http://www.cjmb.org

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 3, No. 3, July 2016, 100–106
eISSN 2148-9696

The impact of Supplementation With Fish Oil on Lipid Profile of Pregnant Mothers: A Randomized Controlled Trial

Ismail Faraji[1], Alireza Ostadrahimi[2], Azizeh Farshbaf-Khalili[3], Hossein Aslani[4*]

Abstract

Objective: The impact of supplementation with omega-3 fatty acid during gestational period on lipid profile levels remains unknown. The objective of this trial was to investigate the impact of supplementation with fish oil on maternal lipid profile.

Materials and Methods: This research was a randomized triple blinded controlled trial. The study population was comprised healthy pregnant subjects who had family records at health care centers in Tabriz, Iran. A total of 150 women who were eligible for study were randomized into two groups, one group took fish oil supplement capsules (1000 mg/day), and another group took placebo. A total of 92 women fulfilled the study which 45 participants were in the supplemented group and 47 participants were in the placebo group. Consumption of fish oil capsules and placebo was daily one capsule from the beginning of the 21th week of gestation until delivery which was about 20 weeks. At the start of trial (16th-20th weeks) and in the fifth care of gestation (during 35th-37th weeks) 3 cc blood samples collected and sent to the laboratory for evaluation of lipid profile levels.

Results: Despite substantial increases in total cholesterol, triglycerides and Low-density lipoprotein (LDL) levels with advancing pregnancy, there was no statistically significant discrepancy between the intervention and placebo groups. ($P=0.345$, 0.299, 0.109, respectively). Despite a significant decrease in the levels of high-density lipoprotein (HDL) cholesterol with advancing pregnancy, there was no statistically meaningful difference between two groups ($P=0.786$)

Conclusion: We found no effect of supplementation with fish oil during gestation on plasma lipid profile of pregnant mothers.

Keywords: Fish oil supplementation, EPA, DHA, Placebo, Pregnancy, Lipid profiles

Introduction

Although obstetric care has been improved, pregnancy complications and perinatal morbidity are still present in western societies (1). Therefore, it is of clinical and economic importance to prevent adverse pregnancy outcomes by exploring causal factors for these outcomes. One of the causal factors for perinatal morbidity and mortality could be the maternal lipid profile in early pregnancy (2-5).

Changes in lipid metabolism during gestation focus on preparation for parturition and lactation. During the first two-thirds of pregnancy, when the energy demands of fetus are limited, fat stores of mothers increase (6). This increased lipid storage is necessary as an energy store to fulfill maternal and fetal metabolic needs (7). It is the result of hyperphagia and enhanced synthesis of lipid and also increased activity of adipose tissue lipoprotein lipase (LPL) (8,9).

In late pregnancy, as the nutritional demands of fetus increase, maternal fat storage reduces and metabolism of maternal lipid shifts to a catabolic condition (8). These changes cause increment in the plasma levels of non-esterified fatty acids (NEFA), glycerol and triglyceride during the third trimester of pregnancy (10,11).

Pregnant women indicate an increment in lipid levels, consisting of total cholesterol (TC) and levels of triglycerides (TG) as the age of normal gestation progresses (2-5). TC and TG both are taken up through the placenta and are metabolized and transported to the fetal circulation in different forms (6,12), this indicates that both lipids are necessary for the fetal development. However, preterm birth (PTB) can be accompanied by high levels of TG and/or TC (13-16), pregnancy-induced hypertension (PIH) (17,18), preeclampsia (18-23), and LGA in mothers (24-26).

The LDL level also increases dramatically as pregnancy progresses and plasma triglyceride increase, referring to change in a more atherogenic lipid profile (27).

The long-term outcomes of these changes have not been explored for coronary heart disease. There is, however, an enhanced occurrence of diabetes, obesity, angina, and cholesterol gallstones in post menopausal women

Received 3 February 2015, **Accepted** 25 May 2016, **Available online** 6 June 2016

[1]Department of Endocrinology, Imam Reza hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. [2]Tabriz Health Services Management Research Center, Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Tabriz Health Services Management Research Center, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences Tabriz, Iran. [4]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

*Corresponding author: Hossein Aslani, hosseinaslani1990@gmail.com

who have had several pregnancies (28). Cardiovascular morbidity and mortality both in patient with established coronary artery disease (CHD) and those with the risk of developing CHD decreases by effective controlling of the blood lipid level (29).

Omega-3 fatty acids (FAs) are a family of polyunsaturated fatty acids (PUFAs). Humans do not have the required metabolic pathways to synthesize the precursor FA (α-linolenic acid), which is necessary for the production of the longer bioactive omega-3 FAs. Therefore, these long chain PUFAs should be intake either from plant foods or by direct intake of DHA and EPA from industrial products or sea foods (30).

Some of the randomized trials in humans suggest that n-3 long chain PUFA (LCPUFA) supplementation during gestational period have modest useful effects on neurodevelopmental outcomes of offspring in comparison with controls (31-33).

Supplementation with n-3 LCPUFAs has also been suggested as a potential strategy to prevent preeclampsia (34). A number of epidemiological studies previously have indicated that high consumption of fish supplements rich in DHA are accompanied with longer pregnancy and higher birth weight (35,36).

There is enhancing evidence that n-3 FAs display anti-inflammatory, anti-thrombotic, anti-arrhythmic and anti-atherogenic effects (37,38). Also, populations who have high consumption of n-3 PUFAs (like the Eskimos) have low rates of heart disease (39,40). Since, a few human studies have been done to assess the impact of supplementation with fish oil on serum lipid profiles of women during pregnancy, the impact of this supplementation during gestational period, a hyperlipidemic state, on levels of lipid profile remains unknown. This trial was aimed to determine the impact of supplementation with fish oil during the second half of gestation on lipid profiles of pregnant women.

Materials and Methods

Subject Recruitment and Study Design

This research was a randomized triple blinded controlled trial. The study population consisted of 18-35 years old pregnant women with first to fifth parity that had family records at health centers in Tabriz, Iran. After receiving permission letter from the Ethics Committee of Research vice-chancellor of Tabriz University of Medical Sciences (No. 92141) and registration in the Iranian registry of clinical trials website (http://www.irct.ir/) (IRCT2013100914957N1), we selected the health centers which had the highest number of patients.

We also tried to select health centers with different socioeconomic situations. We prepared a list of all women in the gestational age of 16-20 weeks from the centers and invited them with phone calls to take part in the trial after introducing the study objectives. We also explained risks and benefits of participating in the study and recalled the voluntariness of participation. Questionnaire number one for evaluation of the inclusion and exclusion criteria was given to people who liked to participate in the study. Inclusion criteria was consisted of willingness to participate in the study, age of 18-35 years, first to fifth pregnancy, pregnant women with 16-20 weeks of gestation, single pregnancy, body mass index (BMI) less than 30, healthy pregnant women with no previous underlying medical condition, including heart disease, kidney disease, gastrointestinal disease, respiratory disease, auto-immune disorders, diabetes, impaired glucose tolerance testing in the current pregnancy, thyroid disorder, epilepsy, hypertension, psychiatric disorders, hyperlipidemia and not to use any drugs because of the above conditions. Also, Exclusion criteria was vaginal bleeding, placenta previa, placenta detachment in current pregnancy, infertility and premature labor history, any allergy to fish, fish products or gelatin, smoking, bleeding disorders or taking anticoagulants, participating in another study. If the women were eligible for the study the second questionnaire was given to collect demographic characteristics and complete their pregnancy events.

Also, the third questionnaire contained a tutorial on how to use capsules; daily record of taking capsules and possible events was given to pregnant women. A total of 150 participants were selected from which 75 women were in the intervention group and 75 women were in the placebo group.

Pregnant women were divided randomly into two groups by use of a table of random computer numbers, in the fish oil supplements capsules receiving group and the placebo receiving group with the ratio of 1: 1. From this population 92 pregnant woman completed the study which 45 were in the fish oil receiving group and 47 was in the control group.

Drug Delivery and Dietary Intake Assessment

Pregnant women were randomly allocated into two groups. One experimental group received fish oil supplement capsules (1000 mg consisted of 120 mg DHA and 180 mg EPA), another experimental group received placebo (1000 mg food grade liquid paraffin with the same shape, size and weight with other capsules). Fish oil capsules and placebo capsules produced by the pharmaceutical company of Zahravi in Tabriz, Iran. Consumption of fish oil and placebo capsules was one capsule from the beginning of the 21th week of gestation until delivery which was about 20 weeks (140 capsules). The capsules were placed inside the opaque and same shaped packets, so that there were two packets for each participant contained medication, one contained 1000 mg, 70 soft capsules to take in 10 weeks, another contained 1000 mg 70 soft capsules to consume in remaining 10 weeks. The two packs were put inside a larger opaque pack. This 150 larger same shaped packs numbered consecutively. Putting the fish oil capsules or placebo capsules into a packet was done by a non-researcher person on the basis of random sequence and thus allocation concealment was considered.

The first pack was delivered in the second prenatal care and the second packet was delivered in the third mater-

nal care after ensuring the continuation of the pregnancy and usage of earlier drugs and receiving daily drug usage check list. We stressed repeatedly on using drugs regularly and not to forget using them. To make sure of getting the medication, in 24th and 34th weeks of pregnancy, drug usage was followed by phone calls.

Samples and Measurements

Sampling was stratified with the order of the parity (first, second or more pregnancy). At the start of the study (weeks of 16-20) and in the fifth care of gestation (between weeks of 35-37) we collected 3 cc blood samples and sent them to the laboratory for evaluation of lipid profiles level. The subjects were entered to the research from February to November 2014 and followed-up till April 2015.

All 150 women had blood samples at baseline, but 12 subjects in the fish oil supplemented group and 11 in the control group had no blood samples at weeks of 35-37. So, 45 subjects in the fish oil and 47 ones in the control group were entered in the final analysis (Figure 1).

Statistical Analysis

All data analyzed by IBM SPSS software. Kolmogorov-Smirnov test were used to check data normality. In case of normal distribution data was offered as mean ± SD or frequency (percentage) and in case of non-normality, data was presented as median and interquartile ranges. For analysis of demographic data, chi-square tests and Fisher exact test were used for comparing qualitative variables and independent *t* test used for comparing quantitative variables with normal distribution between two groups.

For analysis of variables, comparisons inside each group between baseline and after intervention were done by pair sample *t* test. For analysis of variables, in the case of normal distribution, comparisons between groups was done by Independent *t* test and in the case of non-normal distribution, Mann-Whitney test was used.

Also we used general linear model for lipid profile levels after intervention to investigate whether there are meaningful differences between the study groups by considering the baseline value of variable, age, parity and health centers as covariate.

Results

No differences were observed in terms of age, gravid and pre-pregnancy BMI between the groups. Also education, occupation, family income and type of delivery were alike in the study groups (Table 1). With the progression of pregnancy a significant enhancement in TC, TG and LDL and a significant decrement in the serum level of high-density lipoprotein (HDL) was seen in both groups (Table 2)

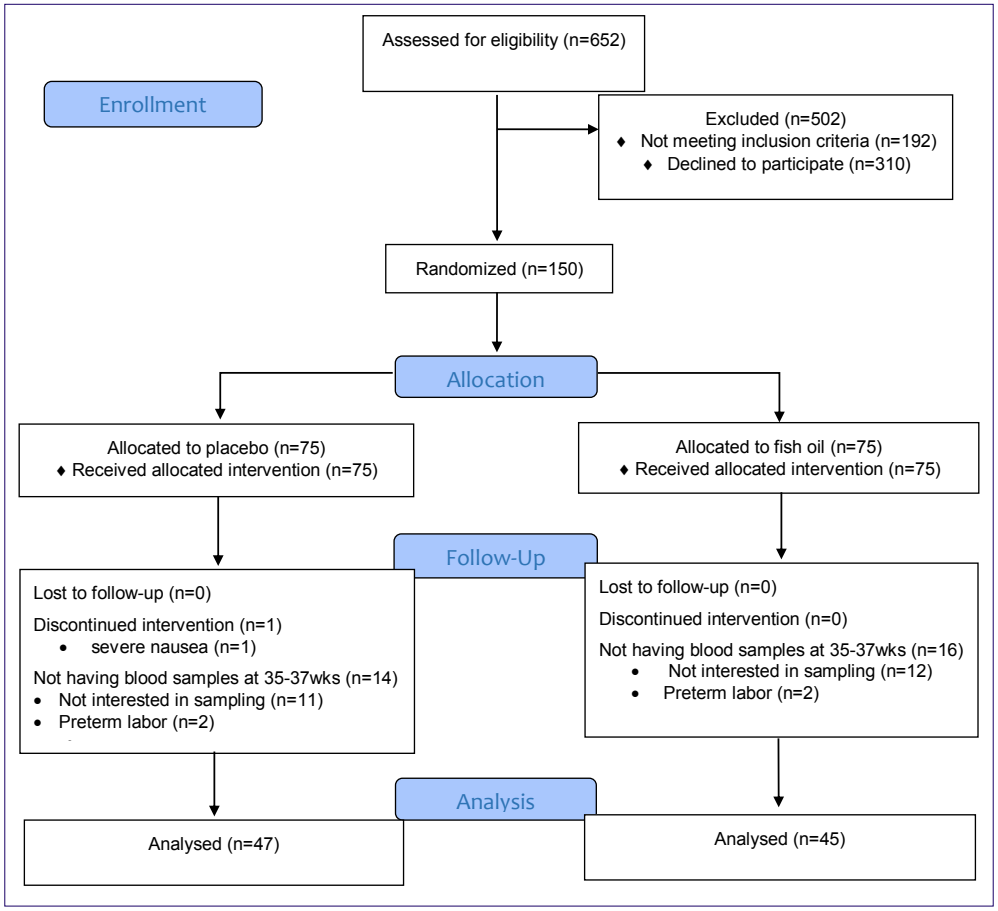

Figure 1. Summary of Patient Flow Diagram.

Table 1. Baseline Characteristics of Participants Received Fish Oil Supplements or Placebo[a]

General Characteristics	Fish Oil (n=45)	Placebo (n=47)	P
Age (years), mean (SD)	25.6 (4.7)	27.3 (4.2)	0.07[b]
Education (years)			
Primary school (1-5)	10 (22.2)	11 (23.4)	
Secondary school (6-8)	14 (31.1)	9 (19.1)	0.62[c]
High school (9-12)	17 (37.7)	24 (51.1)	
University (>12)	4 (8.9)	3 (6.4)	
Occupation			
Housewife	44 (97.8)	47 (100)	0.49[d]
Family income			
Adequate	8 (17.8)	8 (17.0)	
Relatively adequate	28 (62.2)	30 (63.8)	0.98[c]
Non adequate	9 (20)	9 (19.1)	
Pre-pregnancy weight (kg), Mean (SD)	58.8 (9.0)	58.6 (10.8)	0.92[b]
BMI (kg/m^2)			
<18.5	3 (6.7)	4 (8.5)	
18.5-24.9	26 (57.8)	29 (61.7)	0.82[c]
25-29.9	16 (35.6)	14 (29.8)	
Mean (SD)	23.1 (3.6)	23.3 (3.8)	0.81[b]
No. of pregnancy			
1	24 (53.3)	21 (44.7)	
2	16 (35.6)	19 (40.4)	0.85[c]
3-4	5 (11.1)	7 (14.9)	
Wanted pregnancy	37 (82.2)	41 (87.2)	0.77[d]
Mode of delivery			
Vaginal delivery	27 (60.0)	31 (66.0)	0.67[d]
Cesarean section	18 (40.0)	16 (34.0)	

Abbreviation: SD, standard deviation.
[a]All numbers are given as number (percent) except those specified as mean (SD).
[a]Independent *t* test
[b]Chi-square
[c]Fisher exact test.

Effect of Supplementation With Fish Oil on Maternal Serum Lipids

Triglyceride levels were not statistically diverse between study groups before supplementation at entry and there was no significant effect of fish oil given during 20 weeks of pregnancy compared with placebo ($P=0.299$, Table 3).
The serum levels of TC were alike in study groups before supplementation at 16-20 weeks of pregnancy and did not differ between groups after supplementation ($P=0.345$, Table 3).
HDL levels were alike between study groups at weeks of 16-20, and there was no significant effect of fish oil supplementation compare to the placebo group on serum HDL levels ($P=0.786$, Table 3).
LDL levels was alike between study groups at baseline and was not altered by fish oil during supplementation period ($P=0.109$, Table 3).

Discussion

According to the results of this trial the plasma lipid profile of pregnant subjects in the fish oil supplement receiving group had no significant difference compared with the control group. Although a few human studies have been done in this regard, but the results of these studies are compatible with our findings in this study.
Matorras et al studied 162 mother-neonate pairs to determine the relationship between n-3-long chain polyunsaturated fatty acids (n-3 LCPUFAs) intake in pregnancy and their maternal and neonatal serum levels, and the general lipid pattern in the mother and the neonate serum. They concluded that in the dietetic range of their population, the intake of (n-3 LCPUFAs) was not associated to any changes in the general lipid pattern of mothers or neonates serum, whereas the (n-3 LCPUFAs) levels in mothers serum were correlated with the changes in the general lipid pattern outside the pregnancy. They believed that the hyper-triglyceridemia of pregnancy, the placenta and the peculiarities of fetal metabolism are the causes of the aforementioned findings (41).
In the research by Barden et al, 83 pregnant women with allergic disease who were otherwise healthy participated and allocated to receive fish oil supplement or olive oil capsules as 4 g/day, from week 20 of gestation to delivery concluded that fish oil supplements comparing olive oil capsules did not change TGs, TC, LDL-C or HDL-C during gestation or afterward. No impact of supplementation with fish oil was observed on cord blood TGs, LDL HDL or TC (42).
Camilla et al, evaluated the impacts of supplementation with fish oil on the lipid profile and blood pressure in infants. Healthy and full-term infants aged 9-month old randomly were divided into 5 mL daily fish oil or no intervention for 3 months. Fish oil supplemented group had higher plasma TC and higher LDL cholesterol compared

Table 2. Effect of Progress of Pregnancy on Lipid Profile in Participants Received Fish Oil Supplements or Placebo

General Characteristics	Number	Mean Difference (95% CI)	R	*P*
Fish Oil				
TC1-TC2	45	26.82(11.44 to 42.19)	0.571[b]	0.001[a]
TG1-TG2	45	69.49(49.48 to 89.49)	0.401[b]	<0.001[a]
HDL1-HDL2	45	-9.93(-13.06 to -6.80)	0.342[b]	<0.001[a]
LDL1-LDL2	45	36.83(21.49 to 52.17)	0.462[b]	<0.001[a]
Placebo				
TC1-TC2	47	15.36(1.48 to 29.24)	0.542[b]	0.031[a]
TG1-TG2	47	54.63(36.51 to 72.63)	0.557[b]	<0.001[a]
HDL1-HDL2	47	-10.89(-14.45 to -7.33)	0.178[b]	<0.001[a]
LDL1-LDL2	47	23.10(11.81 to 34.39)	0.368[b]	<0.001[a]

[a]Paired t-test.
[b]Pearson correlation.

Table 3. Comparison of Lipid Profile in Participants Received Fish Oil Supplements With Control Group[a]

	Fish oil (n=45)	Placebo (n=47)	MD (95% CI)	P
Variables Before Intervention				
TC1	170.11 (42.3)	172.65 (40.6)	-2.55 (-19.75 to 14.65)	0.769[b]
TG1	129.00 (44.6)	126.15 (36.9)	2.85 (-14.16 to 19.86)	0.740[b]
HDL1	38.86 (9.0)	41.27 (8.2)	-2.41 (-6.00 to 1.18)	0.186[b]
LDL1	96.51 (28.1)	96.72 (25.3)	-.21 (-11.30 to 10.87)	0.970[b]
Variables after intervention				
TC2	196.93 (61.7)	188.02 (54.7)	10.3 (-11.26 to 31.87)	0.345[c]
TG2	198.48 (70.4)	180.78 (73.6)	14.61 (-13.21 to 42.42)	0.299[c]
HDL2	28.93 (9.0)	30.38 (10.4)	-0.587 (-4.88 to 3.71)	0.786[c]
LDL2	133.34 (57.5)	119.82 (39.7)	16.03 (-3.67 to 35.73)	0.109[c]

Abbreviations: MD: mean difference, SD: standard deviation.
[a] Numbers are given as mean (SD).
[b] Independent *t* test.
[c] Univariate general linear model adjusted for baseline variable level, age, parity and center.

other group (43).

Helland et al assessed the impact of supplementation of pregnant and breastfeeding women with marine n-3 PUFAs comparing n-6 PUFAs in relation to mothers and infant lipid levels. 341 women were received either 10 mL n-6 PUFAs (corn oil) or n-3 PUFAs (cod liver oil) daily until 3 months after childbirth. In conclusion, the increment of maternal plasma TG during gestation was less prominent in cod liver oil supplemented subjects comparing corn oil group. Serum HDL level was unaltered during gestation in the cod liver oil group, in contrast it was reduced in the corn oil taking women (44).

The difference between these findings with the results of our study may be correlated to differences in the placebo and type of the fish supplements (fish oil supplements capsule comparing cod liver oil). Our study is opposite with trials in the non-pregnant women, whereas the same doses of fish oil have continuously lead to a significant decrease in normolipidemic and hyper-lipidemic participants (45-48). In the research of Barbosa et al, fish oil attenuated the increment of plasma non-high density lipoprotein, TC, and cholesterol concentrations triacylglycerol resulted from dexamethasone therapy in rats (49).

Although n−3 fatty acids have great impacts on levels of TG in the non-gestational state, in gestational period the effect of nutritional intervention of n−3 fatty acids is neutralized by the physiological factors that keep the circulating TGs in high levels.

Skulas-Ray et al in a study aimed to evaluate the impacts of a nutritional dose of EPA+DHA (0.85 g/d) in comparison with the effects of a pharmaceutical dose (3.4 g/d) on serum level of TG, in healthy subjects with moderate increment of TG concluded that the pharmaceutical dose of EPA+DHA decreased TG by 27% in comparison to control (mean ± SEM: 173 ± 17.5 versus 237 ± 17.5 mg/dL; $P = 0.002$), in contrast no impact of the nutritional dose was displayed on lipids. Also, no impacts on cholesterol (TC, LDL, and HDL), was seen (50).

Study Limitations

One of the main administrative problems was the possibility of irregular use or not to use the capsules by women, so in the beginning of the study, we talked with mothers about the importance of the study and accuracy of the information. Also, daily drug check list were given to them. Drugs were delivered on two steps after receiving previous medication envelope. Also, by phone calls we recalled and emphasized the use of medication.

The frequency of consume foods containing DHA and EPA problems was other administrative problem. First, people who consumed fish 2 times a week or less were enrolled in the study. Meanwhile, randomly dividing of mothers in two groups widely modified this problem. Also in questionnaire the intake of fish and tuna fish per week was asked in order to if there was a difference between the two groups, be controlled as a possible confounding factor. It is recommended that further studies with larger sample sizes and pharmaceutical doses of fish oil be conducted.

Conclusion

We observed no effect of supplementation with fish oil during gestation on lipid profile of maternal plasma.

Ethical issues

We obtained permissive letter from the Ethics Committee of Research and Technology Deputy of Tabriz University of Medical Sciences (No. 92141) and registered the research in the website of Iranian registry of clinical trials. Written informed consent was taken from the participants.

Conflict of interests

We declare no conflicts of interest in this study to disclose.

Financial support

This research was supported financially by the Research deputy of Tabriz University of Medical Sciences.

Acknowledgements

This study was resulted from the proposal confirmed by Research Center of Tabriz Health Services Management (Grant No. 5/77/5241). We are grateful from the Zahravi Pharmacy Company, Health office of Tabriz and personnel of Health Centers and all the women who kindly assisted us in this research. We are besides thankful from Dr. Mozaffari, and all laboratory staff for their effort and precision.

References

1. Green NS, Damus K, Simpson JL, et al. Research agenda for preterm birth: recommendations from the March of Dimes. Am J Obstet Gynecol. 2005;193: 626-635.
2. Brizzi P, Tonolo G, Esposito F, et al. Lipoprotein metabolism during normal pregnancy. Am J Obstet Gynecol. 1999;181:430–434.
3. Mazurkiewicz JC, Watts GF, Warburton FG, Slavin BM, Lowy C, Koukkou E. Serum lipids, lipoproteins and apolipoproteins in pregnant non-diabetic patients. J Clin Pathol. 1994;47:728–731.
4. Sattar N, Greer IA, Louden J, et al. Lipoprotein subfraction changes in normal pregnancy: threshold effect of plasma triglyceride on appearance of small, dense low density lipoprotein. J Clin Endocrinol Metab. 1997;82:2483–2491.
5. Ogura K, Miyatake T, Fukui O, Nakamura T, Kameda T, Yoshino G. Low-density lipoprotein particle diameter in normal pregnancy and preeclampsia. J Atheroscler Thromb. 2002;9:42-47. doi:10.5551/jat.9.42.
6. Villar J, Cogswell M, Kestler E, Castillo P, Menendez R, Repke JT. Effect of fat and fat-free mass deposition during pregnancy on birth weight. Am J Obstet Gynecol. 1992;167(5):1344–1352.
7. Lippi G, Albiero A, Montagnana M, et al. Lipid and lipoprotein profile in physiological pregnancy. Clin Lab. 2007;53(3-4):173-177.
8. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002;19:43-55.
9. Herrera E, Muñoz C, López-Luna P, Ramos P. Carbohydrate-lipid interactions during gestation and their control by insulin. Braz J Med Biol Res. 1994;27(11):2499-519.
10. Ramirez I, Llobera M, Herrera E. Circulating triacylglycerols, lipoproteins, and tissue lipoprotein lipase activities in rat mothers and offspring during the perinatal period: effect of postmaturity. Metabolism. 1983;32(9): 331-341. doi:10.1016/0026-0495(83)90040-9.
11. Barber MC, Clegg RA, Travers MT, Vernon RG. Lipid metabolism in the lactating mammary gland. Biochim Biophys Acta. 1997;1347:101-126.
12. Brites F, Bonavita C, Cloes M, Yael M. VLDL compositional changes and plasma levels of triglycerides and high density lipoproteins. Clin Chim Acta. 1998;269:107-124.
13. Catov JM, Ness RB, Wellons MF, Jacobs DR, Roberts JM, Gunderson EP. Prepregnancy lipids related to preterm birth risk: the coronary artery risk development in young adults study. J Clin Endocrinol Metab. 2010;95:3711–3718. doi:10.1210/jc.2009-2028.
14. Catov JM, Bodnar LM, Kip KE, et al. Early pregnancy lipid concentrations and spontaneous preterm birth. Am J Obstet Gynecol. 2007;197:610–617.
15. Edison RJ, Berg K, Remaley A, et al. Adverse birth outcome among mothers with low serum cholesterol. Pediatrics. 2007;120:723-733.
16. Magnussen EB, Vatten LJ, Myklestad K, Salvesen KÅ, Romundstad PR. Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. Am J Obstet Gynecol. 2011;204(6):526. doi:10.1016/j.ajog.2011.02.016.
17. Jan MR, Nazli R, Shah J, Akhtar T. A study of lipoproteins in normal and pregnancy induced hypertensive women in tertiary care hospitals of the North West Frontier Province Pakistan. Hypertens Pregnancy. 2012;31:292-299. doi:10.3109/10641955.2010.507843
18. Ziaei S, Bonab KM, Kazemnejad A. Serum lipid levels at 28–32 weeks gestation and hypertensive disorders. Hypertens Pregnancy. 2006;25: 3-10. doi:10.1080/10641950500543756.
19. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ. 2007;335;978. doi:10.1136/bmj.39366.416817.BE
20. Clausen T, Djurovic S, Henriksen T. Dyslipidemia in early second trimester is mainly a feature of women with early onset preeclampsia. BJOG. 2001;108:1081-1087. doi:10.1111/j.1471-0528.2001.00247.x
21. Enquobahrie DA, WilliamsMA, Butler CL, Frederick IO, Miller RS, Luthy DA. Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. Am J Hypertens. 2004;17:574–581.
22. Ray JG, Diamond P, Singh G, Bell CM. Brief overview of maternal triglycerides as a risk factor for pre-eclampsia. BJOG. 2006;113:379-386. doi:10.1111/j.1471-0528.2006.00889.x.
23. Kandimalla BH, Sirjusingh A, Nayak BS, Maiya SS. Early antenatal serum lipid levels and the risk of pre-eclampsia in Trinidad and Tobago. Arch Physiol Biochem. 2011;117: 215-221. doi:10.3109/13813455.2010.543137.
24. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG, Cuccuru I, Pellegrini G, Chatzianagnostou K, Boldrini A, Del Prato S. Maternal triglyceride levels and newborn weight in Pregnancy Outcome. J Clin Endocrinol Metab, 2005;97(11):3917-3925.
25. Kitajima M, Oka S, Yasuhi I, Fukuda M, Rii Y, Ishimaru T. Maternal serum triglyceride at 24–32 weeks' gestation and newbornweight in nondiabetic women with positive diabetic screens. Obstet Gynecol. 2001;97:776-780.
26. Kushtagi P, Arvapally S. Maternal mid-pregnancy serum triglyceride levels and neonatal birth weight. Int J Gynaecol Obstet. 2009;106:258-259. doi:10.1016/j.ijgo.2009.03.004.
27. Martin U, Davies C, Hayavi S, Hartland A, Dunne F. Is normal pregnancy atherogenic? Clin Sci. 1999;96:421-425.
28. Bengtsson C, Rybo G, Westerberg H. Number of pregnancies, use of oral contraceptives and menopausal age in women with ischemic heart disease, compared to a population sample of women. Acta Med Scand. 1973;549:75-81.
29. Sarker D. Studies on serum total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, creatinine & creatinine clearance values in hypertensive patients [Thesis]. Mymensingh: University of Dhaka; 2006.
30. Seo T, Blaner WS, Deckelbaum RJ. Omega-3 fatty acids: molecular approaches to optimal biological outcomes. Curr Opin Lipidol. 2005;16:11-18.
31. Hadders-Algra M, Bouwstra H, van Goor SA, et al. Prenatal and early postnatal fatty acid status and neurodevelopmental outcome. J Perinat Med. 2007;35:1-28. doi:10.1515/JPM.2007.034.
32. Helland IB, Smith L, Saarem K, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics. 2003;111:e39.
33. Dunstan JA, Simmer K, Dixon G, Prescott SL. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008;93: 45-50.

34. Dyerberg J, Bang HO, Walters BN, et al. Pre-eclampsia and prosta-glandins. Lancet. 1985;1:1267-1268. doi:10.1016/S0140-6736(85)92330-X.
35. Olsen SF, Joensen HD. High liveborn birth weights in the Faeroes: acom - parison between birth weights in the Faroes and in Denmark. J Epidemiol Community Health. 1985;39:27-32.
36. Leventakou V, Roumeliotaki T, Martinez D, et al. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. Am J Clin Nutr. 2014;99(3):506-516. doi:10.3945/ajcn.113.067421.
37. Holub BJ. Omega-3 fatty acids in cardiovascular care. Clin Nutr. 2002;166:608-615.
38. Harrison N, Abhyankar B. The mechanism of action of omega- 3 fatty acids in secondary prevention post-myocardial infarction. Curr Med Res Opin. 2005;21:95-100.
39. Rissanen T, Voutilainen S, Nyyssönen K, Lakka TA, Salonen JT. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. Circulation. 2000;102:2677. doi:10.1161/01.CIR.102.22.2677.
40. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch Intern Med. 2001;161:2185. doi:10.1001/archinte.161.18.2185.
41. Matorras R, Perteagudo L, Sanjurjo P, Sasieta M, Ruiz JI. Long chain W3 polyunsaturated fatty acids and lipid pattern in the mother and the newborn infant. J Perinat Med. 1998;26(4):313-9.
42. Barden AE, Dunstan JA, Beilin LJ, Prescott SL, Mori TA. n-3 fatty acid supplementation during pregnancy in women with allergic disease: effects on blood pressure, and maternal and fetal lipids. Clin Sci (Lond). 2006;111(4):289-294.
43. Damsgaard CT, Schack-Nielsen L, Michaelsen KF, Fruekilde MB, Hels O, Lauritzen L. Fish Oil Affects Blood Pressure and the Plasma Lipid Profile in Healthy Danish Infants. J Nutr. 2006;136(1):94-99.
44. Helland IB, Saugstad OD, Saarem K, Van Houwelingen AC, Nylander G, Drevon CA. Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. J Matern Fetal Neonatal Med. 2006;19(7):397-406. doi:10.1080/14767050600738396.
45. Harris WS. n−3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids. 1996;31:243-252.
46. Roche HM, Gibney MJ. Effect of long-chain n-3-polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism. Am J Clin Nutr. 2000;71:232-237.
47. Agren JJ, Hänninen O, Julkunen A, et al. Fish diet, fish oil and docosahexaenoic acid rich oil lower fasting and postprandial plasma lipid levels. Eur J Clin Nutr. 1996;50(11):765-71.
48. Raghu B, Venkatesan P. Effect of n-3 fatty acid supplementation on blood glucose, lipid profile and cytokines in humans: A pilot study. Ind J Clin Biochem. 2008;23(1):85-88. doi:10.1007/s12291-008-0020-8.
49. Barbosa AM, Francisco PC, Motta K, et al. Fish oil supplementation attenuates changes in plasma lipids caused by dexamethasone treatment in rats. Appl Physiol Nutr Metab. 2016;41:1-9. doi:10.1139/apnm-2015-0487.
50. Skulas-Ray AC, Kris-Etherton PM, Harris WS, Vanden Heuvel JP, Wagner PR, West SG. Dose-response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy persons with moderate hypertriglyceridemia. Am J Clin Nutr. 2011;93:243-252. doi:10.3945/ajcn.110.003871.