A Comparative Study of Serum Lipids Levels and lipoprotein A in Women with Pregnancy Induced Hypertension (PIH) and Normotensive pregnant women

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Abstract

Introduction:Hypertensive disorders complicating pregnancy is the one of the most common medical problem of pregnancy. Worldwide, hypertensive disorders in pregnancy causes complication in about 10 -16% of pregnancies. 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. Hypertension in pregnancy is diagnosed when blood pressure is 140/90 mm of hg or greater with proteinuria and edema after 20 week of gestation. Plasma lipid and lipoprotein (a) undergo both qualitative and quantitative changes during pregnancy. During the course of normal pregnancy, plasma triglycerides and cholesterol concentration rises by 200-400% and 25-50% respectively. An abnormal lipid profile is known to be strongly associated with atherosclerotic changes and has direct effect on endothelial dysfunction. 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), hence the hyperlipidemia may be an important marker of toxemia of pregnancy.

Aim and Objectives:To asses and compare the serum levels of lipid and lipoprotein (a) in pregnant women with PIH and normotensive pregnant women.

Materials and Methods: A study conducted on total of 100 pregnant patients (50 cases and 50 controls) selected according to inclusion and exclusion criteria. 3ml of venous blood was drawn to estimate total lipid profileand Serum Lipoprotein (a) levels in each subject.The data was analyzed results were expressed as Mean and standard deviation of various parameters in different group. P value < 0.05 is considered as significant. ROC curve analysis was done to assess maximum sensitivity, specificity and diagnostic efficiency

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

Conclusion:A high lipid profile levels is observed to be associate with preeclampsia thus, serum lipid concentration and serum Lipoprotein (a) levels may provide a useful marker for screening patients at risk for developing PIH.

Keywords:Preeclampsia, Dyslipidemia, Lipid profile,Lipoprotein (a).

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, fetal morbidity and 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 oedema after 20 week of gestation

One of the most striking pathopysiological feature of pregnancy induced hypertension is widespread vasoconstriction which causes decreased perfusion to organs[7].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[8,9]. Endothelium seems to be target organ for preeclampsia process[10]

.Lipid peroxidaton degradation products and reactive oxygen species of lipid perioxidation and oxidative damage is increased in the placenta of women with pre eclampsia[12]

Plasma   lipid and lipoprotien (a) undergo both qualitative and quantitative changes during pregnancy [13]

Pregnancy is associated with phsiological hyperlipidemia[15].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 trigyceride and plasma cholesterol.[16]

An abnormal lipid profile is known to be strongly associated with atherosclerotic changes and has direct effect on endothelial dysfunction[18].In preeclampsia women, thromboxane rise more than normal pregnant women.

Increased   lipid synthesis causes increase in $PGI_2:TXA_2$ ratio and take role in pathogensis of pregnancy induced hypertension [19].so hyperlipidemia may be important marker of toxemia of pregnancy[22]

Lipoprotien (a) is variant of LDL,it carries one copy of protien apo (a) joined to apo (b)100 by disulphide linkage[23.]Lipoprotien (a)   levels appears to be lower   in normal pregnancy[21].Lipoprotien (a) has been found to enhance blood coagulation by competing with plasminogen for its binding sites on fibrin clots and endothelial cell.[20]

Lipoprotien (a) levels are elevated in preeclampsia[24].Elevated lipoprotein a may influence the fibrinolysis and have unfavourable effect on pregnancy outcome[25]

In this background the present study was undertaken to asses and compare the serum lipid and lipoprotien (a) levels in normal pregnant women and pregnant women with PIH.

MATERIAL AND METHOD

Setting: A case control study was conducted in the Department of Biochemistry, Osmania

general hospital, Hyderabad.

Sources of samples and Data: Department of Biochemistry, Osmania General Hospital.

Department of Obstetrics, Modern maternity Hospital.

Inclusion criteria

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

Exclusion criteria

  Diabetes Mellitus, Renal disorders, Hepatic disorder, patients in labour, patients on hypertensive drugs prior to pregnancy, Blood disorder, Epilepsy, Chronic drug intake

Specimen collection

  Fasting blood samples were collected. 3ml blood in plain tube for estimation of the

parameters. Grossly hemolysed and lipemic samples were excluded

   The present study was undertaken in the Department of Biochemistry ,osmania   general hospital and Modern Governement maternity hospital

A total of 100 female subjects of which 50 subjects were controls and 50 were pregnancy induced hypertension patients

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)

The data was analysed using graph pad prism demo and SPSS(stastical package for social sciences) software version and results were expressed as Mean and standard deviation of various parameters in different groups

The significance of different mean values of different groups and within the groups is represented by P values and P value < 0.05 is is considered as significant

ROC curve analysis was done to assess maximum sensitivity and maximum specificity and diagnostic efficiency

RESULTS

The mean ±SD values of total cholesterol, trigycerides, LDL,VLDL, are statistically significant higher in PIH cases whereas HDL levels are low in cases when compared to controls

LP(a) levels are statistically significant high in PIH cases when compared to control

TABLE NO 1 .MEAN ±SD OF VARIOUS PARAMETERS IN CONTROL AND CASES

PARAMETRS	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 no 2.MEAN ±SD OF VARIOUS STUDIED PARAMETER OF CASE CONTROL

PARAMETRS	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

The mean ±SD values of values of total cholesterol,trigycerides,LDL,VLDL, are statistically significant higher in PIH cases whereas HDL level are low in cases when compare to control

LP(a) levels are statistically significant high in PIH cases when compare to control.

Pearsons correlation-

In order to asses 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 o indicate no association,-1 indicates strong negative association

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.

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

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 no 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 CHOLESTREROL	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 no: 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

DISCUSSION

Pregnancy induced hypertension continues to be main obstetric problem in present day healthcare practice

Pregnancy induced hyprtension is a syndrome of hypertension in pregnancy with or without edema and proteinuria.[102]

Lipid is mobilized from adipose tissue as free fatty acids attached to albumin.HDL is involved in VLDL and chylomicron metabolism and cholesterol transport [104].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 [103]

The plasma free fatty acid concentration is abnormally high owing to increased mobilization from adipose tissue [105].The plasma free fatty acid concentraion 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 tha plasma FFA concentration falls to normal levels.[106]

Human placental lactogen produced the effect of insulin antagonist and stimulates adipose tissue lipolysis [107].The 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 ,glucorticoids contribute to increased mobilization of FFA that occurs in pregnancy.[108]

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. [108] The net effect is therefore is to save glucose for fetus which requires glucose in preference of fat as its fuel(N.B Mynant)

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-ecampsia over 60 years age [109]

Normal pregnancy results in physiological hyperlipidimia involving a gestation rise in blood total cholesterol and triglycerides [110].There is marked rise in serum triglycerides ,which may be as high as two to three folds in third trimester[111]

The 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 faetal growth in late pregnancy. [112]

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 [112]

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.

Total cholesterol –It is a sterol and essential structural component of cell membrane ,helps to maintain cell membrane permeability and fludity.Normal serum cholesterol level-150-200 mg/dl(Females).[113]

The principle modulator of high TC 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 [113].

In present study mean±sd of total cholesterol in control was 187.2±27, mean ±sd of total cholesterol in cases was 238.4±38.8.Total cholesterol level in pregnancy induced hypertension cases were significantly high when compared to control groups.

The rise in cholesterol may increase the supply of cholesterol needed for placental progesterone synthesis and transplacental chloesterol transport to fetus(Robert and Knoop) .This is similiar to study of Sattar et al[114].However other studies reported no alternation in TC levels(Pizardo et al)[119]

Serum Triglycerides- It is ester derived from glycerol and three fatty acids.It helps in transport of adipose fat from liver.Normal serum triglycerides level -150mg/dl(Females)[114]

 The 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 hyperinsulimia 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 [114]

In present study mean ±sd of serum triglycerides in control was 144±25.Mean ±sd in cases was 205 ±35.Serum triglycerides level in pregnancy induced hypertension cases were significantly high when compared to control groups.

Kokia E et al found that TG were significantly higher in pre-eclampsia.He also concluded that the lipid profile in hypertensive pregnant women could be associated with enhancement of pathological lipid deposition in uterine spiral arteries [106]

It was reported in Finnish and Puruvian population that patients with pregnancy induced hypertension had higher mean triglycerides than control groups [114].James T et reported that TG and fatty acid increases significantly in pre eclampsia women.While Mikahail Ms et al found that here was no direct relationship between the TG and severity of pre eclampsia [120]

The apparent positive relationship between hypertensive disease and lipid metabolism has lead several investigators to study maternal serum lipid patterns in pre eclampsia. Boyd reported elevated plasma cholesterol and phospholipid level in pre eclampsia and Nelsons ,Zuspantal found high values for plasma cholesterol ,total lipids and triglycerides level.[115]It is known that triglycerides accumulation in cells ocur 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.This is in aggreement with majority of workers(Nelson,zuspantal,Nimoura)

HDL- C-It is one of the five major group of lipoproteins in blood.It is synthesized by liver and Intestine. It helps in transport of cholesterol to liver,removes excess cholesterol from cell and has antiatherogenic property.Normal serum HDL >60mg/dl(Females)[116]

The increase in HDL-C in first half of gestation is believed to be caused by estrogen,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.[116,119]

In present study mean ±sd of HDL in controls was 62±14. Mean ±sd in cases was 42±8. Serum HDL-C in pregnancy induced hypertenstion cases was significantly low when compared to control group.

In PIH, HDL decreases due to the effect of estrogen which is known to decreases HDL.In PIH, Low level of HDL is also due to insulin resistance .This is in agreement with study conducted by Kaaja. [117,118]

According to Pirzardo et al ,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[119]

LDL -C--It is one of the five major group of lipoproteins . It helps in transport of fat to peripheral tissues.They are formed as a consequence of the lipolysis of VLDL.Normal serum LDL –C< 100mg/dl.(Females) [120]

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 remain in plasma for longer and leads to accumulation of LDL.An increase in LDL is associated with development of atherosclerosis.[121]   Women with preeclampsia display additional alterations in blood lipids reflecting abnormal lipid and lipoprotein metabolism [122]

In present study mean ± sd of LDL cholesterol in control was 96.1± 33.Mean± 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 worker in gestational hypertension. [124] Rosing et al reported that especially after second trimester ,levels of LDL ,trigylcerides are were significantly increased.Potter et al also reported increase in LDL significantly in PIH cases[124]

Gratacos et al showed that in all hypertensive and pre eclampsia cases   LDL,triglyceride and total cholesterol were significantly higher especially between 20-34 weeks of pregnancy [121],[122].Kokia et al found that triglycerides and LDL were significantly higher in PIH case[106]

VLDL-C- It is 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 tranfer triglycerides from liver to peripheral tissues.Normal serum VLDL 5-50mg/dl(Females)[122]

In present study mean ±sd of VLDL in control was 29.4±5.Mean ±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 upto 3 folds at term over the pre pregnancy state.[122,123]

VLDL level further increases in PIH as evidenced in present study in collabration with those of other workers(Casals E,Herrar G),perhaps due to increased VLDL lipoproteins which may accumulate over the maternal vascular endothelium,particularly those of uterine and renal vessels [124].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 toxaemia[125]

Lipoprotein (a) is a LDL like moiety which contain a lipid core ofcholesteryl esters and triglycerides surrounded by surface layer of phospholipid and free cholesterol.[88]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 helices [129.] Apo (a) is linked to apo B through a single disulphide bond connecting their c -terminal regions .Normal serum level –upto 30 mg/dl[129]

In   present study mean ±sd of lipoprotein (a) in control was 17.3±5.Mean ±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.[126]This is known to contribute to foam cell formation [127] .LP(a) also binds to plasminogen activator receptor in the endothelium,thus inhibiting plasminogen activation and fibroinolysis and ultimately resulting in endothelial thrombosis(Steinberg et al 1989,Harpel et al 1989).LP(a) may provide a useful marker for screening patients at risk of developing PIH.[128,130]

Jacob b et al stated that maternal lipoprotein (a) is higher in second trimister in PIH cases than in normal pregnant women [130].The literature on lipoprotein (a) during normal pregnancy and in PIH was reviewed by Gwendolyn 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.

To conclude from the present study ,high lipid profile levels are associated with preeclampsia. Predominantly low HDL and high triglyceride concentration which may promote vascular dysfunction and oxidative stress seen in 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 such as PIH

Therefore, these women should receive adequate counseling to urge them to adopt healthier habits and lifestyles and to seek periodic checkups, in order to detect cardiovascular disease in its early stages, before irrepairable damage or even death ensues

Hence early detection of these parameters may help in better management of pre eclampsia cases which is important to imporve the maternal and fetal outcome in PIH

From the results of this study ,it appears that raised level of serum lipoprotein (a) occur in pregnant patients with preeclampsia.These 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.

CONCLUSION

Pregnancy induced hypertension is common obstetric problem in present day healthcare practice.

During pregnancy and puerperium it is accountable for 12% of maternal mortality worldwide

Pregnancy induced hypertension is related with incidence of large placental infract and decrease fetal growth,maternal complication like HELLP syndrome,preterm delivary,intra uterine death.

The present study was carried in Department of Biochemistry ,osmania medical college.The study included 2 group, control (normal pregnant women) and cases(pregnancy induced hypertensive patients)

The following parameters were analyzed- Total cholesterol,Serum triglycerides,High density lipoprotein,Low density lipoprotein,Very low density lipoproptein cholesterol,and Lipoprotein (a)

It is observed that elevated lipid profile levels are strongly associated with pre eclampsia.This suggests that elevated lipids may be invoved in pathogensis of pre eclampsia and risk marker in this womens

In present study lipid parameters like total cholesterol,serum triglycerides, LDL,VLDL levels were significantly increased and HDL levels were significantly decreased in cases when compare to controls

Dyslipidemia mediated activation of endothelial cells to the placentally derived factors and trophoblastic component or combination of placentallly derived factors with lipoprotein could be possible contributors for pathogensis of PIH.

The raised TG ,VLDL   may results in rise in lipid peroxides which is very toxic compound and this may contibutes to endothelial cell dysfunction and oxidative stress in severe

PIH,Further more high TG in pre eclampsia may be associated with hypercoagulation state in PIH

Lipoprotein (a) levels were significantly increased in cases when compare to control group. High lipoprotein (a) may influnce fibrinolysis,binds to plasminogen activator and fibrinogen ,ultimately resulting in endothelial thrombosis.It has been demonstrated in many studies that LP(a) is risk factor in cardiovascular disease.