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Elevated serum βhCG and dyslipidemia in second trimester as predictors of subsequent Pregnancy Induced Hypertension

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Abstract

Objectives: To test the hypothesis that pregnant women with high serum βhCG level and serum dyslipidemia in second trimester are more prone to develop subsequent Pregnancy Induced Hypertension (PIH). Materials & Methods: One hundred pregnant women with singleton pregnancy between 14 and 20 weeks of gestation attending antenatal outpatient department (OPD) of SMCH were studied. Serum βhCG was estimated by two-site chemiluminescent-immunometric method. Serum lipid profile was evaluated by enzymatic colorimetric test with Lipid Clearing Factor (LCF). Results: Eighteen cases developed PIH while eighty two cases remained normotensive. The serum βhCG level was significantly high ($p<0.001$) in those women developing PIH. Serum concentration of total cholesterol in women who subsequently developed PIH was significantly higher than that of normotensive group ($p <0.05$). Mean TG value in PIH group was higher than the normotensive group. Level of LDL in PIH group was also significant ($p<0.05$). Conclusion: Present study showed that elevated serum βhCG and Dyslipidemia in second trimester can be considered as predictors of subsequent PIH / Pre-eclampsia. However, there is need of large community based prospective study to validate the result.

Introduction

Hypertensive disorder of pregnancy (HDP) is one of the commonest complications of pregnancy with adverse feto-maternal consequences. It complicates 5 to 10 percent of all pregnancies.[1] There is ethnic disparity of the occurrence of hypertensive disorders in pregnancy as well as in the non-pregnant state.[2,3] It is well established that hypertensive disorder, haemorrhage and infections form a deadly triad that contributes about 57% of maternal mortality in India.[4] About 10% of maternal death is contributed by complications of pregnancy related hypertension in our country.[4] Moreover, half of this hypertension related death is preventable.[5]

The etiologic of pre-eclampsia is still not clear. Considering the high importance of complication during pregnancy, a quite a large number of studies have been performed to evaluate risk factors of high maternal age, young primipara, older multipara, race, genetic factors, environmental factors, obesity, poverty and chronic hypertension all to be considered as contributory.[6-8]

The identification of this clinical condition and its effective and prompt management play a vital role in the outcome of pregnancy. Delineation of a reliable and safe screening test for PIH has been an investigators' dream for many a years. The screening methods that have been tested by many researchers include varieties of biophysical and biochemical tests such as uterine artery doppler velocimetry, anticardiolipin antibodies, urinary kallikrein, placental protein-13, anti-angiogenic factors like-soluble vascular endothelial growth factor receptor-1 (VEGFR-1) (also referred to as sFlt-1), anti-angiotensin II receptor autoantibodies (AT1-AA) pro-angiogenic factors like vascular endothelial growth factors (VEGE) and PIGE and asymmetricdimethylarginine (ADMA), soluble form of $CD_{105.}$, cell free fetal DNA. Inspite of the availability of many modalities for screening none is sensitive and specific enough to be used as a screening method, especially in the low risk group.

In view of the above, we conducted a study to estimated maternal serum beta human chorionic gonadotrophins (βhCG) levels and serum lipids and their combined value during 14 to 20 weeks of pregnancy to ascertain the association with subsequent pregnancy induced hypertension (PIH) / preeclampsia.

Materials and Methods

A prospective analytical study was conducted in the department of Obstetrics & Gynecology, Silchar Medical College & Hospital, Assam, India from September 2010 to August 2011. This government hospital caters the needs of lower-middle class socio economic people. It is also a referral centre in this region.

Selections of cases: A total of 100 pregnant women who attended the antenatal clinic/ or emergency outpatient department (OPD) or admitted in the department of Obstetrics & Gynecology of Silchar Medical College & Hospital were selected for the study. An informed consent was taken from the each subject/guardian. The study protocol was approved by institutional ethics committee before enrollment of subjects.

Sample size: The minimum estimated number of study subjects was calculated by standard formula: $n = (4pq)/d$,[2] where p is the prevalence of PIH (18%) as reported earlier;[5] $q=1-p$ and d is the desire precession (8%). An additional, 10% subjects was added to strengthen the study design. Therefore, final sample size is (91+9) 100 subjects.

Inclusion criteria: Pregnant women with known last menstrual period or first trimester ultrasonography screening and gestational age between 14-20 weeks were selected irrespective of parity. All the pregnancies were dated by last menstrual period (LMP) where examination findings were correlated. Ultrasonography was done to measure the crown-rump length (CRL) (±3.5 days) where it was not consistent with menstrual dating. All the patients in the study were subjected to detailed history taking regarding age, parity, height, pre-pregnancy weight and weight at the time of blood collection was made and recorded. Maternal education, religion, race socio-economic status, family history of pre-eclampsia, past obstetric-medical history, smoking habit, medical histories of first degree family members and physical activity during pregnancy were collected through semi-structured interview schedule. Systemic examination with special reference to edema and blood pressure were carried out and routine antenatal investigations were done.

PIH was defined as systolic blood pressure of at least 140mmHg and/or diastolic blood pressure of at least 90 mmHg, occurring on two or more occasions after 20 weeks of gestations.[1]

Exclusion criteria: Pregnant women with hypertension diagnosed before 20 weeks of gestation, diabetes mellitus, multiple pregnancies and ultrasound scanned congenital malformations were excluded.

Laboratory analyses: estimation of serum β hCG level was done by a solid phase, two-site chemiluminescent-immunnometric assay with the help of Immulite 1000 HCG. Enzymatic colour test for the quantitative determination of serum total cholesterol, triglyceride and HDL cholesterol was done with the help of OLYMPUS analyzers. The values of VLDL and LDL cholesterol in mg/dl were calculated indirectly. Cholesterol reagent OSR6516 for use on the AU2700 and AU5400 systems only was used in our evaluation of lipid profile.

Statistical analysis: Data was presented in terms of mean ± SD for PIH and for normotensive cases separately. To analyse the result of our study statistically, we used independent t-test, p-value, degree of freedom and binomial logistic regression analysis. Student t-test was employed to compare the mean between PIH and normotensive cases. The Binomial Logistic Regression analysis was used to estimate the casual effect of each predisposing factor on response variable i.e. development of PIH / Preeclampsia or remained normotensive. Their effects were measured in terms of Odds Ratio (OR) for better and easy interpretation. P-value <0.05 was considered as statistically significant.

Results

The present study includes 100 pregnant women at 14-20 weeks of gestation. Among them 18 women (18%) developed subsequently PIH/ pre-eclampsia while 82 women (82%) remained normotensive. Both the groups were comparable at baseline with respect to physical and other clinical parameters. Comparison of mean ± SD for blood pressure at the time of enrolment (14-20 weeks) between the PIH and normotensive group does not differ significantly except a higher diastolic blood pressure in PIH/Pre-eclampsia group at this stage. Both diastolic and systolic blood pressure for PIH at the time of delivery is significantly higher than the level of the normotensive group (Table-I).

In this study prevalence rate of PIH/Pre-eclampsia increases as the level of maternal serum β increases, 95% prevalence rate in those women having serum βhCG level 40,000 mlU/ml and above. The mean ± SD concentration of serum βhCG is higher significantly ($p<0.0004$) in those women who developed PIH/ Pre-eclampsia. It is evident that women having very high serum βhCG levels, at an average 42000 mlU/ml at second trimester developed PIH/pre-eclampsia subsequently (Table-I).

Comparison of mean±SD of serum lipid profile between PIH/pre-eclampsia and normotensive

group showing TC and VLDL values for those women who developed PIH/pre-eclampsia were found to be significantly higher than the corresponding TC values for normotensive women. (p=0.0154) but not in the case of VLDL (p=0.0713) (Table-I). Mean TG value is visibly higher in PIH/pre-eclampsia groups than that of the normotensive group. The, mean value of HDL for the groups are alike. It was observed the level of LDL for PIH group is found to be statistically significant (p=0.0208). From these interpretative findings it may be logically be deducted that those women who are having high serum lipid at second trimester are more prone to develop PIH (Table-I).

Table I: Physical, clinical & biochemical characteristics of the studied patients

Variables	PIH / Pre-eclampsia (n=18) Mean ± SD	Normotensive (n=82) mean ± SD	p-value
Weight (Kg)	50.5±4.94	52.45±5.06	0.140
Age (years)	26.11±4.26	28.71±5.03	0.044
Hb %	10.28±0.80	10.16±1.37	0.721
Blood pressure during 14 to 20 weeks:			
Diastolic (mmHg)	76.67±4.85	76.09±5.83	0.695
Systolic (mmHg)	116.11±6.98	122.03±7.76	0.003
Blood pressure at delivery:			
Diastolic (mmHg)	101.67±6.18	76.34±5.77	0.0001
Systolic (mmHg)	167.78±12.15	121.91±8.03	0.0001
Bio-chemical parameter:			
Serum βhCG	41833.33±19.25	24876.83±17.51	0.0004
TC (mg/dl)	223.55±46.75	204.10±25.56	0.0154
TG (mg/dl)	202.23±74.30	183.77±40.73	0.1449
HDL (mg/dl)	52.81±9.65	48.73±11.56	0.1668
VLDL (mg/dl)	41.39±12.61	37.31±7.48	0.0713
LDL (mg/dl)	131.58±30.77	116.55±23.07	0.0208

Based on the binomial logistic regression analysis (Table II), it was observed that the odds ratio for weight is 0.738. This means that for one kg increase in weight, controlling other variables, there was likelihood of decreasing 30.3% of PIH. Similarly, with each year of advancing age, a pregnant woman had 14.4% decreasing chance of developing PIH as evident by odds ratio of age is 0.866 in the table - II. In contrast each number of increasing parity, a pregnant woman had 123% greater risk of developing PIH. Also, with 1000 mlU/ml increase in serum βhCG (OR=1.231; 95% CI=0.000- 3.498), a pregnant woman had 20.8% increasing chance of developing PIH. For the lipid profiles, for one unit increase in total cholesterol (OR=1.003; 95% CI=0.000-6.935) and triglycerides (OR=1.003; 95% CI=0.000- 1.590), a pregnant woman had 0.3% chance of developing PIH. For one unit increase in HDL, it was 7% less chance of developing PIH whereas for one unit of LDL (OR=0.936; 95% CI=0.000- 6.342), there was 6.6% less chance of developing same. On the contrary, with one unit increase in VLDL, a pregnant woman had 29.8% increased chance of developing PIH.

Table II: Binomial logistic regression analysis of maternal characteristics and hypertension status (PIH vs normotensive)

Variables	B	Odds Ratio*
Weight (kg)	-0.303	0.738
Age (years)	-0.144	0.866
Hb%	0.128	1.137
Parity	1.257	3.516
Serum β-hCG (1000 mlU/ml)	0.208	1.231
TC (mg/dl)	0.003	1.003
TG (mg/dl)	0.003	1.003
HDL (mg/dl)	-0.070	0.933
VLDL(mg/dl)	0.298	1.347
LDL (mg/dl)	-0.066	0.936

* Reference category (normotensive)

In this study comparison of percentage of detection of PIH out of 18 PIH cases that had elevated serum, βhCG or maternal dyslipidemia at early second trimester, from the sample of 100 pregnant women, 11 women developed PIH resulting to abnormally elevated maternal serum βhCG against 9 cases due to dyslipidaemic profile in early second trimester. The respective percentage is 61.1% and 50.0%. This variation of percentage was tested by Z-test (proportional) and found to be significant.

Discussion

In this study, a total of hundred (100) pregnant women were recruited from antenatal-OPD. Obviously the limitations of our study are that the sample size was small and the age of the patient was not matched. But still we tried to allocate the cases to either PIH group or normotensive group. PIH group comprising of eighteen (18) pregnant women who subsequently developed PIH/Pre-eclampsia reflecting the prevalence rate of PIH of fifteen percent which closely represent prevalence rate of PIH in India.[9]

Several studies worldwide have reported that parity is an important risk factor for pre-eclampsia.[8,10,11] It is more often developed at young primiparous and older multiparous. However, multiparity is not a modifiable variable in the clinical set up. More importantly, pregnant women having serum β hCG level around 42,000mlU/ml (14-20 weeks) subsequently developed PIH. This is consistent with the findings of several other studies done in other ethnic group of India.[12-15] Evidence points to the placenta as a key source of factors that lead to the maternal endothelial cell destruction in pre-eclampsia. This is already established that the clinical signs and symptoms of pre-eclampsia remit after termination of pregnancy.

Patients with overt pre-eclampsia have been seen with increased maternal serum β-hCG level mainly in the third trimester. Study revealed that the

placenta is the main source of β-hCG in the pre-eclamptic patients but whether this high circulating levels of beta hCG is due to placental overproduction, is not known. Some advocated that hCG secretion may be increased as a consequence of impaired trophoblastic invasion or placental immaturity.[13] It might result from the trophoblastic response to hypoxia with the development of a hyper secretory state.[13] A role for placental factors is further supported by findings of increased lipid peroxidation and oxidation stress in placenta of women with pre-eclampsia.[16]

Compared with normal pregnancies, the placenta of patients with unexplained elevated maternal β-hCG level in the second trimester tend to be larger in size and to have an increased density of β-hCG positive trophoblast along with an increased intensity of β-hCG immunostaining within the placental villi.[17] It was observed that a strong co-relation between serum β-hCG and risk of developing PIH/ pre-ecalmpsia. In this study, data are consistent with that of other investigators regarding hCG as marker of pregnancy induced hypertension.

In the present study, it also observed the co-relation between maternal serum dyslipidemia at (14-20 weeks) and subsequent PIH. Except Triglycerides, total cholesterol, HDL and LDL cholesterols were high during pregnancy.[18] But the pregnant women who subsequently developed PIH had been seen to have more increased serum level of total cholesterol (TC), Triglyceride (TG), VLDL and LDL-cholesterol (14-20 weeks) in comparison to pregnant women who remained normotensive in the same pregnancy. This observation regarding serum lipid profile alteration is in conformation with the reports of several other studies in India as well as in abroad.[13,19-23]

Conclusion: The present study showed that elevated level of serum βhCG and dyslipidemia in early second trimester can be considered as predictors of subsequent PIH/Pre-eclampsia. There is a need of large community based prospective studies to evaluate multiple markers for screening of PIH/Pre-eclampsia and if it predict those mothers who subsequently developed PIH/Pre-eclampsia in the earlier part of pregnancy; they may be benefited by close monitoring as well as by anti platelet drugs.

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