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Original Research Article

An Analytical Study to Investigate the Relationship between Early Trimester Serum Lipid Concentrations and Risk of Preeclampsia

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Abstract

Aim: The present study was aimed to investigate the relationship between early trimester serum lipid concentrations and risk of preeclampsia.

Methods: The present study was conducted in the Department of Obstetrics & Gynecology**,** Madhubani Medical College & Hospital, Madhubani, Bihar, India . With the approval of the institutional ethics committee and written informed consent from each woman, total 230 women between 20-35 years of age with 13-20 weeks of gestation were enrolled.

Results: The baseline demographic characteristics of two groups were similar ($p>0.05$) i.e. not differed statistically. The baseline blood pressures at the time of booking visit (13-20 weeks) were also not statistically different in both the groups. The result showed that levels of all lipid profiles (TC, TG, VLDL-C and LDL-C) except HDL-C, were significantly ($p<0.001$) higher in pre-eclamptic women than normotensive women. While pre-eclamptic women showed significant fall in High density lipoprotein cholesterol (HDL-C) level as compared to normal pregnant women.

Conclusion: The measurement of serum lipid profile in early pregnancy may serve as early predictor of preeclampsia.

Keywords: Dyslipidemia, Lipid profile, Preeclampsia, Pregnancy.

Introduction

Profound local and systemic changes in maternal physiology are initiated by conception and continued throughout pregnancy. [1] During early pregnancy, the maternal metabolic environment is modified by a rise in serum levels of estrogen and progesterone, pancreatic β-cell hyperplasia occurs, and there is an increase in the secretion of insulin. [2]

As pregnancy advances, a well-integrated and systematic metabolic shift occurs to provide sufficient and balanced supply of nutrients to a constantly feeding fetus from an intermittently fasting and feeding mother. Freinkel [3] was the first to describe the maternal metabolic changes of late pregnancy as “accelerated starvation,” when food is unavailable, and “facilitated

anabolism," when food is ingested. Chauffard [4] in 1911 undertook the first chemical study of blood lipids during pregnancy and suggested that an increase occurs in the cholesterol level. Later on, multiple studies demonstrated increase in various fractions of lipids and lipid indices such as total cholesterol (TCH), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). That is, pregnant women develop physiological hyperlipidemia. [5]

The alterations of serum lipid indices are associated with the gestational age. The increase of the lipid and lipoprotein metabolism reaches the level of cardiovascular risk [6,7] during the second trimester. In the later half of pregnancy, there is two- to threefold increase in plasma triglycerides and lesser increase in TCH, HDL-C, and LDL-C.

Preeclampsia is a pregnancy specific disorder, characterized by pregnancy induced hypertension (BP ≥140/90 mm Hg) on two occasion, atleast 6 hours apart and proteinuria of ≥ 300 mg/24 hours or ≥1+dipstick after 20 weeks of gestation in previous normotensive women. It occurs in about 2–8% of pregnancies. [8] It is the most common medical complication of pregnancy, whose incidence has continued to increase worldwide. It is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually [9] and risk is very high in Indian women. [10]

However, various factors are implicated in the pathogenesis of preeclampsia including genetic, immune, vascular, and oxidative stress. [11] Maternal serum lipids are significantly elevated during pregnancy8Women who develop preeclampsia experience even more dramatic lipid changes. [12] Most, studies have shown a preeclampsia–dyslipidemic pattern of increased triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) concentrations. [13-15] There are also evidences suggesting that abnormal lipid metabolism in early pregnancy is associated with an increased risk of preeclampsia. [16]

The present study was aimed to investigate the relationship between early trimester serum lipid concentrations and risk of preeclampsia.

Materials and Methods

The present study was conducted in the Department of Obstetrics & Gynecology**,** Madhubani Medical College & Hospital, Madhubani, Bihar, India. Total 230 women between 20-35 years of age with 13-20 weeks of gestation were enrolled.

Methodology

Women with history of essential hypertension, renal disease, epilepsy, diabetes or any other chronic or preexisting disease were excluded from the study. All enrolled women were suggested to detailed medical, menstrual and obstetrical history followed by general, systemic and obstetrical examination along with all routine investigations. 3 ml of venous blood was collected for serum lipid profile estimation and test was done on same day. Serum lipid profile estimation was done by enzymatic method with the help of accurex diagnostic kit (manufactured by Accurex Biomedical PVT LTD, India) and the test was analyzed on Selectra-E random access analyzer (Merck).

Serum LDL cholesterol (LDL-C) was calculated by Frederickson-Friedwald's formula according to which LDL cholesterol = Total cholesterol - (HDL cholesterol + VLDL cholesterol). VLDL cholesterol (VLDL-C) was calculated as 1/5 of Triglycerides (TG). Lipid profile concentration was measured in milligram per deciliter (mg/dl). The selected subjects were followed for development of

preeclampsia till delivery. Out of total 230 women 30 were lost follow up so only 270 women were followed till delivery. Out of 200 women 50 women developed preeclampsia has taken as study group and 150 normotensive women has been taken as control group. Study group were divided as mild preeclampsia (BP ≥140/90 to <160/110 mm Hg) and severe preeclampsia (BP≥160/110 mmHg).

Statistical Analysis:

The continuous data were summarized as mean and standard deviation while discrete (categorical) in numbers and percentage (%). The continuous variables (Lipid profile: TC, TG, HDL-C, VLDL-C, LDL-C; Blood pressure: SBP and DBP) were compared by independent student's t test. The categorical variables were compared by chi-square ($\chi 2$) test. Univariate binary logistic regression analysis was used to find out lipid profile associated risk factors for preeclampsia. The adjusted multivariate logistic regression analysis was carried out further to find out the significant independent predictor for preeclampsia. The univariate and multivariate analysis were done with adjusted demographic variables. The $p<0.05$ was considered statistically significant. All analysis was carried out using SPSS 15.0 version.

Results

Table 1: Baseline subject characteristics

Variable	Normotensive (n=150)	Preeclampsia (n=50)	p value
Age(yrs)	26.46 ± 3.25	27.10 ± 3.73	0.190
Religion			
Hindu	135 (90%)	46 (92%)	0.850
Muslim	15 (10%)	4 (8%)	
SES			
Lower	6 (4%)	3 (6%)	0.440
Middle	114 (76%)	34 (68%)	
Higher	30 (20%)	13 (26%)	
Diet			
Vegetarian	90 (60%)	22 (44%)	0.120
Non vegetarian	60 (40%)	28 (56%)	
Blood Pressure (BP)			
Systolic BP (mm Hg)	109.83 ± 5.96	111.18 ± 8.03	0.160
Diastolic BP (mm Hg)	80.29 ± 6.26	81.34 ± 9.21	

The baseline demographic characteristics of two groups were similar ($p>0.05$) i.e. not differed statistically. The baseline blood pressures at the time of booking visit (13-20 weeks) were also not statistically different in both the groups.

Table 2: Lipid profile levels of pre-eclamptic and normotensive women

Lipid profile	Normotensive (n=150)	Preeclampsia (n=50)	p value
TC	164.65 ± 18.63	230.48 ± 46.69	p<0.001
TG	155.22 ± 22.31	207.76 ± 47.31	p<0.001
HDL	39.26 ± 21.20	31.33 ± 11.81	0.007
VLDL	31.78 ± 8.24	42.50 ± 11.93	p<0.001
LDL	94.99 ± 25.42	147.64 ± 20.29	p<0.001

Table 2 showed that levels of all lipid profiles (TC, TG, VLDL-C and LDL-C) except HDL-C, were significantly ($p<0.001$) higher in pre-eclamptic women

than normotensive women. While pre-eclamptic women showed significant fall in High density lipoprotein cholesterol (HDL-C) level as compared to normal pregnant women. Women who subsequently developed preeclampsia had 28.6%, 25.3%, 25.2% and 35.7% higher concentration of TC, TG, VLDL-C and LDL-C respectively than normotensive women. HDL-C concentration was 20.2% lower in preeclamptic women as compared with normotensive women (p=0.007).

Table 3: Lipid profile levels of mild and severe pre-eclamptic women

Lipid profile	Mild preeclamptic (n=35)	Severe preeclamptic (n=15)	p value
TC	224.65 ± 49.61	244.54 ± 36.25	0.001
TG	194.75 ± 47.87	239.10 ± 27.64	p<0.001
HDL	35.40 ± 11.45	27.25 ± 15.40	0.030
VLDL	38.71 ± 8.44	51.60 ± 14.29	p<0.001
LDL	146.92 ± 21.58	149.38 ± 17.23	0.360

Comparing the levels of lipid profile between mild and severe preeclamptic women, the levels of TC, TG and VLDLC in severe preeclamptic women were also significantly (p<0.01 or p<0.001) higher than mild preeclamptic women whereas there was no significant difference in LDL-C level between both groups. While severe preeclamptic women showed significant fall in high density lipoprotein cholesterol (HDL-C) level as compared to mild preeclamptic women.

Table 4: Odds ratios (OR) and 95% confidence intervals (CI) of the association between preeclampsia risk and maternal serum lipid and lipoprotein concentrations

Variables	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
TC	2.13 (1.09-7.18)	0.040	2.09 (1.16-6.19)	0.045
TG	3.06 (0.94-9.07)	p<0.001	2.96 (1.04-8.45)	p<0.001
HDL	2.20 (0.98-5.02)	0.038	2.26 (1.08-6.02)	0.020
VLDL	2.12 (0.78-6.16)	0.043	2.15 (1.08-5.46)	0.047
LDL	3.08 (0.96-7.10)	p<0.001	3.01 (1.07-7.12)	p<0.001

The lipid profile associated preeclampsia risk were evaluated by using univariate unadjusted and multivariate adjusted (adjusted for confounders age, parity, religion, SES and diet) logistic regression analysis and summarized in Table 4. Univariate unadjusted logistic regression analysis revealed that the higher lipid values of TC, TG, HDL-C, VLDL-C and LDL-C were significantly (p<0.001) associated with the risk of developing preeclampsia. Further, adjusted multivariate logistic regression analysis confirmed TC (OR=2.09, 95% CI=1.16-6.19, p<0.045), TG (OR=2.96, 95% CI=1.04-8.45, p<0.001), HDL-C (OR=2.26, 95% CI=1.08-6.02, p<0.020) VLDL-C (OR=2.15, 95% CI=1.08- 5.46, p<0.047) and LDL-C (OR=3.01, 95% CI=1.07-7.12, p<0.001), the significant and independent risk factors for pre-eclampsia.

Discussion

Preeclampsia (PE), a non-convulsive form of pregnancy-induced hypertension, accounts for a significant proportion of maternal and fetal morbidity and mortality. [17] Despite an intensive research effect to elucidate the origin of PE, there is a currently no well validated prophylactic treatment, nor is there any effective method of identifying women with an increased risk of PE [18]; however, recent studies have reported that the magnitude of the imbalance between anti-angiogenic (soluble fms-like tyrosine kinase- 1 (sFlt-1)) and pro-angiogenic (placental growth factor (PlGF)) factors correlates well with

disease activity, with a cutoff value of the sFlt-1/PlGF ratio greater than 655 increasing the risk for imminent delivery with a controversial prognostic potential for fetal complications. [19-21] Abnormal lipid profiles have a strong positive correlation with endothelial dysfunction. Specific changes are usually associated with normal pregnancy. Normal serum total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) levels increase toward the term of normal pregnancy. [22-24]

We observed that if TC, TG, VLDL-C and LDL-C levels are higher in early second trimester there was increased risk of developing preeclampsia and severity of preeclampsia was directly related to levels of total cholesterol, triglycerides and VLDL-C which were statistically significant. Whereas LDL-C level was not significantly higher in severe preeclamptic group as compared with mild preeclamptic group. However we find a significant inverse relationship of HDL-C level with severity of preeclampsia. Our results, when taken together with those of earlier prospective studies indicate that dyslipidemia, particularly hypertriglyceridemia and elevated lipoprotein, precede the clinical manifestation of preeclampsia and thus may be of etiologic and pathophysiologic importance in this relatively common complication of pregnancy. [25-28]

However, the differences observed between fasting and non-fasting lipids are usually small. [29,30] A single measurement of blood samples may have resulted in some misclassification of maternal lipid profiles during pregnancy. Longitudinal studies with serial measurements of maternal lipid and lipoprotein concentrations are needed to elucidate patterns of lipid changes and pathophysiologic consequences of such changes during pregnancy. The association between dyslipidemia and risk of preeclampsia is biologically plausible and is compatible with what is known about pathophysiology of preeclampsia.

Three hypothesized mechanisms for dyslipidemia and preeclampsia association has been described. First, investigator noted that elevated plasma lipid and lipoprotein may induce endothelial dysfunction secondary to oxidative stress. They also noted that dyslipidemia may impair trophoblast invasion thus contributing to a cascade of pathophysiologic events that lead to the development of preeclampsia. [32] Second, mechanism is pathologic process of preeclampsia via dysregulation of lipoprotein lipase resulting in a dyslipidemic lipid profile. Enderssen et al [31] and Lorentzen et al [26] showed that sera from preeclamptic women had both a higher ratio of free fatty acids to albumin and increased lipolytic activity, resulting in enhanced endothelial uptake of free fatty acids, which are further esterified to triglycerides. Third, possible mechanism may be via metabolic syndrome. Metabolic characteristic of insulin resistance syndrome namely hyperinsulinemia and hyperurecemia are also present in preeclampsia. [33]

Moreover, women with a history of preeclampsia, as compared with their BMI-matched counterparts without such a history, have higher circulating concentrations of fasting insulin, lipid, and inflammatory and coagulation factors years after delivery. [12] Thus genetic and environmental factors that contribute to the pathogenesis of metabolic syndrome and related to vascular disorders may also be important in determining the occurrence of preeclampsia. [34]

Conclusion

Estimation of maternal lipid profile in early second trimester may bring about early recognition of patients at risk of preeclampsia before the clinical symptoms and complications of preeclampsia appear for a better fetomaternal outcome. The

findings from this study continue to support a role for dyslipidemia in preeclampsia. Prospective studies measuring lipid profiles throughout pregnancy and the postpartum period are needed to further our understanding of the importance of dyslipidemia in preeclampsia and its long-term impact on the cardiovascular health of women.

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