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Original Research Article

Role of lipid profile in early second trimester for prediction of pre-eclampsia

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ABSTRACT

Background: The aim of the study was to determine association of abnormal lipid profile in early second trimester (14 to 20 weeks) with development of pre-eclampsia.
Methods: A prospective observational study included 260 women between 14-20 weeks of pregnancy attending a tertiary care Hospital in New Delhi. Serum lipid profile analysis was performed at the time of enrolment and cohort was followed up for occurrence of pre-eclampsia till 48 hours after delivery. Outcomes measured were difference in mean lipid levels in study (abnormal lipid profile) and control group (normal lipid profile) and accuracy of abnormal lipid profile to predict pre-eclampsia.
Results: The incidence of pre-eclampsia in our study was 11.13%. The mean serum total cholesterol was significantly higher in pre-eclampsia group (199.74 mg/dl vs 171.7 mg/dl; $p<0.05$). The difference in mean triglyceride, HDL, VLDL and LDL levels between two groups was not significant. Total cholesterol has 44.83% sensitivity, 84.85% specificity, 27.08% PPV, 92.45% NPV with diagnostic accuracy of 80.38% in predicting pre-eclampsia (with 0.65% AUC with 95% confidence interval). While VLDL has maximum sensitivity of 68.97% while HDL has maximum specificity of 86.15% in predicting pre-eclampsia.
Conclusions: Abnormal total cholesterol levels have diagnostic accuracy of 80.38% to predict pre-eclampsia and abnormal lipid profile in early second trimester is a simple, non-invasive and economical test for prediction of pre-eclampsia.

Keywords: Cholesterol, HDL, LDL, Pre-eclampsia, Triglyceride, VLDL

INTRODUCTION

Hypertensive disorders of pregnancy occur in about 10% of all pregnant women around the world. Pre-eclampsia affects 3-5% of pregnancies.[1] According to the International Society for the study of Hypertension in pregnancy (ISSHP), hypertension is defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg. A rise in the systolic blood pressure of 30 mmHg or a rise in the diastolic blood pressure of 15 mmHg at least 4 hours apart or a single diastolic blood pressure >110 mmHg is also considered as hypertension.

The early identification of pregnancies at risk of pre-eclampsia permits prophylactic intervention with aspirin which has been found to reduce the risk of early pre-eclampsia, intrauterine growth restriction and preterm birth by improving disordered placentation.[2] It may also enhance the development of new strategies for antenatal monitoring, to detect disease earlier and intervene timely to improve maternal and perinatal outcome.

Thus, so many markers have been proposed as predictors of pre-eclampsia such as Roll over test, angiotensin sensitivity test, mean arterial pressure (MAP), raised uric acid, Raised serum beta hCG at 14-20 weeks of gestation, alpha fetoprotein (AFP), estriol levels, pregnancy associated protein A (PAPP A), inhibin A levels, activin A, placental protein 13, corticotrophin releasing hormone, uterine artery Doppler, platelet count, fms- like tyrosine

kinase receptor-1 (sFlt-1), endoglin plasminogen activator inhibitor (PAI), neurokinin B, p-selectin, decreased levels of pro-angiogenic factors that includes vascular endothelial growth factors (VEGF), placental growth factor (PLGF), endothelial adhesion molecules, C-reactive proteins.[4-11] Lipid profile as a predictor of preeclampsia is attributed to the metabolic alterations and risk factors which are similar in pre-eclampsia and arthrosclerosis and this might suggest a common pathophysiology. Physiological hyperlipidaemia of pregnancy increases by two-fold in preeclampsia. Abnormal lipoproteins levels are responsible for damage to endothelium that leads to high blood pressure, and proteinuria; which are important signs of preeclampsia. Association of serum lipids with pre-eclampsia was highly suggestive of a role for lipid profile analysis as a diagnostic tool. Therefore, detection of dyslipidaemia in early pregnancy could be used as a diagnostic tool in early prediction of pre-eclampsia, decreasing the lag time and preventing the maternal and neonatal morbidity and mortality.

The aim of the study was to evaluate the association of abnormal lipid profile in early second trimester (14 to 20 weeks) with development of pre-eclampsia and its prevalence in low-risk pregnancy.

METHODS

A prospective observational study was conducted on 260 pregnant women, in the department of obstetrics and gynaecology of ABVIMS and Dr. RML Hospital, a tertiary care teaching hospital in New Delhi, India over a period of one year and was approved by institutional ethics committee. Inclusion criteria included gestational age at 14 to 20 weeks irrespective of their parity and age between 18 to 35 years. Exclusion criteria included patients with diabetes mellitus, chronic hypertension or any other cardiovascular disease, smoker, history of renal disease, liver disease or other history of prior medical illness, thyroid disorder, multiple gestation and BMI >25 kg/m^2.

At enrolment, 14 to 20 weeks two groups were made based on lipid profile abnormalities i.e.; normal lipid levels (group X) and abnormal lipid levels (group Y) (even a single deranged lipid level was considered as abnormal lipid profile).

They were followed up till 48 hours after delivery and 4 subgroups were made in postpartum (at the end of study). After correlation of group X and Y, on the basis of normal and abnormal lipid profile with development of pre-eclampsia, the results were divided into 4 subgroups (group a, b, c, d) as follows- (a) group a: pre-eclampsia normal lipid profile; (b) group b: normotensive normal lipid profile; (c) group c: normotensive abnormal lipid profile; and (d) group d: pre-eclampsia abnormal lipid profile.

The normal values of lipid profile considered in the study were: total cholesterol- 176-299 mg/dl, high-density lipoprotein (HDL)- 52-87 mg/dl, low-density lipoprotein (LDL)- 77-184 mg/dl, very low-density lipoproteins (VLDL)- 13-23 mg/dl, triglyceride- 75-382 mg/dl.[12]

Pre-eclampsia defined as hypertension after 20 weeks of gestation with new onset proteinuria Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: (a) thrombocytopenia: platelet count less than 1 lakh; (b) renal insufficiency: serum creatinine concentrations greater than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease; (c) impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration; (d) pulmonary edema; (e) new-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.

All the subjects were normotensive at the time of enrolment and followed up till 48 hours after delivery for the development of pre-eclampsia.

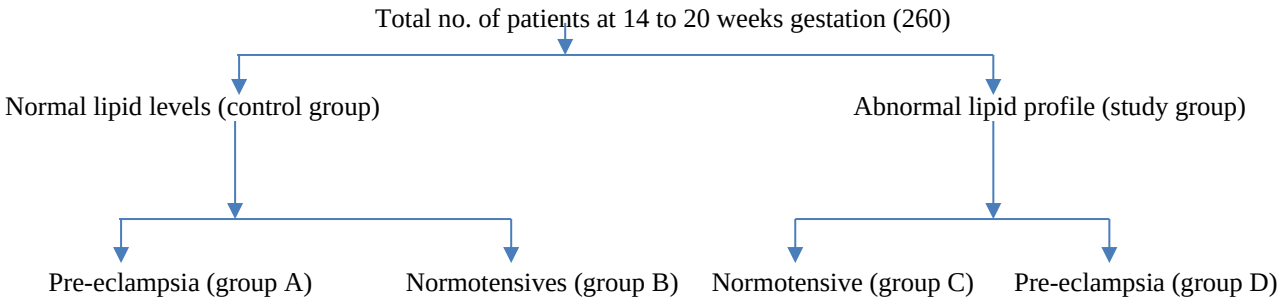

Figure 1:

Group a: pre-eclampsia normal lipid profile; group b: normotensive normal lipid profile; group c: normotensive abnormal lipid profile; group d: pre-eclampsia abnormal lipid profile. Pre-eclampsia study group: a+d (normal and abnormal lipid profile pre-eclampsia study groups), control group: b+c (normal and abnormal lipid profile normotensive groups). All women underwent routine clinical evaluation, management and were followed up till 48 hours after delivery and relevant data entered in pre-defined structured proforma.

The data was entered in MS excel spreadsheet and statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Total 260 women participated in study after applying inclusion and exclusion criteria and were followed up till 48 hours after delivery and there were no lost to follow up.

The overall incidence of preeclampsia in the study was 11.15% (N=29). Lipid profile was found to be normal (group X) in 50 patients (23.8%) and abnormal (group Y) in 210 patients (80.7%). The incidence of preeclampsia in study group 13.33% (28/210) and control group was 2% (1/50).

Baseline characteristics data is shown in Table 1.

Table 1: Distribution of baseline characteristics.

Baseline characteristics	Mean±SD (range)
Age±at enrolment (years)	27.52±3.7 (19-35)
Gestational age at blood sampling (weeks)	16.97±1.57 (14-20)
Systolic blood pressure at enrolment (mmHg)	110.92±8.97 (90-130)
Diastolic blood pressure at enrolment (mmHg)	73.75±7.16 (60-90)
Gestational age at birth (weeks)	38.1±1.56 (27.80-41)
Primigravida	171 (62.07%)

The incidence of preeclampsia was not statistically significant (p value<0.05) between primigravida (62.07%) as compared to 37.93% multigravida patients. Past history of pre-eclampsia was present in 45.45% of pre-eclamptic which was significantly higher as compared to normotensive group (3.80%) (p value=0.005).

Significant difference was seen in the distribution of total cholesterol (mg/dl) between preeclamptic and normotensive group. (p value<0.05), total cholesterol (mg/dl) was deranged in 44.83% of pre-eclampsia patients which was significantly higher as compared to normotensive patients (15.15%). No significant difference was seen in distribution of HDL, LDL, triglyceride and VLDL between preeclamptic and normotensive group as shown in Table 2.

The lipid profile parameters were not normally distributed. Thus, non-parametric test (Kruskal Wallis test; Chi square test) was used for the comparison. Significant difference was seen in total cholesterol (mg/dl), triglyceride (mg/dl), VLDL (mg/dl), LDL (mg/dl) between different sub-groups (a, b, c, d) (p value<0.05). No significant difference was seen in HDL (mg/dl) between different groups (p value>0.05) (Table 3).

VLDL (mg/dl) had sensitivity of 68.97% followed by triglyceride (mg/dl) (55.17%), total cholesterol (mg/dl) (44.83%), LDL (mg/dl) (34.48%). HDL (mg/dl) had specificity of 86.15% followed by total cholesterol (mg/dL) (84.85%), LDL (mg/dl) (69.70%), triglyceride (mg/dl) (50.65%) as shown in Table 4.

In prediction of pre-eclampsia, HDL (mg/dl) had lowest sensitivity of 17.24% and VLDL (mg/dl) had lowest specificity of 46.75%.

Highest positive predictive value was found in total cholesterol (mg/dl) (27.08%) and highest negative predictive value was found in total cholesterol (mg/dl) (92.45%). We compared gestational age at the time delivery between pre-eclampsia and normotensive group and found that patients with pre-eclampsia had higher preterm birth (44.83%, N=13) than control group (12.12%, N=28) which was statistically significant (p value<0.0001).

Table 2: Comparison of lipid profile (mg/dl) between preeclamptic and control groups.

Lipid profiles	Mean values±SD		P value
	Pre-eclampsia (N=29)	Normotensive (N=231)	
Total cholesterol	199.74±54.31	171.56±28.85	0.0001
HDL	48.29±9.23	49.24±11.69	>0.05
LDL	88.17±27.22	84.14±28.68	>0.05
Triglyceride	193.03±99.23	151.49±41.1	>0.05
VLDL	51.29±36.39	37.08±31.62	>0.05

Table 3: Comparison of lipid profile between different sub-groups.

Lipid profile (Mean±SD) (mg/dl)	Group A (N=1)	Group B (N=49)	Group C (N=182)	Group D (N=28)	Total	P value
Total cholesterol	186±0	158.95±19.44	174.95±30.05	200.23±55.24	174.7±33.72	0.0003
HDL	55±0	53.19±8.3	48.18±12.25	48.05±9.3	49.14±11.43	0.081
Triglyceride	145±0	114.1±23.99	161.55±38.91	194.74±100.61	156.12±52.31	<0.0001
VLDL	21.1±0	22.97±4.78	40.87±34.58	52.37±36.58	38.66±32.42	<0.0001
LDL	58.6±0	71.07±14.93	87.66±30.46	89.22±27.11	84.59±28.5	<0.0001

Table 4: Sensitivity, specificity, PPV and NPV of lipid profile for predicting preeclampsia.

Variables	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Total cholesterol	44.83	84.85	0.65	27.08	92.45	80.38
HDL	17.24	86.15	0.52	13.51	89.24	78.46
Triglyceride	55.17	50.65	0.53	12.31	90	51.15
VLDL	68.97	46.75	0.58	13.99	92.31	49.23
LDL	34.48	69.7	0.52	12.5	89.44	65.77

DISCUSSION

Vidyabati et al shows that there is hypertriglyceridemia among the patients who subsequently developed pre-eclampsia.[13] Their study also showed that total cholesterol, LDL, VLDL levels were also higher in preeclampsia women which was similar to our study. But the mean value of HDL for both the groups were similar in their study and similar result also seen in our study. They also concluded that with one unit increase in total cholesterol, triglycerides, VLDL and LDL the probability of developing PIH in pregnant women- 12.6%, 0.3%, 12.4% and 7.1% respectively. And with one-unit increase in HDL- 11.4% less chances of developing PIH

Ewa et al concluded that higher levels of triglycerides and remnant cholesterol in early pregnancy are associated with an increased risk of pre-eclampsia and sustained hypertension long term postpartum.[14] Similarly, in our study early second trimester triglycerides value was higher in pre-eclampsia group than normotensive group, the p value being <0.05. HDL is statistically not significant in other studies like in ours such as in Yadav et al, Kumari et al, Siddiqui et al and many more studies.[15-17]

Iftikhar et al in the study relationship between leptin and lipids during pre-eclampsia found that severity of pre-eclampsia increases as levels of total cholesterol increases and which was higher due to raised leptin levels.[18] They concluded that increased cardiovascular risk that has been linked to hyperleptinemia and significant correlation between serum leptin and total cholesterol (p value <0.05) whereas relation with other lipid variables in not significant. Leptin levels were not included in our study.

Singh et al in their study found that the women with pre-eclampsia with poor fetal outcome had to be induced resulting in preterm deliveries, similar results were seen in our study.[19] Post-partum eclampsia was higher in pre-eclampsia group (17.24% vs 0%; p value<0.0001) than in normotensive group. No mortality was seen from pre-eclampsia in the study.

Thus, estimation of maternal lipid profile in the early second trimester will bring about early recognition and allow better management of patients at risk of pre-eclampsia, before the clinical syndrome and complications of pre-eclampsia appear. Also, early treatment of such cases with aspirin can improve feto-maternal outcome.

The strength of our study includes its prospective design and the high follow-up rate. Several important limitations must be considered when interpreting the results of our study. First, only one sample has been taken for lipid profile measurement. It has been suggested by various studies that with lipid levels increased with increase in gestational age and serial monitoring may be more useful. Small sample size may hinder inferences from some of our analyses and large prospective studies are recommended. Third, although we compared for many potential confounders, we cannot exclude the possibility of the other confounding from unmeasured covariates. Finally, another limitation of the present study is that it was done in only one medical centre.

Our study evaluated role lipid profile estimation between 14-20 weeks pregnancy to predict pre-eclampsia and found that total cholesterol values are significantly increased in pre-eclampsia group (p value<0.05). Accuracy of abnormal total cholesterol for prediction of pre-eclampsia was 80.38. Significant difference was seen in the distribution of preterm deliveries between preeclamptic and normal study subjects (p value<0.05). The detection of dyslipidaemia before 20 weeks of gestation is a simple, non-invasive and economical test for prediction of pre-eclampsia and would help us to recognise pregnancies at high-risk for preeclampsia even before the clinical syndrome.

CONCLUSION

The detection of dyslipidaemia before 20 weeks of gestation is a simple, non-invasive and economical test for prediction of pre-eclampsia and would help us to recognise pregnancies at high-risk for preeclampsia even before the clinical syndrome.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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