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Effects of Fish Oil Supplementation on Gestational Diabetes Mellitus (GDM): A Systematic Review

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Abstract

Context: One of the most common complications of pregnancy is gestational diabetes mellitus (GDM), which is increasing worldwide. Experimental and epidemiological studies have shown that higher intake of n-3 long-chain polyunsaturated fatty acids may decrease the risk of various diseases such as diabetes. The objective of this study was to assess the effect of fish oil supplementation on the prevention and treatment of GDM.

Evidence Acquisition: This systematic review was performed by searching several databases, including PubMed, Scopus, Google Scholar, the Cochrane Library, ProQuest, Science Direct SID, Magiran and IranMedex since 1983. The researchers also searched for references in reviewed clinical trial articles in which fish oil supplementation was compared with placebo or no supplementation.

Results: Only two published and in-press articles are included in this review. Based on these studies, docosahexaenoic acid (DHA)-enriched fish oil (800 mg/d) had no effect on prevention of GDM [0.97 (95% CI: 0.74, 1.27)]. Furthermore, omega-3 fatty acid supplementation containing 180 mg of eicosapentaenoic acid (EPA) and 120 mg DHA had beneficial effects on insulin resistance in women with GDM (change from baseline: 1.5 ± 7.5 vs 3.5 ± 8.5 mIU/mL, $P = 0.02$) but did not influence fasting plasma glucose, homeostatic model assessment-Beta cell function (HOMA-B), the quantitative insulin sensitivity check index (QUICKI), or lipid profiles ($P > 0.05$).

Conclusions: There is not enough evidence to support or refute the routine use of fish oil supplements during pregnancy for the prevention or treatment of diabetes. It is suggested that further randomized controlled trials be conducted to evaluate the role of fish oil supplementation in pregnancy.

Keywords: GDM, Fish Oil, Supplementation, Randomized Controlled Trials

1. Context

1.1. Description of the Condition

1.1.1. Diabetes Mellitus and its Classification

Diabetes mellitus is a chronic and complex disease that requires ongoing medical care, with multiple strategies to reduce the risk for glycemic control (1). Diabetes can be classified into four clinical categories. Type 1 diabetes is caused by the destruction of beta cells, and usually results in absolute insulin deficiency, while Type 2 diabetes results from a progressive defect in insulin secretion that occurs in an insulin resistance context. Other specific types of diabetes are caused by other factors, such as genetic defects of beta-cell function, genetic incompetence in insulin action, and diseases related to exocrine pancreas, chemical, or drug-induced diabetes. Finally gestational diabetes mellitus (GDM) is recognized during pregnancy and is not clearly overt diabetes (2).

1.1.2. Gestational Diabetes Mellitus (GDM) and Health Outcomes

GDM is one of the most common complications of pregnancy with a prevalence rate of 3-8% (3), and is increasing globally (4, 5). It is well-established that GDM is accompanied by an enhanced risk for adverse perinatal consequences and long-term health consequences for both mother and child. Women with a history of GDM have a higher risk for developing type 2 diabetes, whereas children born to mothers with gestational diabetes are at

higher risk for metabolic syndrome and obesity during their lifetimes (6, 7). Screening for GDM is done through one of two strategies: a one-step 2-hour OGTT with 75g, or a two-step strategy 1-hour with 50g (non-fasting) which is followed by a 3-hour OGTT with 100g for women with a positive screen (1, 8).

1.2. Medical Nutrition Therapy for Preventing GDM

Medical nutrition therapy is one of the most important strategies for the prevention of diabetes, and can prevent or at least slow the progression rate of diabetes complications and manage the disease (9, 10). Wijendran and colleagues (1999) demonstrated significant differences in n-3 fatty acids between control subjects and women with GDM (11). Many studies have demonstrated that the higher intake of n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFA) may decrease the risk of some types of diseases, including cardiovascular disorders, immunological and neurological problems, cancer, diabetes, ulcerative colitis, asthma, and multiple sclerosis (12-19).

1.3. Essential Fatty Acids

In humans, the essential fatty acids are the n-3 PUFA alpha-linolenic acid (ALA, 18:3(n-3)) and the n-6 PUFA linoleic acid (LA, 18:2 (n-6)) (20). Although humans can elongate the dietary α-linolenic acid to the eicosapentaenoic acid (EPA, 20:5 n-3 LC-PUFA) and also docosahexaenoic acid (DHA, 22:6 n-3 LC-PUFA) (21, 22), the synthesis rate may be insufficient to meet the body's needs, and therefore, it is recommended that proper sources of these fatty acids, such as oily fishes, should be considered in one's diet (23). Not only is ALA consumption very low, but conversion of ALA into the longer chain fatty acids is also reduced because of competition with large amounts of LA for the identical enzymes (24). The ratio of omega-6/omega-3 is important (20, 25).

1.4. How n-3 LCPUFAs Might Work

Women with and without GDM have different plasma fatty acid profiles, indicating a possible change in the metabolism of fatty acids in GDM. The researchers demonstrated that consumption of n-3 LCPUFA fatty acids in rats increases the utilization of peripheral glucose (26). Also enhancing the intake of oily fishes which are rich in n-3 LCPUFAs by people who are already glucose intolerant delays the development of diabetes (27). Epidemiological studies that examined the relationship between consumption of n-3 LCPUFA and GDM have given contradictory results (28-30). Despite increasing the evidence that suggest beneficial effects of n-3 LCPUFA gain on improved insulin sensitivity (31) and improved glucose metabolism in animals and humans (3, 32-35), the effects of fish oil supplementation in pregnancy to prevent or treatment of GDM have only been investigated in a few clinical trials.

1.5. Why It Is Important to Do This Review

Despite the enhanced risk of adverse perinatal consequences and adverse long-term health outcomes in GDM for the mother and child, we didn't find any review study on the effects of fish oil supplementation on GDM.

1.6. Objective

The aim of this study was to assess the effect of fish oil supplementation intake on GDM in pregnant women.

2. Evidence Acquisition

2.1. Criteria for Considering Studies for this Review

2.1.1. Types of Studies

RCTs that compared fish oil supplementation with placebo or without supplementation in pregnant women were included in this review. We intended to conduct our review on GDM after the initial assessment of the included clinical trials. In addition, we searched for any data related to adverse events. Although intake of the precursors is likely less effective with respect to glycemic response or the risk of GDM, clinical trials in which the intervention group received precursor essential fatty acids (α-linoleic acids and linoleic acids) were included. Trials with only biochemical outcomes were also included. Irrelevant studies, i.e. those without location, systematic articles, case control articles, cohort articles, animal studies, duplication articles, and letters were considered as exclusion criteria. Also, several related articles obtained manually from references of review articles were added to the set.

2.1.2. Types of Participants

Pregnant women of any gestational age and parity with singleton pregnancies were included. Women at either a normal or high risk of GDM were included. Women were excluded if they were already taking a dietary supplement containing DHA or EPA.

2.1.3. Types of Interventions

We considered all randomized comparisons of fish oil supplementation given to pregnant women with placebo or no supplementation, regardless of dose regimens, times, and durations of intervention. Trials conducted with the aim of preventing GDM in pregnant women, and those that surveyed the effect of fish oil supplementation on various indexes such as fasting plasma glucose, homeostatic model assessment-Beta cell function (HOMA -B),

quantitative insulin sensitivity check index (QUICKI), lipid profiles, etc. in women with GDM, were included. Impaired glucose tolerance was defined by the respective trial authors. Fish oil administered orally was compared with placebo or no supplementation with fish oil. The clinical trials in which food was supplemented with fish oil were also included. Trials with a single dose treatment were excluded. Trials in which fish oil was investigated in combination with other nutrients or drugs that may affect GDM were also excluded.

2.1.4. Types of Outcome Measures

- Primary Outcomes

Incidence of gestational diabetes mellitus in pregnant women, whether measured by one-step, 2 hour, 75 g OGTT or by a two-step strategy with a 1 hour, 50 g (non-fasting) followed by a 3hour 100 g OGTT for women with a positive screen (1, 8).

Fasting plasma glucose, insulin concentration, homeostatic model assessment-Beta cell function (HOMA - B), homeostasis model of assessment-insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), or lipid profiles in pregnant women with GDM

- Secondary Outcome

Side-effects (gastrointestinal and non-gastrointestinal)

2.2. Search Strategy to Identify Studies

Our search strategy involved the use of a valid filter to identify RCTs (36), with a topic specific strategy using PubMed's MeSH terms. The search terms included *fish oil, omega 3 fatty acids, n-3 LCPUFA, n-3 PUFA, n-3 long chain polyunsaturated fatty acids, marine oil, gestational diabetes mellitus,* and *GDM*. This systematic review was performed by searching several databases including PubMed, Scopus, Google Scholar, the Cochrane Library, ProQuest, Science Direct, SID, Magiran, and IranMedex since 1983, as well as searching the references in reviewed articles for RCTs comparing fish oil supplementation with placebo or no supplementation.

We conducted our search by surveying published and in-press papers. References in the reviewed articles were used as additional resources. We searched theses through websites of Iranian universities, and attempted to search conference proceedings, but it was impossible to gain complete access to grey literature. We included English and Persian articles with respect to the language of publication. Two of the authors maintained the searches through:

1. Monthly searches on the Cochrane Database and Cochran Central Register of Controlled Trials (CENTRAL);

2. Weekly searches on Medline;

3. Weekly searches on Embase;

4. Weekly searches of Scopus, Google Scholar, ProQuest, Science Direct

5. Weekly searches of Persian databases such as SID, Magiran, and IranMedex.

2.3. Statistical Analysis

We could not pool the data using meta-analysis because of the high heterogeneity of data related to clinical heterogeneity. One of the studies used the omega-3 supplements for prevention of diabetes, but another studied it as a treatment.

2.4. Data Collection and Analysis

2.4.1. Selection of Trials

Two authors independently assessed the eligibility of studies identified by the searches in this review. Azizeh Farshbaf-Khalili (AFKH) assessed all the potentially eligible papers and Alireza Ostadrahimi (AOR), Mojgan Mirghafourvand (MM), and Sakineh Mohammad-Alizadeh (SMA) each assessed one-third of the articles. All the articles were investigated in terms of duplication, and disagreements were resolved by discussion.

2.4.2. Data Extraction and Management

We designed a form to extract data. For eligible studies, two review authors (AFKH, MM) extracted the data independently using the form. Discrepancies were resolved through discussion or, if required, through consultation with the third author (AOR).

2.4.3. Assessment of Risk of Bias in Included Studies

Two authors of this review (AFKH, MM), using the criteria determined in the Cochrane handbook for systematic reviews of interventions, independently surveyed the risk of bias for each study (37). Any disagreement was resolved by discussion or by involving a third assessor (AOR). AOR and AFKh, investigators on long chain-PUFA clinical trials, could potentially include trials in this review. The clinical trials included were independently assessed concerning risk of bias, and the data were extracted.

2.4.3.1. Random Sequence Generation (Checking for Possible Selection Bias)

The method applied in this regard was assessed as low, unclear, or high risk of bias. Trials were assessed as low risk of bias if there were certainly random process such as computer-based random numbers or tables of random numbers, and high risk of bias if the sequence generation was non-random, e.g. birth date, even or odd numbers, health center, clinic, or hospital record numbers.

2.4.3.2. Allocation Concealment (Checking for Possible Selection Bias)

Strategies applied for allocation concealment before assignment and during recruitment were explained for each entered trial. The strategy was assessed as low, unclear, or high risk of bias. Trials were assessed as low risk of bias if they used sealed opaque envelops or packs through central or telephone allocation, and high risk of bias if random allocation was open, e.g. using non-opaque or unsealed packs or envelopes, birth date, even or odd numbers, or alternating numbers.

2.4.3.3.1. Blinding of Participants and Personnel (Checking for Possible Performance Bias)

Strategies applied for blinding participants and personnel in relation to the type of intervention in the studied groups were expressed for each included trial. The strategy was assessed for blinding as low, unclear, or high risk of bias. Trials were assessed as a low risk of bias if both personnel and participants were blinded.

2.4.3.3.2. Blinding of Outcome Assessment (Checking for Possible Detection Bias)

Strategies applied for blinding assessors of outcome in relation to the type of intervention received in the studied groups were mentioned for each included trial. The method of blinding assessors was assessed separately for each outcome. The strategy was assessed for blinding outcome assessment as low, unclear, or high risk of bias. Trials were assessed as low risk of bias if the assessors were blinded.

2.4.3.4. Incomplete Outcome Data (Checking for Possible Attrition Bias Due to the Amount, Nature, and Handling of Incomplete Outcome Data)

The completeness of data comprising exclusions from the study or analysis and attrition was explained for each entered trial or outcome. Exclusions, attrition, and the number of participants entered in each stage of the analysis, in comparison with the total number of subjects, was surveyed and reported. Reasons for exclusion and attrition, if reported in the studied trials, and methods for balancing missing data between groups or relating to outcomes were described. The strategy was assessed as low, unclear, or high risk of bias. Trials were assessed as low risk of bias if there wasn't any missing outcome data or if it was balanced between groups, and were assessed as high risk of bias if the reasons for or amount of missing data were imbalanced between groups.

2.4.3.5. Selective Reporting (Checking for Reporting Bias)

Each included trial was investigated in terms of the bias of the selective outcome reporting and reported. The strategy was assessed as low, unclear, or high risk of bias. Trials were assessed as a low risk of bias if all predetermined outcomes of trial have been reported, and as a high risk of bias if all pre-determined outcomes of trial have not been reported, or if there was a primary outcome report that had not been determined previously, or if the trial could not indicate a major outcome which it had expected to report.

3. Results

The review of the literature revealed that there were only two clinical studies in this field. One of them was a published RCT done in the perinatal centers of Australia between October 2005 and January 2008, which investigated the efficacy of fish oil supplementation in prevention of GDM (3). The other study was an in-press RCT conducted in Kashan, Iran, during January 2014-March 2014, which investigated the effects of omega-3 fatty acid supplementation on insulin metabolism in pregnant women with GDM (38). It must be mentioned that we found 13 related articles in the primary search but only two papers satisfied our quality assessment. 11 articles were related to diabetes mellitus in non-pregnant people and so were excluded from the study. No study regarding GDM was excluded.

In the study by Zhou and co-authors (3) 2399 pregnant women were randomly assigned to two groups. The groups received DHA-rich fish oil capsules at a dose of 800 mg daily or vegetable oil capsules without DHA from 21 weeks gestation until delivery. Clinical criteria showed that the overall incidence of GDM was 8%. The RR was calculated as 0.97 (95% CI: 0.74-1.27) for GDM, and there was no significant difference between the groups. Zhou et al. concluded that the risk of GDM cannot be reduced with daily 800 mg supplementation of DHA during the second half of pregnancy. In the other randomized, double-blind, placebo-controlled clinical trial by Samimi et al. (38), 56 women with GDM were studied. Subjects were randomly assigned to receive either 1000 mg omega-3 fatty acid supplements containing 180 and 120 mg eicosapentaenoic acid and docosahexaenoic acid respectively (n = 28), or a placebo (n = 28), for 6 weeks. In their study, fasting blood samples were taken at baseline and after 6 weeks of intervention.

Samimi and colleagues' results (38) indicated that omega-3 fatty acid supplementation did not lead to a significant change in serum insulin levels and HOMA-IR in the intervention group, but there was a significant difference in changes in serum insulin levels (change from baseline:

1.5 ± 7.5 vs. 3.5 ± 8.5 mIU/mL, P = 0.02) and HOMA-IR (0.4 ± 2.1 vs. 1.1 ± 2.4, P = 0.02) between the two groups. Furthermore, a significant reduction in serum high sensitivity C-reactive protein (hs-CRP) levels was seen in the intervention group compared with placebo (236.3 ± 1541.9 vs. 898.6 ± 2292.7 ng/mL, P = 0.03). Omega-3 fatty acid supplementation did not influence fasting plasma glucose, homeostatic model assessment-Beta cell function (HOMA-B), quantitative insulin sensitivity check index (QUICKI), or lipid profiles. They concluded that Omega-3 fatty acid supplementation in women with GDM has beneficial effects on insulin resistance; however, it doesn't affect plasma glucose, HOMA-B, QUICKI, and lipid profiles.

3.1. Risk of Bias in Included Studies

The risk of bias for the included RCTs is described in the tables in the characteristics of the included RCTs. Based on the CONSORT checklist (39), the study by Zhou et al. (2012) used appropriate methods for randomizing the allocation sequence, such as using containers numbered sequentially, describing the measures used to conceal the allocation until intervention, and referring to the person who created the sequence of random allocation, but the reference to the person who assigned participants to the intervention groups is not clear.

It seems that the study of Zhou et al. (2012) was at the risk of incomplete outcome data caused by attrition of subjects in the clinical trial, because it is unclear how many subjects followed the treatment completely until the end of the study. In the study of Samimi et al. (2014), there was also an unclear risk of bias with regard to type of randomisation and its details, e.g. blocking and block size, strategies applied to conduct the random allocation sequence such as sequentially numbered packs, and explaining each action to conceal the sequence until assigning interventions. It seems the risk of bias is low in terms of generating random sequence and blinding of participants. Blinding of outcome assessment and selective reporting were also at low risk of bias.

4. Discussion

Pregnancy is accompanied by insulin resistance and glucose metabolism disorders. There is a progressive augmentation during the gestation course in the maternal insulin secretary response to glucose and a variety of other stimulations (40, 41). Data from this systematic review indicated that DHA-enriched fish oil (800 mg/d) has no effect on the prevention of GDM. Also, Omega-3 fatty acid supplementation containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid had beneficial effects in women with GDM on insulin resistance, but did not influence fasting plasma glucose, function of homeostatic model assessment-B cell (HOMA-B), quantitative insulin sensitivity check index (QUICKI), or lipid profiles.

The useful effects of short- and long-chain n-3 fatty acids on animal insulin function are well-documented (42-45). For example, omega-3 fatty acids can perfectly counteract the diet-induced insulin resistance by a diet with high saturated fat, and it has been found that the dietary intake of n-6 and n-3 fatty acids is strongly and directly associated with insulin resistance in rats (46). However, the results of observational studies regarding the effect of Omega-3 fatty acid on GDM are controversial. Some of these studies showed a positive association (11, 47) while others indicated no or inverse associations (29, 48).

Zhou and colleagues (2012) applied DHA-enriched fish oil, but the dose of EPA is unclear (3). In the study by Samimi et al. (2014), the fish oil supplementation contained 180 mg of eicosapentaenoic acid (EPA) and 120 mg of docosahexaenoic acid (DHA). It seems that the type and dose of these fatty acids may have diverse effects. Radesky et al. (2008) conducted one prospective cohort study to investigate associations between n-3 fatty acids, *trans* fats, whole grains and dietary patterns, and risk of GDM. The intake of n-3 fatty acids was associated with increased GDM risk. They carried out post hoc analyses to further explore the direct relationship between omega-3 fatty acids with risk of GDM. ALA was merely associated with an increased risk of GDM [OR (95% CI): 1.29 (1.04, 1.60)] per each 300 mg/day after adjustment for confounders, and DHA and EPA had no association with increased GDM risk (29).

The results of an uncontrolled pilot study suggested that DHA probably has more beneficial effect on insulin sensitivity compared to EPA fatty acids in humans (49), and cannot be fully rejected by other research in which researchers applied a relatively higher dosage of EPA supplementation (50). However, more research is needed in order to compare the effects of EPA, DHA, and EPA & DHA in separate interventional groups with higher dosage. The study of Samimi and colleagues (2014) was done in only one center (38). According to the three-day dietary records completed during the intervention, there was no statistically significant discrepancy between the two studied groups concerning dietary intake of polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), cholesterol, omega-3, and omega-6 fatty acid. However, the effects of fish oil on insulin sensitivity might be regulated by a different habitual intake of n-6 and n-3 polyunsaturated fatty acids through different possible mechanisms, such as competition for the transcriptional factors and/or the same enzymes, different membrane fluidity, and production of eicosanoids with different anti-inflammatory potency (51,

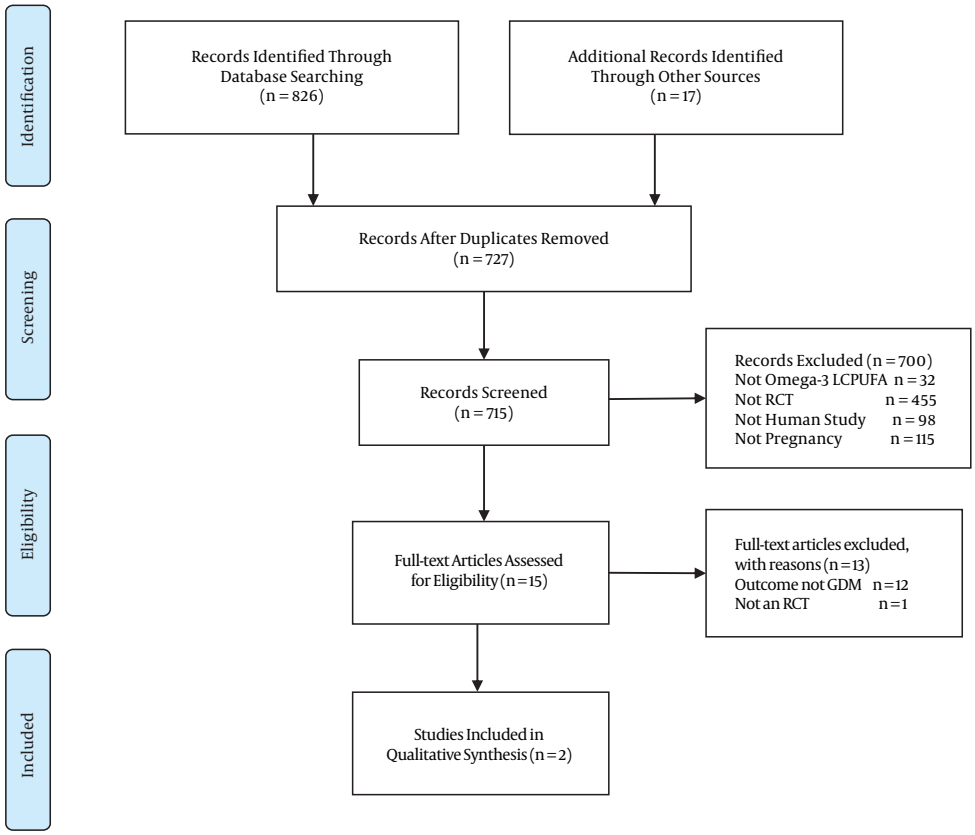

Figure 1. Study Flow Diagram

52). So, we suggest conducting a multicenter study on people from different regions with different habitual intake of n-6 and n-3 polyunsaturated fatty acids.

In Samimi and colleagues' study (38), the effect of fish oil was measured on 28 diabetic women. Further studies with larger sample sizes are needed for meta-analysis. In the included trials, the methods used for random assignment of participants and allocation concealment were not described. Blinding of personnel, care providers, and outcome assessors were unclear. Attrition was also a problem in the Zhou et al. study. Neither study reported on the side-effects associated with fish oil supplementation. Furthermore, it should be considered that the fish oil supplements may be able to modulate insulin function rather than restore an created insulin resistance (46). Thus, the beneficial effects may be observed in healthy subjects but not in diabetics, especially among pregnant women.

The present systematic review has some limitations. First, it may be that we did not identify unpublished reports thoroughly. Furthermore, we had a limited number of randomized clinical trials; hence, our analysis did not address issues relating to dose and duration of intervention. Third, we included only English and Persian articles in this review. According to the authors', search, no review study has investigated the effect of n-3 LCPUFA fish oil on GDM to date. Due to the enhanced risk of adverse consequences of GDM on mothers and neonates, this study can highlight scientific gaps in this field of study.

4.1. Conclusions

Although one included study indicated that omega-3 fatty acid supplementation containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid had beneficial effects in women with GDM on insulin resistance, there is not enough evidence to support or refute the routine use of fish oil supplements during pregnancy for the prevention or treatment of diabetes. Further randomized trials are required to evaluate the role of fish oil supplementation in pregnancy. Considering the undesirable consequences of GDM for mothers and their babies, conducting such studies seems necessary.

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Footnotes

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Conflict of Interest: There is no conflict of interest in this review.

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Table 1. Characteristics of Included Studies

Character		Description
		Zhou 2012
Methods		This randomized control trial was a multicenter double-blinded study named "DHA to optimize mother and infant outcomes" (DOMInO). The RCT aimed to investigate the effects of n-3 LCPUFA supplementation during pregnancy on reducing the incidence of preeclampsia or GDM. The study's secondary outcome was to investigate the effect of n-3 LCPUFA supplementation on complications of perinatal period. Pregnant women (n = 2399) randomly received DHA-rich fish oil 800 mg/d or vegetable oil capsules free of DHA from 21 week gestation to birth. Blinded searching of medical records was used to detect the incidence of GDM or preeclampsia. Perinatal complications and birth outcomes were also specified.
Participants		Participants in the DOMInO trial consisted of 2399 pregnant women whose gestation was less than 20 week and who had singleton pregnancies. These subjects were recruited between October 2005 and January 2008 from five perinatal centers in Australia. Exclusion criteria were: consumption of dietary DHA supplementation, having a known major abnormality in the fetus, having a coagulation disorder and contraindication for taking fish oil, taking anticoagulant agents, having a specified history of alcohol or drug abuse, English was not their main spoken language at home, and participation in another clinical trial. The human research ethics committees related to each study center issued approval to conduct the study, and all participants submitted written informed consent forms.
Interventions		Women allocated to the DHA-enriched fish-oil group received three 500-mg DHA-enriched fish oil capsules daily, providing 800 mg DHA (Incromega 500 TG; Croda Chemicals), whereas women in the control group received three capsules of 500-mg vegetable oil free of DHA from RCT entry to birth time.
Outcomes		The primary outcomes were the incidence of GDM and preeclampsia. Secondary outcomes were pregnancy and birth outcomes, as well as perinatal complications. GDM was defined by two diverse approaches, and each of them was used separately to report the GDM incidence.
Notes		Prevalence of GDM or preeclampsia was calculated between 3% and 8% (1, 16). Outcome data were accessible from 2301 (96%) women for preeclampsia and 2144 (89%) women for GDM. The power to identity a 3% absolute reduction (from 7% to 4%) in the risk for preeclampsia or GDM (2-sided $\alpha = 0.05$) was provided by the listed sample sizes.
Risk of Bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	low risk	"The randomization schedule was generated independently with balanced, variable-sized blocks and was stratified by center and parity (first birth compared with subsequent birth)."
Allocation concealment (selection bias)	Unclear risk	No specific information regarding allocation concealment was given.
Blinding of participants (performance bias)	Unclear risk	"This was a double-blind, multicenter randomized control trial." Method of personnel blinding not mentioned.
Blinding of personnel (performance bias)	Low risk	The content of vegetable oil capsules (placebo) was a composite of 3 non-genetically altered oils consisting of rapeseed, sun [U+FB02]ower oil, and palm oil in identical proportions. This composition was designed for adaptation to the MUFA, PUFA, and SFA profiles in the average Australian diet. All capsules were identical in shape, size, and color.
Blinding of outcome assessment: (detection bias)	Unclear risk	Blinding of assessors was not mentioned.
Incomplete outcome data (attrition bias)	Unclear risk	All participants in both groups were included in the intention to treat analysis. No significant differences were found in terms of adherence between randomized groups. The numbers of women who withdrew from treatment and their reasons were not specified. "Small numbers had no data for clinical diagnosis of diabetes in each arm: DHA n = 13, Placebo n = 21, but no reasons were mentioned."
Selective reporting (reporting bias)	Unclear risk	
		Samimi 2014
Character		**Description**

Methods		This randomized, double-blind, placebo-controlled clinical trial was performed among 56 women with GDM to investigate the effects of omega-3 fatty acid supplementation on insulin metabolism and lipid profiles of pregnant women with GDM. 1000 women were assessed for eligibility. 944 were excluded for not meeting inclusion criteria (n = 934) or because they needed to start insulin therapy (n = 10). 56 were randomized to receive either 1000 mg omega-3 fatty acid capsules or matched placebo capsules.
Participants		Pregnant women aged 18 to 40 years with GDM that had been diagnosed with one-step 2hour 75g OGTT at 24 to 28 weeks of pregnancy were recruited and included. Gestational age was measured by the date of the first day of the last menstrual period and clinical examination simultaneously. Pregnant women were screened with no previous diagnosis of glucose intolerance. American diabetes association criteria for diagnosis of GDM were applied. Subjects who had no placenta abruption, premature preterm rupture of membrane, chronic hypertension, pre-eclampsia, eclampsia, urinary tract infection, hypothyroidism, kidney or liver diseases, smoking history, and who were not taking estrogen therapy were included in the current trial. The exclusion criterion for the study was the need to commence insulin therapy during the intervention.
Interventions		Enrolled participants were randomly assigned to receive either 1 pearl of 1000 mg omega-3 fatty acid per day, containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid (n = 28), or one placebo per day (n = 28), for 6 weeks.
Outcomes		Insulin concentrations and lipid profiles among pregnant women with GDM.
Notes		For calculating sample size, the authors considered type one and type two errors equaling 0.05 and 0.20 respectively ($\alpha = 0.05$, $\beta = 0.20$, power = 80%), and the homeostasis model of assessment-insulin resistance (HOMA-IR) score as a key variable. Based on a previous study, the standard deviation (SD) of HOMA-IR was 0.8 and the difference in mean (d) of HOMAIR was 0.6. They considered a sample size equal to 24 subjects for each group through the formula suggested for parallel clinical trials.
Risk of bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Random assignment was done by using computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Randomization and allocation concealment from the participants and researchers were done until completion of the main analysis. A trained midwife at a maternity clinic performed the sequence of randomized allocation. The method of concealment was not mentioned.
Blinding of personnel (performance bias)	Unclear risk	A trained midwife at a maternity clinic carried out the randomized allocation sequence, and enrolled and assigned participating women into the intervention.
Blinding of participants (performance bias)	Low risk	"The omega-3 pearl contained 70% long-chain omega-3 polyunsaturated fatty acids as a one-gram pearl that contained 180 mg of eicosapentaenoic acid (EPA), 120 mg of docosahexaenoic acid (DHA) and 400 mg of other omega-3 fatty acids; the placebo pearl contained 500 mg of liquid paraffin. The appearance of placebo, its color, shape, size, and packaging, were identical to the omega-3 fatty acid capsule."
Blinding of outcome assessment (detection bias)	Low risk	Randomization and allocation concealment from the researchers and participants until completion of the main analysis.
Incomplete outcome data (attrition bias)	Low risk	3 participants were lost to follow-up due to insulin therapy (n = 1) and hospitalization (n = 2) in the intervention group, and 3 lost to follow-up due to placenta abruption (n = 1) and insulin therapy (n = 2). All 56 subjects were analyzed.
Selective reporting (reporting bias)	Low risk	The outcomes determined in the Iranian Registry of Clinical Trials appear to have been reported in the results.