

A Comparative Study of Serum Lipids and Lipoprotein - A Levels of Women with Pregnancy Induced Hypertension (PIH) and Normal Pregnant Women

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1. Introduction

Hypertensive disorders complicating pregnancy is the one of the most common medical problem of pregnancy.¹ Worldwide, hypertensive disorders in pregnancy causes complication in about 10 -16% of pregnancies and are important source of maternal and fetal morbidity or mortality.^{1, 2} High blood pressure in pregnant women is related with incidence of large placental infarct and decreased placental growth resulting in intra uterine fetal growth restriction and intrauterine death.² Hypertension in pregnancy is diagnosed when blood pressure is 140/90 mm of hg or greater using kortakoff phase 5 to define diastolic pressure with proteinuria and edema after 20 week of gestation.³

One of the most striking pathophysiological feature of pregnancy induced hypertension (PIH) is widespread vasoconstriction which causes decreased perfusion to organs.⁴ Uterine endovascular trophoblast invasion remains superficial and as a result the spiral arteries remain muscular, undilated and responds to vasomotor influence. Widespread disturbance of maternal vascular endothelium is responsible for hypertension.^{5, 6} Endothelium seems to be target organ for preeclampsia process.⁷

Lipid peroxidation degradation products and reactive oxygen species (ROS) of lipid peroxidation and oxidative damage is increased in the placenta of women with pre eclampsia.⁸ Plasma lipid and lipoprotein (a) undergo both qualitative and quantitative changes during pregnancy.⁹ Pregnancy is associated with physiological hyperlipidemia.^{1, 5} During the course of normal pregnancy, plasma triglycerides and cholesterol concentration rises by 200-400% and 25-50% respectively. From 10 weeks to 35 weeks of pregnancy mean serum estradiol concentration increased steadily and there is a strong relationship between rise in estradiol and the increment in plasma triglyceride and plasma cholesterol.¹⁰

An abnormal lipid profile is known to be strongly associated with atherosclerotic changes and has direct effect on endothelial dysfunction.¹¹ In preeclampsia women, thromboxane rise more than in normotensive pregnant women. Increased lipid synthesis causes increase in PGI₂:TXA₂ ratio and plays a role in pathogenesis of

pregnancy induced hypertension (PIH)¹², hence the hyperlipidemia may be an important marker of toxemia of pregnancy.¹³

Lipoprotein (a) is variant of LDL, it carries one copy of proteinapo (a) joined to apo (b) 100 by disulphide linkage^{14, 15}. Lipoprotein (a) levels appears to be lower in normal pregnancy.¹⁶ Lipoprotein (a) has been found to enhance blood coagulation by competing with plasminogen for its binding sites on fibrin clots and endothelial cell.¹⁴ Lipoprotein (a) levels are found to be elevated in preeclampsia.¹⁷ Elevated lipoprotein a may influence the fibrinolysis and have unfavorable effect on pregnancy outcome.¹⁸

In this background the present studies was undertaken to asses and compare the serum levels of lipid and lipoprotein (a) in pregnant women with PIH and normotensive pregnant women.

2. Material and Method

A total of 100 female patients of which fifty pregnant women, both primigravida and multigravida who have been clinically diagnosed with pregnancy induced hypertension and fifty apparently healthy pregnant women of more than 20weeks of gestation, with no bad obstetric history attending the Antenatal clinic in Department of Obstetrics and Gynecology, Modern Maternity Hospital, Hyderabad, were the cases and controls of our study respectively.

Sources of samples and Data:

Department of Obstetrics, Modern Maternity Hospital
Department of Biochemistry, Osmania General Hospital

Inclusion criteria

Pregnant women with hypertension and proteinuria at 20 -42 weeks of gestation

Exclusion criteria

Pregnant women with h/o Smoking, Alcoholism, Gestational diabetes, Diabetes Mellitus, Renal disorders, Hepatic disorder, patients in labour, patients on hypertensive drugs prior to pregnancy, Blood disorder, Epilepsy, Chronic drug intake other chronic diseases that interfere with the study were excluded from the study

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Specimen collection

After obtaining informed consent and under full aseptic precautions, from both the study groups, 3 ml of fasting venous blood sample was collected in plain tube for estimation of the parameters included in the study. Grossly hemolysed and lipemic blood samples were excluded from the study. Lipid profile was estimated in Erbaautoanalyzer EM 360 by enzymatic method using kits supplied by Transasia.

The following parameters were analyzed

- 1) Serum Cholesterol
- 2) Serum Triglycerides
- 3) Serum High density lipoprotein (HDL)
- 4) Serum Low density lipoprotein (LDL)
- 5) Serum Very low density lipoprotein (VLDL)
- 6) Serum Lipoprotein (a)

Statistics

The data was analyzed using graph pad prism demo and SPSS (Statistical Package for the Social Sciences) software version and results were expressed as Mean and standard deviation of various parameters in different group. The significance of different mean values of different groups and within the groups is represented by P values and P value < 0.05 is considered as significant. ROC curve analysis was done to assess maximum sensitivity and maximum specificity and diagnostic efficiency

3. Results

It was a cross sectional study with fifty pregnant women with clinically diagnosed pregnancy induced hypertension (PIH) (cases) and fifty apparently healthy pregnant women (controls). In our study lipid profile values observed in cases and controls are depicted in Table no.1.

In our study the mean ±SD values of total cholesterol, triglycerides, LDL, VLDL, are statistically significant higher in PIH cases whereas HDL levels are low in cases when compared to controls. Serum Lipoprotein (a) levels are statistically significant high in PIH cases when compared to control.

Table 1: MEAN ±SD of various parameters in control and cases

Parameters	Mean±SD of Control	Mean±SD of Cases
Serum Cholesterol	187.20±27.30	238.46±38.80
Serum Triglycerides	144.22±22.99	205.12±35.81
Serum HDL	62.49±14.73	42.32±8.12
Serum LDL	96±33.58	155.15±35.83
Serum VLDL	29.45±5.35	40.90±7.15
SERUM LP (a)	17.33±5.59	48.16±15.41

Table 2: Mean ±SD of various studied parameters of case control

Parameters	Mean±SD of Control	Mean±SD of Cases	t value	P value
Serum Cholesterol	187.20±27.30	238.46±38.80	7.66	0.0001
Serum Triglycerides	144.22±22.99	205.12±35.81	10.18	0.0001
Serum HDL	62.49±14.73	42.32±8.12	8.52	0.0001
Serum LDL	96±33.58	155.15±35.83	8.60	0.0001
Serum VLDL	29.45±5.35	40.90±7.15	9.10	0.0001
Serum LP (a)	17.33±5.59	48.16±15.41	13.2	0.0001

Pearsons correlation

In order to assess the existence of correlation between various parameter in control and in PIH women, the data is subjected to pearsons correlation and coefficient of correlation (r) values and p values are calculated. The r value is graded from +1 to -1.r value +1 indicate strong association and 0 indicate no association, -1 indicates strong negative association.

Table 3: Pearson’s Correlation between different parameters in Control group

	T.C	T.G	HDL	LDL	VLDL	LP (a)
T.C						
Pearsons correlation	1	0.1116	-0.1484	0.8676	-0.0623	-0.2760
Sig.2 tailed	-	.4404	0.0220	0.0001*	0.6674	0.0525
N	50	50	50	50	50	50
T.G						
Pearsons Correlation	0.1116	1	-0.0456	0.00071	0.6286	-0.1947
Sig.2 tailed	0.4404	-	0.7531	0.9608	0.0001*	0.1755
N	50	50	50	50	50	50
HDL						
Pearsons Correlation	-0.1484	-0.0456	1	-0.5507	-0.0901	0.0176
Sig.2 tailed	0.0220	0.7531	-	0.0001*	0.5336	0.9033
N	50	50	50	50	50	50
LDL						
Pearsons Correlation	0.8676	0.00713	-0.5507	1	-0.1768	0.2032
sig.2 tailed	0.0001*	0.9608	0.0001*	-	0.2211	0.1570
N	50	50	50	50	50	50
VLDL						
Pearsons Correlation	-0.0623	0.6288	-0.0901	-0.1762	1	-0.253
Sig.2 tailed	0.0524	0.0001*	0.5336	0.2210	-	0.8613
N	50	50	50	50	50	50
LP (a)						
Pearsons Correlation	0.8076	-0.1947	0.01762	-0.2032	-0.0253	1
Sig.2tailed	0.0524	0.1755	0.9033	0.1570	0.8613	-
N	50	50	50	50	50	50

* Correlation significant at the 0.05 level (2-tailed).

** Correlation significant at the 0.01 level (2-tailed).

Pearson correlation of control group

> Total cholesterol is significantly correlated with Low density lipoprotein

>Triglycerides is statistically significantly correlated with Very low density lipoprotein

>High density lipoprotein is statistically significant correlated with Low density lipoprotein

>Very low density lipoprotein is statistically significant correlated with Triglycerides

>Low density lipoprotein is statistically significant correlated with Total cholesterol, High density lipoprotein

Table 4: Pearson’s Correlation between different parameters in CASES group

	T.C	T.G	HDL	LDL	VLDL	LP (a)
T.C						
Pearsons correlation	1	0.4386	0.0888	0.9701	0.9706	-0.2156
Sig.2 tailed		0.0014*	0.5394	0.0001*	0.0001*	0.1369
N	-	50	50	50	50	50
T.G						
Pearsons Correlation	0.4386	1	-0.2500	0.3278	0.9706	-0.03636
Sig.2 tailed	0.0014*	-	0.0786	0.0201*	0.0001*	0.8020
N	50	50	50	50	50	50
HDL						
Pearsons Correlation	0.0888	-0.2500	1	-0.0827	-0.2288	0.00071
Sig.2 tailed	0.5394	0.0789	-	0.0201	0.1100	0.9960
N	50	50	50	50	50	50
LDL						
Pearsons Correlation	0.9701	0.3278	-0.0827	1	0.3327	-0.2326
Sig.2 tailed	0.0001*	0.0201*	0.5680	0	0.0183*	0.1040
N	50	50	50	50	50	50
VLDL						
Pearsons Correlation	0.9706	0.9706	-0.2288	0.3327	1	-0.0438
Sig.2 tailed	0.0001*	0.0001*	0.1100	0.0183*	-	0.7622
N	50	50	50	50	50	50
LP (a)						
Pearsons Correlation	-0.2156	-0.3636	0.00071	-0.2326	-0.04388	1
Sig.2tailed	0.1369	0.8020	0.9960	0.1040	0.7622	-
N	50	50	50	50	50	50

* Correlation significant at the 0.05 level (2-tailed).

** Correlation significant at the 0.01 level (2-tailed).

Pearson correlation of CASES group

>Total cholesterol is significantly correlated with Triglycerides, Low density lipoprotein, Very low density lipoprotein

>Triglycerides is significantly correlated with Total cholesterol, Low density lipoprotein, Very low density lipoprotein

>Low density lipoprotein is significantly correlated with Total cholesterol, Triglycerides, Very low density lipoprotein

>Very low density lipoprotein is significantly correlated with Total cholesterol, Triglycerides, Low density lipoprotein

ROC curve Analysis

In order to assess the maximum sensitivity, specificity and diagnostic efficiency of various parameters in identifying abnormality, the best cut off values are calculated using ROC analysis. Best cut off values are established by selecting a point closer to the left hand curve, that provides greatest sum of sensitivity and specificity

Diagnostic efficiency is defined as the portion of all currently classified as having or not having disease.

$$\text{Diagnostic Efficiency} = \frac{\text{True positive} + \text{True Negatives} \times 100}{\text{Total no of patients evaluated}}$$

Area under curve provides unbiased estimates of sensitivity and specificity. It is a comprehensive representation of pure accuracy discriminating ability over the entire range of the test.

Table 5: Sensitivity, specificity, diagnostic efficiency at best cutoff value in discriminating Total cases and controls

Parameter	Best cut off value (mg/dl)	Sensitivity (%)	Specificity (%)	Diagnostic Efficiency (%)
Total Cholesterol	197	78	88	80
S.Triglycerides	143	96	74	90
HDL	51	92	80	93
LDL	130	80	83	92
VLDL	33	86	80	90
LP (a)	27	98	96	96

Table 6: Area under curve for analyzed parameters in controls and total cases

Parameters	AUC	Significance	95% CI
Total cholesterol	0.8784	0.0001	0.8079-0.9490
Total triglycerides	0.9284	0.0001	0.8774-0.9490
HDL	0.9198	0.0001	0.8681-0.9715
LDL	0.9010	0.0001	0.8402-0.9618
VLDL	0.9080	0.0001	0.8468-0.9692
LP (a)	0.9958	0.0001	0.9877-0.004

4. Discussion

Pregnancy induced hypertension (PIH) continues to be main obstetric problem in present day healthcare practice. PIH is a syndrome of hypertension in pregnancy with or without edema and proteinuria.¹⁹Lipid is mobilized from adipose tissue as free fatty acids attached to albumin.HDL is involved in VLDL and chylomicron metabolism and cholesterol transport.^{20, 21}The plasma total cholesterol and triglycerides rise during second and third trimester in most pregnant women. The increase in lipid concentration amounts to mild to moderate physiological hyperlipidemia.²⁰

The plasma free fatty acid concentration is abnormally high in pregnancy owing to increased mobilization from adipose tissue.²²The plasma free fatty acid concentration begins to rise at 20 weeks and eventually reaches a level 4-5 times that in post partum period. Within 2 to 3 days of delivery the plasma FFA concentration falls to normal levels.²³Human placental lactogen produced the effect of insulin antagonist and stimulates adipose tissue lipolysis.²⁴The physiological properties of HPL and time course of its appearance in blood of pregnant women suggest that it is responsible for metabolic effect of pregnancy. Other catabolic hormone including ACTH, glucagon, glucocorticoids contribute to increased mobilization of FFA that occurs in pregnancy.²⁵

The high plasma FFA concentration together with the presence of circulating insulin antagonist, diminish glucose utilization by maternal skeletal muscle and heart muscle and substitute FFA for glucose as the main source of energy for these tissues.²⁵The net effect is therefore is to save glucose for fetus which requires glucose in preference of fat as its fuel.

Disturbed lipid metabolism, including hypertriglyceridemia, which is primary due to enhanced entry of TG rich lipoprotein in circulation, was noted to be feature of pre-eclampsia over 60 years age.²⁶Normal pregnancy results in physiological hyperlipidemia involving a gestation rise in blood total cholesterol and triglycerides.²⁷There is marked rise in serum triglycerides, which may be as high as two to three folds in third trimester.²⁸The principal modulator of this hyperlipidemia is hyperoestrogenemia in pregnancy that induces hepatic biosynthesis of TG. The anabolic phase of early pregnancy encourage lipogenesis and fat storage in preparation for rapid fetal growth in late pregnancy.²⁹

Lipolysis is increased as a result of insulin resistance, leading to increased influx of fatty acid to liver promoting the synthesis of very low density lipoproteins and increased triglycerides concentrations.²⁹The principle modulator of high Total cholesterol in PIH is due to hyperoestrogenemia that cause increase lipogenesis, increase in hepatic lipase activity and hyperlipidemia.The major rise in cholesterol occurs in second trimester.³⁰

Therefore this study was designed to ascertain whether there is any change in lipid profile and LP (a) in pregnancy induced hypertension group compared to those with normal pregnancy.

In present study mean \pm SD of total cholesterol in control was 187.2 \pm 27, mean \pm SD of total cholesterol in cases was 238.4 \pm 38.8.Total cholesterol level in PIH cases were significantly high when compared to control groups. This finding are similar to study of Winkler Ket al.³¹However other studies reported no alternation in TC levels (Pizarro et al)³⁸

Serum Triglycerides are ester derived from glycerol and three fatty acids and helps in transport of adipose fat from liver.³¹The major modulator of hypertriglyceridemia in PIH is due to oestrogen. Oestrogen induced hepatic biosynthesis of endogenous triglycerides, by rising the hepatic VLDL-C synthesis, this process may be modulated by hyperinsulimiam in pregnancy. During gestation these interactions along with increased endothelial triglycerides accumulation may result in endothelial cell dysfunction. In PIH increased triglycerides are deposited in predisposed vessel, such as the spiral arteries and contribute to endothelial dysfunction, both directly and indirectly through generation of small, dense low density lipoproteins cholesterol. Moreover, this hypertriglyceridemia may be linked with hypercoagulability.³¹

In present study mean \pm sd of serum triglycerides in control was 144 \pm 25and Mean \pm sd in cases was 205 \pm 35.Serum triglycerides level in PIH cases were significantly high when compared to control groups. Study done by Kokia E et al⁵ had also reported that TG were significantly higher in pre-eclampsia and also concluded that the lipid profile in hypertensive pregnant women could be associated with enhancement of pathological lipid deposition in uterine spiral arteries.⁵ Hubel et al³²also reported that TG and fatty acid increases significantly in preeclampsia women.

The apparent positive relationship between hypertensive disease and lipid metabolism has lead several investigators to study maternal serum lipid patterns in pre eclampsia. Kaaja et al³⁷reported elevated plasma cholesterol and phospholipid level in pre eclampsiaand. Hubel et al³²found high values for plasma cholesterol, total lipids and triglycerides level. It is known that triglycerides accumulation in cells occur as a result of cellular damage. It is possible that increased triglycerides content in pregnancy induced hypertension reflects that placenta is main diseased organ in this condition.

HDL- C-It is one of the five major group of lipoproteins in blood. It is synthesized by liver and Intestine and it helps in transport of cholesterol to liver, removes excess cholesterol from cell and has antiatherogenic property.³³The increase in HDL-C in first half of gestation is believed to be caused by estrogen and after 30 weeks of pregnancy, HDL-C level decreases. This is due to human placental lactogen and its lipolytic activity, increase plasma level of free fatty acids. The free fatty acids then are incorporated into triglycerides and VLDL in liver. The increased activity of hepatic lipase induced by progesterone in turn likely to result in increased HDL.^{33, 36}

In present study mean \pm sd of HDL in controls was 62 \pm 14. Mean \pm SD in cases was 42 \pm 8. Serum HDL-C in PIH cases was significantly low when compared to control group. In

PIH, HDL levels decreases due to the effect of estrogen. In PIH, Low level of HDL is also due to insulin resistance. This is in agreement with study conducted by Kaaja et al³⁷. According to Pirzado et al,³⁸ there is a direct correlation between adipose tissue lipoprotein lipase activity and plasma HDL cholesterol. This direct correlation may be responsible for low level of HDL cholesterol.³⁸

LDL-C is one of the five major groups of lipoproteins. It helps in transport of fat to peripheral tissues. They are formed as a consequence of the lipolysis of VLDL.³⁷ A significant fall in LDL -C in normal pregnancy is observed in this study may be attributed to hyperestrogenaemia, while LDL-C level increases significantly in PIH cases. Because of decrease in activity of lipoprotein lipase, LDL remains in plasma for longer and leads to accumulation of LDL. An increase in LDL is associated with development of atherosclerosis. Women with preeclampsia display additional alterations in blood lipids reflecting abnormal lipid and lipoprotein metabolism³⁹

In present study mean \pm sd of LDL cholesterol in control was 96.1 ± 33 and Mean \pm sd of of LDL cholesterol in cases was 155.1 ± 35 . Serum LDL -C is significantly high in cases when compare to control group. A significant higher level of beta lipoprotein was also reported by many workers in gestational hypertension. Rosinget al⁴⁰ reported that especially after second trimester, levels of LDL, triglycerides are significantly increased. Gratacos et al⁴¹ showed that in all hypertensive and pre eclampsia cases LDL, triglyceride and total cholesterol were significantly higher especially between 20-34 weeks of pregnancy. Kokia et al⁵ found that triglycerides and LDL were significantly higher in PIH case.

VLDL-C is also one of the five major lipoproteins in blood. It is produced by liver. They are rich in triglycerides and are major carriers of endogenous triglycerides and transfer triglycerides from liver to peripheral tissues. Normal serum VLDL 5-50mg/dl (Females).³⁹

In present study mean \pm SD of VLDL in control was 29.4 ± 5 . Mean \pm SD of VLDL in cases was 40.9 ± 7.1 . Serum VLDL was significantly high in cases than in control, which may be due to hypertriglyceridemia leading to enhanced entry of VLDL that carries endogenous triglycerides into circulation. The VLDL -C level as reported by some researches, might rise up to 3 folds at term over the pre pregnancy state.³⁹ ⁴⁰VLDL level further increases in PIH as evidenced in present study in collaboration with those of other workers like Casals E et al⁴¹, perhaps due to increased VLDL lipoproteins which may accumulate over the maternal vascular endothelium, particularly those of uterine and renal vessels ⁴¹. VLDL -C may cause injury to the endothelium, while a particular toxicity preventing activity protein protects against the VLDL induced damage in the pathogenic process of toxemia⁴²

Lipoprotein (a) is a LDL like moiety which contain a lipid core of cholesteryl esters and triglycerides surrounded by surface layer of phospholipid and free cholesterol.¹⁷ In addition to lipids, each particles of LP (a) has one molecule of apoprotein B -100. Both apo b lipid core are

proatherogenic. However, LP (a) contains unique protein apoprotein (a) which is structurally different from other apolipoproteins having a hydrophilic, carbohydrate rich structure with no amphipathic helices⁴⁶. Apo (a) is linked to apo B through a single disulphide bond connecting their c - terminal regions. Normal serum level -up to 30 mg/dl.⁴⁶

In present study mean \pm sd of lipoprotein (a) in control was 17.3 ± 5 and Mean \pm sd of lipoprotein (a) in cases was 48 ± 15 . Serum lipoprotein (a) was significantly high in cases than in controls. LP (a) bound to glycosaminoglycan is incorporated into fibronectin in the intimal layer of the arteries.⁴³ This is known to contribute to foam cell formation.⁴⁴ LP (a) also binds to plasminogen activator receptor in the endothelium, thus inhibiting plasminogen activation and fibrolysis and ultimately resulting in endothelial thrombosis. LP (a) may provide a useful marker for screening patients at risk of developing PIH.^{45, 47}

Jacob b et al⁴⁶ stated that maternal lipoprotein (a) is higher in second trimester in PIH cases than in normal pregnant women. The literature on lipoprotein (a) during normal pregnancy and in PIH was reviewed by Ordovas et al for period of may 1996 to 2003. It come out from the review that remains unchanged in normal pregnancy and is significantly increased in PIH cases.⁴⁸

In the present study, a high lipid profile levels is observed to associate with preeclampsia. Predominantly low HDL and high triglyceride concentration which may promote vascular dysfunction and oxidative stress is observed in PIH. From the results of this study, it also appears that raised level of serum lipoprotein (a) occur in pregnant patients with preeclampsia. This high level of lipoprotein (a) significantly correlated with blood pressure and proteinuria. Lipoprotein (a) levels may provide a useful marker for screening patients at risk for developing PIH. It is therefore essential that serum lipid concentration should be estimated in all pregnant women during antenatal care, since it could be useful in the early diagnosis and prevention of obstetric complications like PIH. Hence early detection of these parameters may help in better management of pre eclampsia cases, which is important to improve the maternal and fetal outcome in PIH.

5. Conclusion

PIH, an obstetric problem observed in present day healthcare practice is accountable for 12% of maternal mortality worldwide. PIH is related with incidence of large placental infarct and decrease fetal growth, maternal complication like HELLP syndrome, pre-term delivery, intra uterine death. From the results of the present study, it is observed that elevated lipid profile levels are strongly associated with pre-eclampsia suggesting that elevated lipids may be involved in pathogenesis of pre-eclampsia. In present study lipid parameters like total cholesterol, serum triglycerides, LDL, VLDL, Lipoprotein (a) levels were significantly increased and HDL levels were significantly decreased in cases when compare to controls. Dyslipidemia mediated activation of endothelial cells to the placental derived factors and trophoblastic component or combination of placental

derived factors with lipoprotein could be possible contributors for pathogenesis of PIH.

6. Limitation of the study and Recommendations

It is a cross sectional study with small sample size. Study of serum levels of lipid and lipoprotein (a) in pregnant women with PIH has to be performed in larger population to firmly establish the role of Dyslipidemia in pathogenesis of PIH.

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Conflict of interest- None

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