Original Article

Serum β hCG and lipid profile in early second trimester as predictors of pregnancy induced hypertension

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Abstract

Objectives: The study aims at testing the hypothesis that women with high serum β hCG levels and lipid profile in early second trimester have risk of developing pregnancy induced hypertension. **Methods:** Serum β hCG estimation was done by enzyme linked immunoabsorbent assay (ELISA) method. Serum lipid profile was done by Enzymatic Colorimetric Test with Lipid Clearing factor (LCF) in 164 pregnant women between 14 and 20 weeks of gestation. **Results:** Twenty nine cases developed PIH, while 135 cases remained normotensive. The serum β hCG level increased very significantly ($P<0.000$) in those women who developed PIH. Concentration of total cholesterol and VLDL in women who subsequently developed PIH were significantly higher than that of normotensive women ($P<0.0000$ and $P<0.027$ respectively). Mean triglyceride value was visible higher in PIH groups. Increased of LDL in PIH group was very highly significant ($P<0.000$). Analysis of the response variable, viz. development of PIH or those that remained normotensive through multiple logistic regression model showed that for every 1,000 mIU/ml increase in serum β hCG a pregnant women has 10.7% increasing chance of developing PIH. For one unit increase in TC, TG, VLDL and LDL there are 12.6%, 0.3%, 12.4% and 7.1% respectively increased chance of developing PIH. On the contrary, with one unit increase in HDL, the woman has 11.4% less chance of developing PIH. Out of the 29 cases, 21 women had elevated β hCG while 28 women had dyslipidemia. **Conclusions:** Maternal dyslipidemia and elevated maternal serum β hCG at second trimester are very good non-invasive predictors of PIH. However, dyslipidemia seems to be a more efficient marker in predicting PIH at early second trimester.

Key words: β hCG lipids, obesity, pre-eclampsia.

Introduction

Hypertensive disorder of pregnancy affects upto 8% of all gestations¹. A variety of biochemical and biophysical markers, have been proposed for the

purpose of predicting the development of pre-eclampsia later in pregnancy. In the pathogenesis of preeclampsia, many authors believed endothelial cell activation or dysfunction to be the central theme. At present four hypotheses are the subjects of extensive investigations, (i) placental ischemia, (ii) altered endothelial cell function, possibly secondary to altered lipid metabolism (iii) immune maladaptation and (iv) genetic imprinting. Placenta is the known primary trigger of pregnancy induced hypertension (PIH). Women with PIH have hyperplacentosis or an abnormal placentation. β subunit of human chorionic gonadotropin (β hCG) is

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secreted in abundance from placenta. β hCG level in mid trimester is elevated in patients with chromosomally normal fetuses who later on develop pre-eclampsia². Maternal plasma lipids are significantly elevated during pregnancy. There are also evidences suggesting that abnormal lipid metabolism in early pregnancy could be one of the factors for subsequent development of PIH^{3,4}.

In the present study, we estimated maternal serum β hCG and serum lipids during 14-20 weeks of pregnancy to investigate the clinical utility of second trimester maternal serum β hCG level with serum lipid profile as a predictive test for PIH. In this study PIH will refer to both transient hypertension (de novo hypertension of pregnancy unaccompanied by proteinuria) and pre-eclampsia (Proteinuric hypertension of pregnancy).

Material and Methods

The study was carried out between November 2005 and October 2006.

Selection of cases

A total of 180 pregnant women who attended the antenatal clinic of the Department of Obstetrics and Gynaecology of Regional Institute of Medical Sciences as well as those admitted in the antenatal ward were selected for the study.

Inclusion criteria

Those with known last menstrual period or first trimester ultrasonography screening and gestational age between 14-20 weeks were selected irrespective of parity. If menstrual history and examination findings were not correlating, ultrasonography was done to find the exact period of gestation. All the patients in the study were subjected to detailed history regarding age, parity, height, pre-pregnancy weight, and weight at the time of blood collection was noted down. Maternal education, religion, race, socio-economic status, family history of pre-eclampsia, past obstetric history, past medical history, smoking habit, medical histories of first degree family members and physical activity during pregnancy were noted. Systemic examination with special reference to edema, blood pressure and gestational week were carried out and routine antenatal investigations were done.

Exclusion criteria

Women with hypertension diagnosed before 20 weeks

of gestation, diabetes mellitus, multiple pregnancy and ultrasound proved congenital malformations were excluded.

Out of the 180 pregnant women selected initially, 164 women who completed their pregnancies and who delivered at our hospital were evaluated and statistically analyzed. Definitions were used for pregnancy induced hypertension and proteinuria. PIH was defined as systolic blood pressure of at least 140 mmHg with a >30mmHg rise and/or diastolic blood pressure of at least 90 mmHg with a rise of >15 mmHg occurring on two or more occasions after 20 weeks of gestation. Pre-eclampsia was defined as gestational hypertension and proteinuria of at least '2+' or 1 g/L on dipstick or 24 hour urinary protein excretion >0.3g. Fasting venous blood (3ml) was collected and tests were carried out on the same day.

Estimation of serum β hCG level was done by Enzyme linked immuno absorbent assay. The quantitative determination of chorionic gonadotropin in human serum was carried out by Microplate Immuno enzymometric assay, with kits obtained from Monobind, Inc Costa Mosa, CA 92627 (USA) through Lilac Medicare (P) Ltd. Serum Lipid profile estimation was done by Enzymatic Colorimetric Test with Lipid clearing factor (LCF) using kits marketed by Human Gesellschaft fur Biochemica and Diagnostica mbH Max – Planck – Ring 21 D65205 Wiesbaden, Germany. LDL – cholesterol and VLDL – cholesterol values in mg/dL are indirectly calculated. The cases were followed up regularly in the antenatal OPD till delivery. All the detailed data was collected from the delivery logbook, and data was analyzed statistically.

Statistical analysis

Mean $\pm$ SD of all the parameters of interest were calculated for PIH and for normal separately and difference of means between the two groups was tested by t-test.

Again, 25th and 75th percentiles with median values for all parameters were also calculated for each group separately and compared. A higher statistical formula – Multiple Logistic Regression Model was used to estimate the causal effect of each predisposing factor on response variables i.e., development of PIH or normotensive. Their effects were measured in terms of Odds Ratio (OR) for better and easy interpretation.

Results and Observation

Out of the 164 cases who completed the study, 29 cases developed PIH (termed as study group) while 135 cases remained normotensive.

Maximum PIH developed in the elderly primiparous group (52%) belonging to the age group of 31-35 years and the mean age $\pm$ SD was 27.17 ± 4.08 . Comparison of the weight, age and Hb% level for both the study and the normotensive groups are almost alike despite a slightly higher mean noticed in normal than that of PIH group (Figure 1).

Comparison of blood pressure at the time of booking (14-20 weeks) between the study and the normotensive group did not vary significantly. Blood pressure for PIH cases at the time of delivery was significantly higher in comparison to the BP of the normotensive group. This is true for both diastolic and systolic blood pressure readings. ($p=0.000$) (Table 1).

The prevalence rate of PIH increases as the level of maternal serum β hCG level increases. A 95% prevalence rate is observed in those women having serum β hCG level 40000 mIU/ml and above (Figure 2). The mean $\pm$ SD concentration of serum β hCG is increased very significantly ($P<0.0000$) in those women who developed

PIH (Table 2). Total cholesterol (TC) and very low density lipoprotein (VLDL) values for those women who developed PIH were found significantly higher than the corresponding TC and VLDL values for normotensive women ($p<0.000$ and $p<0.027$ respectively). Mean $\pm$ SD of triglyceride (TG) values was visibly higher in PIH group than that of the normotensive group. The mean value of high density lipoprotein (HDL) for both the groups was almost alike. Low density lipoprotein (LDL) for PIH group was found to be very highly significant ($p<0.0000$) (Table 2).

Median values for weight, age and Hb% were found to be the same for both the groups. However, median values of serum β hCG, TC, TG, VLDL and LDL for PIH group were found visibly higher than the corresponding values of normotensive group (Table 3).

Analysis of response variable, viz development of PIH or remaining normotensive through multiple logistic regression model shows that odds ratio for weight 1.127 shows that for one kg increase in weight, controlling other variables, there was a likelihood of developing 12.7% of PIH. Similarly with each year of advancing age a pregnant woman had 9.95% increasing chance of developing PIH as evident by $OR=1.099$. For unit increase in Hb%, a pregnant woman would have 28.8% decreasing chance of developing PIH.

Figure 1. Comparison of Mean $\pm$ SD of age, weight and Hb% between PIH and normal groups.

Table 1. Comparison of Mean $\pm$ SD of diastolic and systolic (mm/Hg) blood pressure between PIH patients and normal group.

Variable (B.P) Mean $\pm$ SD	PIH (n=29) Normotensive	Normal (n=135)	t-value	df	p-value
At 1st visit (14-20 wks)					
Diastolic	78.96 $\pm$ 3.93	77.24 $\pm$ 4.45	2.069	162	0.040*
Systolic	120.69 $\pm$ 8.42	122.81 $\pm$ 7.48	1.352	162	0.178
At Delivery					
Diastolic	98.66 $\pm$ 18.09	76.74 $\pm$ 5.15	12.077	162	0.000**
Systolic	165.52 $\pm$ 10.88	122.33 $\pm$ 7.08	26.805	162	0.000**

* Significant

** Very highly significant.

Figure 2. Showing the Serum βhCG levels in normotensive and of PIH and prevalence rate (%) of PIH.**Table 2. Comparison of Mean $\pm$ SD of Serum βhCG and serum lipid profile between PIH patients and normotensive women group.**

Variable	PIH (n=29) Mean $\pm$ SD	Normotensive Mean $\pm$ SD (n=135)	p-value
Serum βhCG	45103.45 $\pm$ 17028.01	21762.39 $\pm$ 6133.92	0.000**
TC	237.19 $\pm$ 33.95	204.15 $\pm$ 23.74	0.000**
TG	213.94 $\pm$ 51.07	197.78 $\pm$ 59.20	0.590
HDL	48.88 $\pm$ 11.76	48.08 $\pm$ 12.59	0.753
VLDL	52.70 $\pm$ 11.86	46.48 $\pm$ 13.08	0.27*
LDL	135.47 $\pm$ 27.12	109.30 $\pm$ 17.28	0.000**
Total Cholesterol (TC)		Triglyceride (TG)	High Density Lipoprotein (HDL)
Very Low Density Lipoprotein (VLDL)		Low Density Lipoprotein (LDL)	

Table 3. Comparison of median (25th–75th centile) of serum β hCG and serum lipid profiles between PIH and normal groups.

Variable	Unit	PIH (n=29) Median (25 th – 75 th centile)	Normotensive (n=135) Median (25 th – 75 centile)
Serum β hCG	mIU/ml	52000 (27500 – 55500)	22000 (18000 – 27000)
TC	mg/dL	238.40 (211.10 – 257.55)	200.20 (186.60 – 220.20)
TG	mg/dL	210.00 (180.10 – 237.40)	185.50 (157.20 – 202.20)
HDL	mg/dL	48.00 (38.45 – 60.25)	45.00 (37.50 – 60.00)
VLDL	mg/dL	48.48(45.02 – 63.60)	45.04 (35.20 – 58.33)
LDL	mg/dL	136.00 (109.88 – 156.50)	107.00 (100.80 – 117.10)

Table 4. Findings of Multiple Logistic Regression Model.

Variable	β	d.f.	P-value	OR
Weight (kg)	0.120	1	1.000	1.127
Age (Year)	0.095	1	1.000	1.099
Hb%	-0.346	1	1.000	0.712
Parity	-0.085	1	1.000	0.919
Diastolic (mm of Hg)	0.029	1	1.000	1.029
Systolic (mm of Hg)	0.016	1	1.000	1.017
Serum (1000) β hCG (mlu/ml)	0.101	1	1.000	1.107
TC mg/dl	0.119	1	1.000	1.126
TG mg/dl	0.003	1	1.000	1.003
HDL mg/dl	-0.121	1	1.000	0.886
VLDL mg/dl	0.117	1	1.000	1.124
LDL mg/dl	0.069	1	1.000	1.071
Diastolic at delivery	0.144	1	1.000	1.155
Systolic at delivery	1.620	1	0.998	5.055

Table 5. Comparison of percentage of detection of PIH using serum β hCG and dyslipidemia as indicators.

Variable	No. of PIH (n=29)	% of detection
Serum β hCG	21	72.41
Dyslipidemia	28	96.55

Z=251.45; p=0.000

With 1000 mIU/ml increase in serum β hCG a pregnant woman had 10.7% increasing chance of developing PIH (Table 4).

For the lipid profile, for one unit increase in total cholesterol and total triglycerides, a pregnant woman had 12.6% and 0.3% respective probability of developing PIH. For one unit increase in VLDL and LDL there is 12.4% and 7.1% increased change of developing PIH. On the contrary, with one unit increase in HDL, the woman had 11.4% less chance of developing PIH (Table 4).

Out of the 29 PIH cases 21 had elevated β hCG whereas 28 had dyslipidemia (Table 5). The percentage detection of PIH using β hCG and dyslipidemia as markers was 72.41% and 96.55% respectively and the difference between the two was found to be highly significant.

Discussion

A total of 164 pregnant women which included 65% primigravidas were recruited from antenatal OPD and antenatal ward. The cases were divided into the study group comprising of 29 pregnant women who subsequently developed PIH and the remaining 135 women who remained normotensive as the control group giving the prevalence rate of 17.68%.

It was evident from figure II that those pregnant women having very high serum β hCG level around 45000 mIU/ml at the second trimester of pregnancy would develop PIH. This is consistent with the findings of several authors^{2,5}. Patients with overt pre-eclampsia in the third trimester had increased maternal serum β hCG levels. There is general agreement that the placenta remains the main source of β hCG in patients with pre-eclampsia, but whether the cause of high circulating levels of hormone is placental overproduction is still debated. Some advocate that hCG secretion may be increased as a consequence of abnormal placental invasion or placental immaturity⁶. It may also be linked to the trophoblast response to hypoxia with the development of a hypersecretory state⁷. A role for placental factors is further supported by the findings of increased lipid peroxidation and oxidation stress in placentas of women with pre-eclampsia⁸. Compared with normal pregnancies, the placenta of patients with unexplained elevated maternal β hCG levels in the second trimester tend to be larger and tend to have an increased density of β hCG positive trophoblast along with an increased intensity of β hCG immunostaining within the placental

villi⁹. Our findings suggest a very strong correlation between serum β hCG and the risk of developing PIH. The risk factors and metabolic alterations are similar in pre-eclampsia and atherosclerosis and this might suggest a common pathophysiology. Oxidative stress secondary to reduced placental perfusion leads to endothelial dysfunction, linking the two stages of the syndrome¹⁰.

In the present study, we observed an association between maternal early pregnancy dyslipidemia, particularly hypertriglyceridemia, and the subsequent risk of pre-eclampsia. Pregnant women who subsequently developed pre-eclampsia had increased total cholesterol and LDL cholesterol concentrations as compared to pregnant women who remained normotensive. The expected inverse relationship between pre-eclampsia risk and HDL concentrations, however, was not evident. Our results, when taken together with those of earlier prospective studies indicate that dyslipidemia, particularly hypertriglyceridemia and elevated lipoprotein, precede the clinical manifestation of pre-eclampsia and thus may be of etiologic and pathophysiologic importance in this relatively common complication of pregnancy. The association between dyslipidemia and the risk of pre-eclampsia is biologically plausible and is compatible with what is known about the pathophysiology of pre-eclampsia. At least three hypothesized mechanisms for the dyslipidemia and pre-eclampsia association have been described in the literature. First, investigators have noted that elevated plasma lipid and lipoprotein may induce endothelial dysfunction secondary to oxidative stress¹¹. They also noted that dyslipidemia may impair trophoblast invasion thus contributing to a cascade of pathophysiologic events that lead to the development of pre-eclampsia.

The second mechanism is the pathologic process of pre-eclampsia via dysregulation of lipoprotein lipase resulting in a dyslipidemic lipid profile¹². Sera from pre-eclamptic women had both a higher ratio of free fatty acids to albumin and increased uptake of free fatty acids, which are further esterified to triglycerides¹³. A third possible mechanism may be via the metabolic syndrome. Metabolic characteristics of "insulin resistance syndrome" namely, hyperinsulinemia and hyperuricaemia are also present in pre-eclampsia¹⁴. Moreover, women with a history of pre-eclampsia, 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 delivery¹⁵. Thus, genetic and environmental factors that contribute to the pathogenesis of metabolic syndrome and related vascular disorders may also be important in determining the occurrence of pre-eclampsia.

Conclusion

The present study showed that maternal dyslipidemia as well as abnormally elevated maternal serum β hCG at second trimester are very good noninvasive predictors of PIH. However, considering the percentage of detection, the divergent points of maternal serum β hCG, with wide range of cut-off values, dyslipidemia seems to be a more efficient marker in predicting PIH at second trimester. It may be concluded that the estimation of maternal lipid profile in early second trimester will bring about early recognition of patients at risk of PIH before the clinical syndrome and complications of PIH appear for a better fetomaternal outcome.

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