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Original Research Article

Evaluation of the variations and potential clinical use of second trimester serum markers for the detection of pre-eclampsia

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ABSTRACT

Background: In many areas of world, hypertensive disease in pregnancy is the single most common cause of maternal death. Pregnancy associated hypertension remains unsolved despite decades of intensive research and remains the most significant problem in obstetrics. The aim of present study is to evaluate the variations and potential clinical use of second trimester serum markers for the detection of pre-eclampsia.
Methods: In an observational study, estimations of serum of human chorionic gonadotropin (β-hCG) were done in 347 randomly selected women at 13-20 weeks of gestation in august 2015 to may 2016. Multiple of median (MOM) was calculated from charts of norms available for that weeks of pregnancy. The subjects were followed up till delivery for the development of hypertension in pregnancy and results analysed statistically with Chi-square test.
Results: Out of 347, 47 women developed hypertyension and 2MOM of β hCG was significantly (P<0.001) elevated in those who developed hypertension compared to normotensive women. In our study group a significant associations between elevations in second trimester β-hCG and development of hypertension was observed. Thus with second trimester serum marker study, prediction of pre- eclampsia is possible at incipient stage and adverse pregnancy outcome can be minimized.
Conclusions: Maternal serum β-hCG level was found to be significantly higher in hypertensive group than normal group.

Keywords: β-hCG, Observational study, Pregnancy, Preeclampsia

INTRODUCTION

Hypertension in pregnancy is a unique disease seen only in pregnancy affecting 12-15% of all pregnant women. In spite of improvement in maternal and neonatal care, preeclampsia and its sequelae are a dreaded complication of pregnancy. It is indeed a constant endeavour of obstetricians to identify the risk involved in pregnancy and if possible its prediction. If prediction becomes possible, prevention will follow naturally. Several tests have been proposed but none has been accepted widely due to their low predictive value. Pre-eclampsia is a pregnancy specific disorder characterized by newly onset of blood pressure more than 140/90 mmHg, in at least two consecutive occasion and proteinuria (> 300 mg per 24 hours collection) after 20 weeks of pregnancy gestational hypertension is a major pregnancy complication associated with significant fetal risks and maternal morbidity and mortality.[1-3] It is responsible 25% of all fetal growth retardation and 15% preterm birth in developed countries. The incidence of pre-eclampsia in India is about 8-10% and maternal mortality due to be reported 8%.[4] Placentas is the known primary trigger of gestational hypertension. Recent placental transcriptome theory supports the view.[5] The abnormal placentation has been considered as one of the initial event in the disease

process. Hsu et al, hypothesized that during mid trimester, immunological changes occur in the trophoblasts, resulting in secretory response, which is seen as a rise in the beta hCG levels.[6]

The human chorionic gonadotropin (hCG) is a glycoprotein composed of two non covalently linked subunits, α and β, and is produced by syncytiotrophoblast cells of the placenta. Maternal serum hCG peaks at 8 - 10 week of gestation and then declines to reach a plateau at 18 - 20 wk of gestation. The free β-subunit can derive from three sources, namely, direct trophoblast cell production, dissociation of hCG into free α- and free β-subunits, and by macrophage or neutrophil enzymes nicking the hCG molecule.[7] The free β-hCG circulating in maternal serum corresponds to only about 0.3-4% of the total hCG.[8,9]

In pre-eclampsia histological examination reveal focal cellular necrosis in the syncytiotrophoblast and increased mitotic activity with cellular proliferation in the cytotrophoblast.[10] In addition the proliferating trophoblast in severe preeclampsia is rapidly transformed into syncytiotrophoblast within 72 hours. The normal placenta differentiates during pregnancy with the cytotrophoblast dominant in early gestation and the syncytotrophoblast dominant in late pregnancy. Placental vascular damage leading to decreased oxygen supply might result in increased hCG production by hyperplasic cytotrophoblastic cells.[11]

There is a strict relationship between PIH and elevated serum β-HCG levels, indicating that there should be an abnormal placental secretary function in patients with severe pre eclampsia. Understanding the disease process and the impact of hypertensive disorders on pregnancy is of the utmost importance, because these disorders remain a major cause of maternal and perinatal morbidity and mortality worldwide. There has been an exponential increase in basic science literature exploring etiology of pre-eclampsia, yet it remains a disease of theories. Many etiological (genetic, nutritional, immunological and infectious) and pathophysiological (abnormal placentation, oxidative stress and endothelialdysfunction) pathways have been proposed as causal hypotheses for pre-eclampsia.[1,4]

Hypertension in pregnancy is one the most common ailments encountered during pregnancy, complicating 10-15% of pregnancies

WHO reviews hypertensive disorders of pregnancy causes 16% of maternal mortality (greater than hemorrhage 13%, abortion 8%, sepsis 2%).

Complications of pre-eclampsia include eclamptic seizures, intracerebral hemorrhage, liver cell damage, DIC, pulmonary edema and acute renal failure. But importantly, it is reported now that half of this hypertension related deaths are preventable. At present there is no reliable screening test for hypertensive disorder of pregnancy during second trimester.

In our Indian set up where the follow up is poor, an initial screening test like serum β HCG levels may help in categorising patients that require more attention.

METHODS

This present study was conducted in Department of Obstetrics and Gynaecology St Stephens hospital delhi. This present observational prospective study was done on 347 pregnant, normotensive, non-proteinuric women selected randomly between the gestational age of 13-20 weeks and the cases were followed till delivery for the development of hypertension. A structured interviewer administered questionnaire was filled for all the patients to obtain information on age, educational status, parity, occupation, ethnic group, gestational age, body mass index (BMI) and cell phone number. All pregnant women age above 18 years and below 35 years, primi gravida and multigravida were included. Women with multiple pregnancy, congenital malformation, extreme hypertension, diabetes mellitus and history of Down syndrome were excluded from the study. Gestational age was calculated from the reliable menstrual history dates and early ultrasonographical measurement of fetal crown-rump length. Urinalysis for protein and glucose was done at subsequent visits when blood pressure was found to be elevated, i.e., 140/90 mmHg .Blood pressure was done by Richter's mercury sphygmomanometer, the gold standard for measuring blood pressure with a properly sized cuff and the patient in a seated position. Hypertension disorder of pregnancy was identified in case of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions at least four hours apart. The Korotkov phase IV which is the fading of the blood flow murmur is recognized as the diastolic blood pressure. The beta- HCG estimation in maternal serum was done by chemiluminescent immunometric assay (CLIA) method. Multiple of median (MOM) was calculated from the median of the diagnostic test employed for the current study (Diagnostic Products Corporation, U.S, Immulite 2000- HCG), having the central 95% values accuracy.

Results were evaluated and analyzed statistically. Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean±SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The comparisons of normally distributed continuous variables between the groups were performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann Whitney U test. A receiver operating characteristics (ROC) analyses were calculated to

determine optimal cut-off value for beta HCG. The area under the curve, the sensitivity, and the specificity were also being calculated to analyze the diagnostic value of beta HCG levels. Odds ratio and 95% CI was also be done. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

347 women were enrolled and completely followed till term. Whether they developed preeclampsia or not. Out of 347 women, 47 women developed PIH. Out of 47 PIH patients 33 patients developed non severe PIH and 14 patients developed severe PIH. Incidence of PIH in our hospital was found 13.5%. Incidence of non-severe PIH was 9.5% and of severe PIH was 4%. (Table 1 and 2)

Table 1: Incidence of pre-eclampsia.

Groups	Frequency	%
Normal	300	86.5%
PIH	47	13.5%

Table 2: Incidence of severe and non-severe pre-eclampsia.

Groups	Frequency	%
Severe pre-eclampsia	14	30%
Non-severe pre-eclampsia	33	70%

In present study majority of antenatal women were in 26-30 years (47.7%) of age group. Majority of patients developing non severe preeclampsia were in 26-30 years age group and majority of patients developing severe preeclampsia were in 20-25 years age group.

No statistically significant difference was seen in age distribution of severe, non-severe preeclampsia and normal patients. But 47.7% patients developed non-severe pre-eclampsiain 26-30 years age group and 35.7% patients developed severe preeclampsia in 20-25 years age group.

The mean value of maternal serum level of β-hCG in pre-eclamptic group was significantly higher than the normal group (p=<0.001) (Table 3).

Table 3: Maternal serum level of β-hCG in normal and pre-eclamptic group.

	PIH				P value	
	Normal	Total preeclampsia	Non severe	Severe	Normal Vs PIH	Normal, severe and Non severe PIH
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	<0.001	<0.001
HCG	25992±14985	38498±18749	38914±17182	37517±22710		

Table 4: Multiple of median value of maternal beta HCG.

MOM	Preeclampsia				P value	
	Normal Frequency (%)	Total Frequency (%)	Non severe Frequency (%)	Severe Frequency (%)	Normal Vs Preeclampsia	Normal, severe and non severe preeclampsia
<=2	282 (94%)	27 (57.4%)	20 (60.6%)	7 (50%)	<0.001	<0.001
>2	18 (6%)	20 (42.6%)	13 (39.4%)	7 (50%)		
Total	300 (100%)	47 (100%)	33 (100%)	14 (100%)		
Chi square test P value-<.001						

Table 5: Distribution of patients according to <=2 MOM and >2 MOM.

MOM	Normal		Preeclampsia	
	Frequency	%	Frequency	%
<=2	282	94.0%	27	57.4%
>2	18	6.0%	20	42.6%
	300	100%	47	100%

Table 6: Maternal serum level of ≥2mom of β-hCG as a predictor test for pre-eclampsia.

Sensitivity	Specificity	PPV	NPV	Accuracy
42.6%	94.0%	52.6%	91.3%	87.0%

Among PIH of 47 patients ≥2MOM value of beta hcg was found in 27 patients that was found statistically significant. 18 patients with ≥2MOM value of beta hcg were found normotensive (Table 4).

In our study sensitivity and specificity of ≥2MOM value of beta hcg as second trimester preeclampsia predictor was found 42.6%, and 94%, accuracy of test is found 87% (Table 6).

In our study 20 cases out of 47 (42.6%) with values of beta HCG ≥2MOM developed PIH 18 cases out of 300 (6%), having a beta HCG value ≥2MOM. The difference was found statistically significant.

DISCUSSION

Since the year 1950, HCG is reported to be elevated in toxemic pregnancy. In preeclampsia the rise of blood pressure is due to vasoconstriction and impaired angiogenesis leading to hypoxia and hyperplasia of trophoblastic cells which causes hyper secretion of placental hormone ultimately leading tohigh level of circulation β-hCG. In pre-eclampsia, the cytotrophoblast transformed into syncytiotrophoblast. Human placenta synthesizes steroid, protein, and glycoprotein hormones throughout gestation.[12] The production of hCG by the placenta in early pregnancy is critical for implantation and maintenance of the blastocyst. Since it is postulated that preeclampsia is likely a trophoblastic disorder. RemziGokdeniz et al, found a strict relationship between severe pre - eclampsia and elevated serum β - hCG levels, indicating that should be an abnormal placental secretary function in patients with severe pre - eclampsia.[13] In 1934, Smith et al talked about increasing hCG levels in severe preeclampsia for the first time.[14]

In our study women with higher levels of beta HCG (≥2 MOM) during the second trimester of pregnancy, developed PIH later in their pregnancy, with P value <0.001 which was statistically highly significant. 42.6% of women with elevated levels of beta HCG developed PIH with sensitivity 42.6%, specificity 94% and the positive predictive value 52.6%.

In a study by Kaur G. et al, they found sensitivity was 90.91%, specificity was 97.44% and positive predictive value was 83.33% for beta HCG as mid trimester predictor test.[15]

In a study conducted by Chaudhari et al, they observed that the higher absolute levels of beta HCG strongly correlate with occurrence of gestational hypertension. Out of 190 Pregnant women, 25 women who developed gestational hypertension were having higher absolute levels of beta HCG as compared to 165 pregnant women who did not (Mean±SD; 54907±29509 vs 41095±19103; p<0.001).[16]

In a study conducted by Ashour et al on 6286 non-diabetic women with singleton pregnancies, the sensitivity of beta-human chorionic gonadotropin as a screen for development of hypertension was 15.6%, the specificity was 90.0%, and the positive predictive value was 12.8%.[17]

Sharma V et al in their study observed that out of 387 cases with beta-HCG levels 2MOM, 49 cases (81.67%) developed pregnancy induced hypertension (p<0.001).[18]

In our study, 20 cases out of 47 (42.6%) with values of beta HCG ≥2MOM developed PIH 18 cases out of 300 (6%), having a beta HCG value ≥2MOM. The difference was found statistically significant.

CONCLUSION

The study concluded that measuring second trimester serum Beta- HCG levels is a good predictor of pregnancy induced hypertension and helps in risk stratification of women destined to develop pregnancy induced hypertension in the same pregnancy. Thus these women can be followed up in a tertiary care centre for further management of beta HCG which is associated with severity of PIH.

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