

Original Article:**Role of dyslipidaemia and lipid peroxidation in pregnancy induced hypertension**

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ABSTRACT

Background: Pregnancy induced hypertension (PIH) contributes greatly to maternal morbidity and mortality. Altered lipid profile and increased lipid peroxidation activate endothelial dysfunction and atherothrombosis leading to PIH. Therefore, estimation of lipid profile with serum malondialdehyde (MDA) in pregnancy may be helpful in predicting the development of PIH and further progression.

Material and methods: In this prospective case-control study, serum lipid profile and MDA were estimated in 70 PIH subjects with gestational hypertension, pre-eclampsia, eclampsia; and 70 normotensive pregnant women aged 18 - 40 years, with gestational age of over 20 weeks.

Results: A statistically significant higher serum total cholesterol, very low density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), TC/HDL-C, LDL-C/HDL-C and MDA, and a significantly lower HDL-C was noted in PIH subjects as compared to control subjects. When compared with the severity of PIH, all the lipoproteins (except HDL-C) along with MDA were found to be higher in women with eclampsia when compared with gestational hypertension, pre-eclampsia and normotensive pregnant women.

Conclusions: An abnormal lipid metabolism along with oxidative stress may add to the promotion of vascular dysfunction leading to PIH. Lipoproteins and MDA alter significantly in eclampsia. Therefore, during pregnancy, early diagnosis and management of dyslipidaemia may prevent lipid peroxidation and progression of PIH thereby preventing obstetric complications.

Key words: *Pregnancy Induced Hypertension, Eclampsia, Dyslipidaemia, Malondialdehyde*

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INTRODUCTION

Hypertensive disorders complicate 5%-10% of all pregnancies and together they form a member of the deadly triad, along with haemorrhage and infection that contribute greatly to maternal morbidity and mortality rates.¹ Pregnancy induced hypertension (PIH) includes a group of hypertensive disorders developed due the gravid state after 20 weeks of pregnancy. Pregnancy is a physiological phenomenon accompanied by a high-energy

demand with an increased oxygen requirement. This triggered aerobic environment should primarily be responsible for raised oxidative stress in pregnancy and its complication PIH that adversely affects the mother and the foetus.

The pathophysiology of PIH is still unclear. An imbalance between reactive oxygen species (ROS) and antioxidants, also called oxidative stress, appears to be an important contributing factor.² Altered lipid profile and increased lipid peroxidation leading to decrease in prostacyclin

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(PGI₂): thromboxane A₂ (TXA₂) ratio causes the vasospastic phenomenon in kidney, uterus, placenta and brain as seen in PIH.³ Abnormal lipid metabolism is responsible for the endothelial dysfunction,⁴ and it was proposed that oxidized low-density lipoproteins (LDL) may add to endothelial dysfunction in pre-eclampsia.⁵ Triglyceride (TG) rich lipoproteins may also activate endothelial dysfunction⁶ and atherothrombosis.⁷

Malondialdehyde (MDA) is the end product of lipid peroxidation and reflects the oxidative status of the biological system⁸ which causes damage to LDL molecules. The oxidized LDL is taken up by macrophages via scavenger receptors and form foam cells⁹ resulting in atherogenesis.

The association of dyslipidemia and lipid peroxidation with PIH has been highly suggested and therefore estimation of lipid profile with serum MDA in pregnancy may be helpful in predicting the development of PIH and further progression can be monitored and managed, thereby preventing and reducing maternal and fetal complications. The aim of this study was to study the correlation between the serum lipid profile and lipid peroxidation product MDA with the severity of PIH.

MATERIAL AND METHODS

This prospective case-control study was conducted during January-December 2012 at the Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh. The study was approved by the Institutional Ethical Committee. Study population included 70 women diagnosed to have PIH (cases) and 70 normotensive pregnant women (controls) belonging to age group 18 - 40 years, with gestational age of over 20 weeks. Informed consent was taken from each subject for participation in this study.

Patients with PIH (Table 1)¹⁰ included gestational hypertension (n=25); pre-eclampsia (n=25); and eclampsia (n=20).

Table 1: Pregnancy included hypertension

Gestational hypertension

Systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg for first time during pregnancy (after 20 weeks of gestation) without proteinuria.

Pre-eclampsia Systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg after 20 weeks gestation with proteinuria ≥ 300 mg/24 hours or $\geq 1+$ on dipstick testing

Eclampsia was defined by women presenting with convulsions/coma along with features of pre-eclampsia i.e., hypertension and proteinuria.

BP = blood pressure

Subjects with the history of familial hyperlipidaemia, using lipid lowering agents, vitamin C, vitamin E, or antioxidant supplementation, obesity, gestational diabetes, diabetes mellitus, chronic hypertension, coronary artery disease, impaired renal function, liver disorders, hypothyroidism, smoking, tobacco use and alcoholism were excluded from the study. Blood pressure was measured in sitting or reclining position after a period of 5 minutes rest with a standard mercury sphygmomanometer and standard arm cuff in the right arm. Three recordings were taken at intervals of 5 minutes, and their mean value was recorded. Women found to have hypertension, were screened for presence of proteins in urine by dipstick method. Four mL of peripheral venous blood was collected after 10-12 hours of fasting in a serum separator vacutainer. Samples were allowed to clot at 37°C for 30 minutes and were centrifuged at 2000 rotations per minute (rpm) for 15 minutes to get a clear and cell free serum. Biochemical analysis was performed on Chem-5 plus V2 semiautoanalyzer manufactured by Transasia Bio-Medicals Limited, India and spectrophotometer GENESYS 10S UV-Vis manufactured by Thermo Fischer Scientific Inc. USA.

Total Cholesterol (TC), was estimated by cholesterol oxidase-peroxidase-aminoantipyrine (CHOD-PAP) enzymatic method

(Modified Roeschlau's method).^{11,12} High density lipoprotein - cholesterol (HDL-C) was estimated by phosphotungstic acid method.¹³ Very low-density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C) were calculated by Friedewald's formula.¹⁴ TG were estimated by glycerophosphate oxidase-peroxidase (GPO)-Trinder method.¹⁵ Malondialdehyde (MDA) was estimated by thiobarbituric acid (TBA) method.¹⁶

Statistical analysis

All values were expressed as mean \pm standard deviation (SD). Mean values of test variables between the PIH subjects and controls were compared using unpaired Student's t-test, one way analysis of variance (ANOVA) and Tukey's (HSD) post-hoc test. A two-tailed p-value of <0.05 was considered significant. Statistical analysis was done using Statistical Package for Social Science (SPSS) software version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of PIH subjects was 25.5 ± 4.9 years; their mean gestational age was 35.7 ± 3 weeks. The mean age of control subjects was 25 ± 3.7 years; their mean gestational age was 36.3 ± 2.4 weeks.

Patients with PIH had a significantly higher TC ($p=0.002$), VLDL-C ($p<0.001$), LDL-C ($p=0.023$), TG ($p<0.001$), TC/HDL-C ratio ($p<0.001$) and LDL-C/HDL-C ratio ($p<0.001$) compared to control subjects (Table 2). Further serum MDA level in PIH subjects was significantly higher compared to the control subjects ($p<0.001$) (Table 2).

Table 3 shows the distribution of serum lipoproteins in PIH sub-groups and control subjects. TC was found to be significantly higher ($p<0.001$) in PIH patients with eclampsia when compared with normotensive pregnant women. HDL-C levels in patients with PIH ($p<0.01$) and eclampsia ($p<0.05$) were significantly lower compared with the control subjects. TG levels in PIH patients with gestational hypertension ($p<0.01$), pre-eclampsia ($p<0.01$) and eclampsia ($p<0.001$) were significantly higher compared to control subjects. VLDL-C was also significantly higher in patients with PIH as compared to the control group. LDL-C was significantly higher ($p<0.001$) in patients with eclampsia compared with pregnant women. Ratio of TC/HDL-C was higher in patients with GH ($p<0.05$) and preeclampsia ($p<0.05$) compared with control group. Ratio of LDL-C/HDL-C was significantly higher in patients with eclampsia ($p<0.001$) compared with the control group.

Table 2: Comparison of lipid profile and MDA

Variables	PIH subjects (n = 70)	Control subjects (n = 70)	Significance
TC (mg/dL)	226.2 ± 43.9	203.6 ± 39.0	0.002
HDL-C (mg/dL)	41.6 ± 9.0	46.97 ± 7.3	<0.001
VLDL-C (mg/dL)	56.7 ± 14.8	42.8 ± 10.9	<0.001
LDL-C (mg/dL)	127.8 ± 39.5	113 ± 37.3	0.023
TG (mg/dL)	283.4 ± 73.9	214 ± 54.3	<0.001
TC/HDL-C	5.7 ± 1.8	4.5 ± 1.1	<0.001
LDL-C/HDL-C	3.3 ± 1.5	2.5 ± 1	<0.001
MDA (mmol/L)	1.1 ± 0.3	0.4 ± 0.1	<0.001

All data are presented as mean \pm standard deviation; all values corrected to first decimal place

PIH = pregnancy induced hypertension; MAD = malondialdehyde; TC = total cholesterol; HDL-C = high-density lipoprotein-cholesterol; VLDL-C = very low-density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; TG = triglycerides

Serum MDA was found to be significantly higher in all PIH sub-groups ($p < 0.001$) groups compared with normotensive pregnant women (Table 3).

Table 3 depicts comparison of lipid profile and MDA within PIH subgroups. Serum TC was significantly higher in patients with eclampsia ($p < 0.001$) when compared with other subgroups. Serum VLDL-C was significantly higher in patients with eclampsia ($p < 0.01$) compared to the other subgroups. The TC/HDL-C ratio was significantly lower ($p < 0.01$) in patients with eclampsia compared to patients with GH ($p < 0.01$) and preeclampsia ($p < 0.001$) LDL-C/HDL-C ratio was significantly higher in patients with eclampsia compared to GH ($p < 0.05$) and preeclampsia ($p < 0.01$).

MDA in patients with eclampsia was significantly higher compared with the other sub-groups ($p < 0.001$).

DISCUSSION

Dyslipidaemia is thought to have pathophysiological role in PIH. During pregnancy, serum lipoproteins except HDL-C increase considerably¹⁷ and are two-to three-times higher in PIH. Worldwide, various studies^{5,18-24} have reported elevated lipid levels in PIH subjects similar to our observations. In the present study, TC was significantly increased ($p < 0.01$) in PIH subjects compared to control subjects consistent with other studies.²⁰⁻²⁷ But no significant changes in TC could be observed by some other workers.^{5,19,24,28,29}

Finnish and Peruvian PIH subjects had higher mean TG and lower HDL-C than the control group.^{30,31} In our study, HDL-C was significantly lower ($p < 0.001$) in PIH patients as compared to the control subjects as was observed in other studies.^{19,21-26,28,29} A similar difference was not evident in one study,²⁰ while other researchers^{32,33} observed higher HDL-C level in PIH women.

The increased triglycerides play a part to decrease the maternal HDL-C level. A direct correlation between adipose tissue lipoprotein lipase activity and plasma HDL-C has been established which may be responsible for low levels of HDL-C. Hypertriglyceridaemia, leading to low HDL-C is mainly due to the action of cholesteryl ester transfer protein (CETP).²⁹ In present study, serum VLDL-C level was significantly higher ($p < 0.001$) in the PIH group as compared to the control group consistent with observations from other studies^{21,23-26} However, no such significant difference was observed by other workers.^{32,33}

Raised level of VLDL-C may be due to hypertriglyceridaemia that carries endogenous triglyceride into circulation. According to a report³⁴ the VLDL-C level might rise up to 2.5-folds at term over the pre-pregnancy level. VLDL-C level further increase in PIH as observed in the present study and other studies.^{5,21,35} Increased VLDL-C which is further metabolised to LDL-C, accumulates over the maternal uterine and renal vascular endothelium and contribute to the endothelial dysfunction in PIH.

In the present study, LDL-C was significantly higher ($p < 0.05$) in PIH subjects compared to control subjects as was observed in other reports.^{19-26,28,29} In contrast, recent studies^{24,32} showed no significant difference of LDL-C. The significant lower levels of LDL-C was noted in hypertensive patients compared to the normotensive.³³

In our study, significantly higher serum TG levels were observed in PIH subjects compared to the control subjects. Similar observations were reported by other researchers.^{19,20,22-26,29} No significant correlation with triglycerides was observed in another study.³³ The principle modulator of the hypertriglyceridaemia is oestrogen as pregnancy is linked with hyperoestrogenaemia. Oestrogen induces

Table 3: Comparison of lipid profile and MDA between PIH sub-groups and control subjects

Variables	PIH-subgroups			Control subjects (n=70)	Significance
	Gestational hypertension (n=25)	Pre-eclampsia (n=25)	Eclampsia (n=20)		
TC (mg/dL)	213.5 ± 34.5	210.2 ± 34.9	261.8 ± 45.7	203.6 ± 39.0	Group III vs Controls = p<0.001 Group I vs Group III = p<0.001 Group II vs Group III = p<0.001
HDL-C (mg/dL)	40.45 ± 9.2	43 ± 8.1	41.3 ± 10.1	47 ± 7.3	Group I vs Controls = p<0.01 Group III vs Controls = p<0.05
VLDL-C (mg/dL)	53.6 ± 12.8	53.7 ± 16.6	64.3 ± 12.3	42.8 ± 10.9	Group I vs Controls = p<0.05 Group II vs Controls = p<0.05 Group III vs Controls = p<0.001 Group I vs Group III = p<0.05 Group II vs Group III = p<0.05
LDL-C (mg/dL)	119.4 ± 35.3	113.6 ± 31.4	156.2 ± 40.7	112.96 ± 37.3	Group III vs Controls = p<0.001 Group I vs Group III = p<0.01 Group II vs Group III = p<0.01
TG (mg/dL)	267.9 ± 64.1	268.2 ± 83	321.7 ± 61.5	214 ± 54.3	Group I vs Controls = p<0.01 Group II vs Controls = p<0.01 Group III vs Controls = p<0.001 Group I vs Group III = p<0.05 Group II vs Group III = p<0.05
TC/HDL-C	5.4 ± 0.9	5.1 ± 1.4	6.8 ± 2.50	4.5 ± 1.1	Group I vs Controls = p<0.05 Group III vs Controls = p<0.001 Group I vs Group III = p<0.01 Group II vs Group III = p<0.001
LDL-C/HDL-C	3.0 ± 0.1	2.8 ± 1.1	4.15 ± 1.99	2.5 ± 1	Group III vs Controls = p<0.001 Group I vs Group III = p<0.05 Group II vs Group III = p<0.01
MDA (mmol/L)	0.8 ± 0.2	1.2 ± 0.12	1.3 ± 0.1	0.4 ± 0.1	Group I vs Controls = p<0.001 Group II vs Controls = p<0.001 Group III vs Controls = p<0.001 Group I vs Group II = p<0.001 Group I vs Group III = p<0.001 Group II vs Group III = p<0.001

All data are presented as mean ± standard deviation; all values corrected to first decimal place

PIH = Pregnancy induced hypertension; TC = Total cholesterol; HDL-C = high-density lipoprotein-cholesterol; VLDL-C = very low density lipoprotein-cholesterol;

LDL-C = low-density lipoprotein cholesterol; TG = trigly urides; MDA = malon dialdehyde

hepatic biosynthesis of endogenous TG, by increasing the hepatic VLDL-TG synthesis, secretion and plasma TG concentration.³⁶ Activities of adipose tissue lipoprotein lipase and hepatic lipase are substantially decreased during pregnancy due to insulin resistance and oestrogen respectively. This results in impaired removal of TG-rich lipoproteins from the circulation. In PIH, increased TG⁵ is probably deposited in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, both directly and indirectly through generation of small, dense low density lipoprotein cholesterol.

In the present study, the ratio of TC/HDL-C and LDL/HDL-C was significantly ($p < 0.001$) higher in PIH subjects compared with the control subjects. Similar observations have been observed in PIH subject in other studies.^{24,37} The TC/HDL-C ratio is one of the determinants of the predisposition to the risk of atherosclerosis. A high TC/HDL-C ratio (>4.5 in men, >5 in women) is considered to be a risk factor for atherosclerosis.³⁸ We noted TC/HDL-C ratio more than 4.5 in PIH subjects denoting the risk for atherosclerosis. Similarly LDL-C/HDL-C ratio was also found to be higher further contributing to the risk.

In PIH subjects MDA was significantly higher compared to control subjects. Similar observations were reported in other studies.^{19,21,22,39,40} Further, MDA level in eclamptic women was also found significantly higher ($p < 0.001$) when compared to gestational hypertension and pre-eclampsia in the present study. Other studies^{41,42} have also shown that MDA was significantly elevated in mild and severe PIH. Excessive lipid peroxidation occurring in PIH can be attributed to hypercholesterolaemia and hypertriglyceridaemia that promote the formation of free radicals. Increased oxygen demand to meet the bodily functions in pregnancy is also a contributory factor for the oxidative stress

resulting the formation of free radicals. Thus, lipid alterations observed, may promote oxidative stress, leading to endothelial dysfunction in preeclampsia.

Within sub-groups of PIH, we found significantly increased levels of TC, TG, LDL-C and VLDL-C in eclampsia when compared with GH, preeclampsia as well as control subjects. On the other hand, HDL-C was found significantly decreased in eclampsia when compared with control group. Ratio of TC/HDL-C and LDL-C/HDL-C were also significantly increased in eclampsia when compared with GH, preeclampsia and normotensive pregnant women. In contrast to our observations, in another study²³ no statistically significant difference was observed in these parameters between mild and severe groups except for TC which was significantly higher in severe preeclampsia as compared to the mild group subjects. Mean TC levels were not statistically different in pre-eclampsia, eclampsia and in normal subjects.²⁸ The authors²⁸ concluded that increased TG, delayed TG clearance and high blood pressure were the reasons for the development of preeclampsia and eclampsia. Similar results were reported in another study.³⁷ LDL-C/HDL-C ratio has been found to be considerably higher in women with eclampsia compared to normotensive pregnant women.^{35,43} TC/HDL-C has been found to be lower during pregnancy but elevated significantly in both pre-eclampsia and eclampsia.³⁵ Our findings are consistent with these observations.

The results of our study suggest that abnormal lipid metabolism characterized by low HDL-C, high TG and LDL-C concentrations, TC/HDL-C and LDL-C/HDL-C ratios along with oxidative stress resulting in lipid peroxidation may add to the promotion of vascular dysfunction leading to PIH. Estimation of serum lipid profile and MDA in pregnant women during antenatal care can be useful in

the early diagnosis of PIH and prevention of obstetric complications. Further, optimal treatment of dyslipidaemia in antenatal period may prevent lipid peroxidation and thereby endothelial injuries which may further prevent the development and progression of PIH.

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