

Search results

A total of 306 citations were retrieved during the initial search after removing duplicates (Figure 1). Among

them, 293 articles were excluded upon review of title and abstract. An additional four studies were excluded as one had an inappropriate intervention, and three had an inappropriate outcome. Final dataset comprised of, nine RCTs including 2979 women, that were eligible for review. The inter-reviewer agreement on study eligibility was 100%.

Figure 1: PRISMA flow diagram showing the selection criteria of included studies.

Study characteristics

Nine RCTs (2,979 women) studied the effect of fish oil supplements (DHA, EPA, or both) on perinatal depression. The dose of the O3FA in fish oil supplements ranged from 200-3300 mg per day. The intervention was commenced at various stages of gestations, with 8/9 (88%) studies starting during 12-32 weeks of gestation and one starting during postpartum period. The duration of intervention ranged between 6-24 weeks. Five studies included healthy women [31,39-42] and evaluated the efficacy of fish oil supplements in prevention of perinatal depression while others investigated its role as therapeutic intervention in women already suffering from depression [31,43,44]. Characteristics of included studies in the systematic review of fish oil supplementing the prevention and treatment of perinatal depression are presented in table 1.

Study quality assessment

The randomization was adequate in all studies. Seven of the nine studies (78%) had adequate allocation concealment and blinding. The analysis was by intentions to treat in 56% (5/9) of the included studies.

Table 1: Characteristics of included studies in the systematic review of fish oil supplementin the prevention and treatment of perinatal depression¹.

Author	Country	Population		intervention	placebo	duration	timing	Outcome
Llorente et al, 2003 [39]	USA	89	Healthy women	200 mg of DHA per day	Not specified	3 months	after delivery	BDI
Freeman et al, 2007 [43]	USA	59	perinatal depression	1.1grams of EPA and 0.8g of DHA per day	Corn oil	8 weeks	12w-32w of gestation	EPDS
Rees et al, 2007 [23]	Australia	26	perinatal depression	27.3% DHA, 6.9% EPA per day	Sunola oil	6 weeks	28 weeks and 6 months post-delivery.	EPDS
Su KP et al, 2008 [44]	Taiwan	36	perinatal depression	2.2 g of EPA and 1.2 g of DHA Per day	Olive oil	8 weeks	16-32 weeks of gestation	EPDS
Makrides et al, 2010 [31]	Australia	2320	Healthy women	800 mg of DHA per day	Vegetable oil	Until delivery	20 weeks of gestation or more	EPDS
Mozurkewich et al, 2013 [33]	USA	126	Healthy women at risk	1060 mg EPA plus 274 mg DHA or 900 mg DHA plus 180 mg EPA	Soy oil	until 6-8 weeks after delivery.	12-20 weeks of gestation	BDI
Kaviani et al, 2013 [49]	Iran	80	mild de-pression	Omega-3 fatty acid ,1 g per day	Olive oil	6 weeks	20 weeks of gestation or more	BDI
Vaz JDS et al, 2017 [41]	Brazil	60	Healthy women at risk	1.08 g of EPA and 0.72 g of DHA Per day	Soybean oil	16 weeks	22-24 weeks of gestation	EPDS
Khalili et al, 2017 [18]	Iran	150	Healthy women	120 mg of DHA, and180 mg of EPA per day	Paraffin	Until 1 month after delivery	20 weeks of gestation	EPDS

⁽¹⁾DHA: docosahexaenoic acid; EPA: Eicosapentaenoic acid; EPDS: Edinburgh Postpartum Depression Scale; BDI: Beck Depression Inventory.

Clinical outcomes assessment

All studies were grouped into two major cohorts. Prevention cohort if intervention was used to prevent perinatal depression in healthy women and treatment cohort if it was used to treat it in women who are already suffering from depression. As these are clinically heterogeneous cohorts we carried out analyses in each individual cohort and summarized the finding.

Prevention Cohort: Fish oil supplementation during pregnancy was associated with reduced risk of developing perinatal depression (OR: 0.87; CI: 0.076 to 0.99; $p = 0.03$) (Figure 2A).

Treatment Cohort: Fish oil supplementation during pregnancy was associated with reduced risk of persistent perinatal depression during postpartum period but did not reach statistical significance. (OR: 0.51; CI: 0.13 to

1.93; $p = 0.31$) (Figure 2B).

Heterogeneity and bias assessment

Prevention Cohort: No significant difference between study variance was noted in the prevention cohort (Cochrane $Q = 2.20$; $df = 5$; $p = 0.82$; $I^2 = 0.0\%$). Contour enhanced funnel plot with 90, 95 and 99% confidence intervals showing missing studies reveal no evidence of publication bias (Figure 3A).

Treatment Cohort: We noticed a significant difference between study variance in the treatment cohort (Cochrane $Q = 22.32$; $df = 3$; $p = 0.00$; $I^2 = 84.7\%$). Contour enhanced funnel plot with 90, 95 and 99% confidence intervals did not reveal missing studies or evidence of publication bias (Figure 3B). Meta regression looking at the impact of study year on overall effect size revealed that study year accounts for 18% of the between study variance (Table S2; Figure 4). No sensitivity analyses were performed

looking at the impact of study quality and dose of fish oil supplement on effect size because of small number of studies (n = 4) available.

Figure 2A: Forest plot showing the results of five studies examining the effect of the fish oil supplements on prevention of perinatal depression.

Figure 2B: Forest plot showing the results of 4 studies examining the effect of the fish oil supplements on treatment of perinatal depression.

Figure 3A: Contour enhanced funnel plot showing 90 (White), 95 (gray), 99% (dark gray) confidence intervals, and missing studies (white dots) and reference line centered around pooled effect size in prevention cohort (n = 5 studies).

Figure 3B: Contour enhanced funnel plot showing 90 (White), 95 (gray), 99% (dark gray) confidence intervals, with reference line centered around pooled effect size in treatment cohort (n = 4 studies).

Figure 4: Meta regression demonstrating the impact of study year on effect size (odds ratio).

Discussion

This meta-analysis of 9 randomized clinical trials, involving 2,949 women, showed that receiving fish oil supplementation during pregnancy had a significant impact on preventing perinatal depression, while fish oil supplementation had no effect on treatment of perinatal depression.

In contrast to previous studies, this meta-analysis

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provides new evidence, specifically that fish oil supplementation could be implemented in preventing prenatal depression.

Despite the strong scientific plausibility [19,27,28,45,46], previous clinical studies showed inconsistent results, and did not provide a conclusive evidence of the beneficial effect of fish oil supplements on maternal health, specifically preventing prenatal depression [15,32]. This inconsistency was mainly between observational studies and randomized clinical trials. The reasons for the discrepant results of the previous trials of fish oil supplementation on prenatal depression are unclear. On one hand, large epidemiological studies, including previous meta-analyses, found a significant inverse relation between sea food consumption and the rate of perinatal depression and related outcomes. On the other hand, several randomized clinical trials showed no significant reduction in the incidence of postpartum depression nor a benefit of fish oil in treatment of perinatal depression. Most notably, Markids et al. (2010) which concluded that the use of DHA-rich fish oil did not have a significant effect on lowering postpartum depression (adjusted RR 0.85, 95% CI 0.7-1.02 P = 0.09) [31]. While other trials investigating the effect of fish oil supplement on perinatal depression can be criticized on small sample size and lack of sufficient power [26], Markids et al. (2010) had 2320 patients and was power to detect 4% change in perinatal depression. It is unclear

whether baseline differences between study subjects may explain the results [31].

Findings of this updated meta-analysis generally contradict with previous clinical trial and meta-analyses which showed no effect of fish oil supplement and perinatal depression. After pooling data from 9 randomized clinical trials we showed an OR of 0.87 ($p < 0.03$) in favor of fish oil supplementation. This can be explained by the larger number of observations and the statistical power compared to previous results. There are, however, other possible explanations.

The strengths and limitations of this review merit consideration. The strengths of our study are the systematic assessment of the effects of fish oil supplementation on perinatal depression, and the careful selection of the analyzed studies. Our search was comprehensive, and we assessed the quality of the included studies carefully. Although there was evidence of heterogeneity across studies, the prenatal depression prevention subgroups showed little heterogeneity. Compared to the previously published meta-analyses [32], our analysis relayed only on RCTs, and we implied different inclusion criteria and perinatal outcomes.

Furthermore, we assessed the results for publication bias. Additionally, our findings may have several implications, they reinforce a potentially beneficial role of fish supplementation in preventing perinatal depression. Thus, providing a possibly cost effective [47], and relatively safe [26] alternative for women at risk of perinatal depression. Furthermore, our findings are in line with current Federal Drug Administration (FDA) [48], American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) dietary guidelines, which encourage prenatal fish consumption. Moreover, our result highlights the scientific gaps in the current literature and provides a rationale for future studies to investigate the effect of fish oil supplementation on pregnant women.

The limitations of our review are the heterogeneity between the included studies. The included studies varied in the inclusion criteria, type of fish oil supplement, dose and timing of intervention. Heterogeneity was lower in the subgroup analyses for prevention ($I^2 = 0.0\%$) compared with the subgroup analysis for treatment ($I^2 = 84.7\%$). Contour enhanced funnel plot demonstrate no evidence of publication bias in prevention cohort or treatment cohort. Most importantly, 80% of the subjects included

in the analysis comes from one clinical trial. Finally, we included only 9 studies and most of the studies were from high-income countries.

In conclusion, meta-analysis of included RCTs data shows a significant reduction in incidences of perinatal depression in women who received fish oil supplements during pregnancy. However, there was no evidence for similar effect among women diagnosed with perinatal depression or women with major depressive disorder. The possible beneficial effect of fish supplement on prenatal depression risk might be mediated through inhibition of pro-inflammatory pathway. However, the result of this meta-analysis should be interpreted carefully as further large scale clinical trials are needed to determine the effect of fish oil supplements on prevention and treatment of perinatal depression.

Declarations

Consent for publication

The authors of this paper consent for publication.

Availability of data and material

All data and material are available.

Competing interests

The authors of this paper declare no competing interests.

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Authors' contributions

SH researched and analyzed the data. RBB analyzed the data and edited the manuscript. MH, TN, JY and VV analyzed the data and wrote the manuscript. SH and VV are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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