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The Ability of Biochemical Markers of the First and Second Trimesters, in Particular Beta hCG to Predict Hypertensive Disorders of Pregnancy

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ABSTRACT
Several biochemical markers measured in the first and second pregnancy trimester have been used to predict occurrence of GH/PE in the later course of pregnancy. Still, although different biomarkers of placental function and vascularisation have been associated with GH/PE occurrence in the literature data, few are used diagnostically in routine clinical settings. All women satisfying the inclusion criteria are enrolled into the study. Informed consent obtained from the women. The details required for the clinical study were obtained with the help of a preform, which contained the demographic details, details of clinical symptomatology, past history, personal history, drug history, clinical examination details, laboratory investigations and imaging studies and the treatment details. ß-hCG and the statistical characteristics of the ß-hCG for prediction of PIH were calculated. The sensitivity of the study was 73% with a specificity of 100%. The positive predictive value and the negative predictive value were 100% and 89% respectively.

INTRODUCTION

The clinical syndrome of hypertensive disorders of pregnancy mostly develops in the third pregnancy tri mester, but in some women can be apparent in the first half of pregnancy, which is a more severe condition[1]. Many underlying factors causing gestational hypertension and preeclampsia actually already exist from early weeks of gestation in many patients. However, there is currently no reliable screening method in the first trimester of pregnancy with sufficient accuracy to identify women at high risk of developing gestational hypertension (GH) or pre eclampsia (PE)[2]. Several biochemical markers measured in the first and second pregnancy trimester have been used to predict occurrence of GH/PE in the later course of pregnancy. Still, although different biomarkers of placental function and vascularisation have been associated with GH/PE occurrence in the literature data, few are used diagnostically in routine clinical settings. The most commonly assessed in daily practice are those biochemical markers that are already proven as predictors of genetic aberrations and adverse pregnancy outcomes incorporated in first and second trimester screening. However, heterogeneous results from different studies have been obtained and therefore, relevance of placental biomarkers is not still defined. Further research should clarify the reliability and usefulness of these biochemical markers for GH/PE prediction[3,4]. Chorionic villi is the one that is needed for development of preeclampsia. Fetus is not an important factor. Human chorionic gonadotropin is synthesized from syncytiotrophoblast in chorionic villi. Incomplete trophoblastic invasion that is replacement of vascular endothelial and muscular linings by endovascular trophoblast to enlarge the vessel diameter is incomplete[5,6]. The aim of our study was to estimate the ability of biochemical markers of the first and second trimesters, in particular Beta hcg to predict hypertensive disorders of pregnancy.

MATERIALS and METHODS

Type of Study: A prospective observational study.

Sample Size: 150 patients.

Inclusion Criteria: Primigravida and mutligravida with singleton pregnancy with gestational age 14-20 weeks as determined by last menstrual period or ultrasound scan.

Those with past history of

- PIH remote from term.
- Recurrent spontaneous abortion.
- Recurrent still births.
- Accidental haemorrhage.
- IUGR.
- Those with the family history of PIH.
- Elderly primi-gravida more than 35yrs.

Exclusion Criteria:

- Gestational age <14weeks and >20 weeks.
- H/O chronic hypertension.
- IVF.
- Multiple pregnanices.
- Diabetes mellitus.
- Congential abnormalities.
- Preexisting renal disease.
- Cardiovascular disease.

Methods of Collection of Data: All women satisfying the inclusion criteria are enrolled into the study. Informed consent obtained from the women. The details required for the clinical study were obtained with the help of a proforma, which contained the demographic details, details of clinical symptomatology, past history, personal history, drug history, clinical examination details, laboratory investigations and imaging studies and the treatment details. All the women were subjected to detailed history regarding age, parity, past obstetric history, medical history and family history. Routine clinical examination included measurement of Height, weight, blood pressure. Routine antenatal investigations were carried out. 5 ml of venous blood sample was collected and tests were done. Estimation of serum ß hcg level was done by enzyme linked fluorescence immunize. The cases were followed up in antenatal clinic and were examined 4 weekly till 28 weeks, fortnightly up to 34 weeks and thereafter weekly till delivery. At every visit, blood pressure was recorded and urine was examined for albumin. PIH included gestational hypertension and preeclampsia. Gestational hypertension was defined as blood pressure more than 140/90mmHg on two occasions at least 6 hours apart after 20 weeks of gestation. Preeclampsia was defined as gestational hypertension and proteinuria of at least 1+on dipstick. The patients who developed preeclampsia were followed till 6 weeks after delivery.

RESULTS and DISCUSSIONS

Table 1: Comparison of ß-hCG Among PIH and Normal Women

Parameters	PIH		Normal		Mann-Whitney U Test	
	Mean	Std. Deviation	Mean	Std. Deviation	P Value	Significance
Beta hCG (mIU/ml)	122385.6	152776.7	23461.1	15458.3	P<0.001	Highly Sig

The above table and the chart depicts the distribution of the levels of ß-hCG amongst the PIH and normal women. The mean values in the normal women was 23461.1mIU/ml with a standard deviation of 15458.3mIU/ml which is very low compared to the PIH group which had amean of 122385.6mIU/ml with a standard deviation of 152776.7mIU/ml. The P value was <0.001, which is statistically very significant. This indicates that a strong correlation exists between the ß-hCG and the PIH (Table 1).

In the above table and the chart, the distribution of the subjects, in the PIH and in the normotensive group,

Table 2: Distribution of Study Subjects According to Different Levels of ß-hCG

Beta hCG (mIU/ml)	PIH		Normal		
	N	%	N	%	Total
< 20000	0	0	51	44.3	51
20000-30009	0	0	43	37.4	43
30000-39999	0	0	11	9.6	11
40000-49999	0	0	5	4.3	5
50000-59999	0	0	2	1.7	2
60000-69999	0	0	0	0	0
70000-79999	4	11.4	1	0.9	5
80000-89999	2	5.7	1	0.9	3
90000-99999	22	62.9	0	0.0	22
=100000	7	20.0	1	0.9	8
Total	35	100.0	115	100.0	150

Chi Square test P<0.001, Highly Sig

according to the levels of ß-hCG which are plotted at 10000mIU/ml intervals. In the group of normal women majority had their ß-hCG values on the lower side as opposed to the women in the PIH group who had values on the higher side. About 81.7% of women in the normotensive group had ß-hCG values less than 30000mIU/ml. Conversly in the PIH group about 82.9% of the women had ß-hCG value above 90000mIU/ml. The P value calculated was <0.001 which is highly significant. From third it can be made out that, with increasing values of ß-hCG the probabilities of PIH increases (Table 2).

Table 3: Comparison of ß-hCG with SBP/DBP at Booking and at Delivery

	Correlation between ß HCG with booking SBP and DBP and with at delivery SBP and DBP			
Time	Variable-1	Variable-2	r Value	Sig
At booking	ß HCG	SBP	-0.079	P>0.05
	ß HCG	DBP	-0.099	P>0.05
At delivery	ß HCG	SBP	0.407	P<0.001
	ß HCG	DBP	0.431	P<0.001

The above table shows the relation of ß-hCG measured at booking or at delivery with that of the SBP and DBP. The P value of ß-hCG for SBP/DBP measured at the time of booking the case, was >0.05, which was statistically not significant. In contrast the ß-hCG for SBP/DBP measured at the time of delivery was <0.001 which was statistically significant. Thus indicating a good correlation between the ß-hCG measured at the midtrimester and the SBP/DBP measured at the time of delivery. This shows the credibility of ß-hCG in prediction of the PIH (Table 3).

Table 4: Distribution of PIH in Relation to the Cut-off ß-hCG

PIH	Beta hCG (mIU/ml)		
	≥35000	< 35000	Total
Present	35	0	35
Absent	13	102	115
Total	48	102	150

Table 5: Attributes of ß-hCG Calculated in the Study

Sensitivity	73%
Specificity	100%
Positive predictive validity	100%
Negative predictive validity	89%
Diagnostic Accuracy	91%
AUC	86%

In the above tables the distribution of the study subjects amongst the group with PIH and group without PIH plotted with respect to the cut-off ß-hCG and the statistical characteristics of the ß-hCG for prediction of PIH were calculated. The sensitivity of the study was 73% with a specificity of 100%. The positive predictive value and the negative predictive value were 100% and 89% respectively (Table 4,5).

The abnormal placentation has been considered as one of the initial event in the disease process. Hsu[1] 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. In this study we have tried to nd out whether beta HCG can predict the development of PIH[7]. Our study comprised of 150 study subjects who were in the 13-20 weeks of gestation, attending the antenatal clinics in the department of obstetrics and Gynecology. Out of the study sample, 90.7% i.e., 136 women belonged to the age group of 21-30 years. The age distribution pattern is comparable to other studies which had similar pattern of age distribution[8]. With respect to the socioeconomic status a major portion of the study subjects belonged to the class II and class III. On statistical analysis there was a good correlation between the socioeconomic status and the occurrence of PIH, which has been found in many literature works. The study had a evenly distributed population with respect to the parity having 75 each of primi and mutligravida. In case of parity and PIH, no significant correlation was observed in the present study which is in terms with other studies. The blood pressure recorded at the time of booking did not had much difference between the PIH and the normotensive women, with respect to both SBP and DBP (P value>0.05). But the SBP and DBP recorded at the time of delivery had significant differences between the PIH and the Normotensive group (P-value<0.001). In addition to this when the BP recorded at the time of booking was compared with that recorded at the time of delivery, in the PIH women group, good correlation was shown. (P-value<0.001). But conversely, similar correlation was not seen in the normal women with respect to SBP/DBP measured at booking and at delivery. (P-value>0.05)[9]. Though some studies have shown association between the BMI and the occurrence of PIH, in the present study no significant correlation was seen between the BMI and the PIH. (P value>0.05). The ß-hCG measured in this study had wide distribution, minimum recording being 11134mIU/ml and maximum being 998765mIU/ml, with a mean of 46543.5mIU/ml+/-85271.7. Majority of the values of ß-hCG recorded were in the lower range, upto30000mIU/ml, which is understandable as majority of the study subjects were normotensive. A second cluster of distribution was in the values of

>90000mIU/ml corresponding to the occurrence of PIH cases[10]. The cut-off value for the ß-hCG was determined to be 35000mIU/ml using the ROC curve and 68% of the study subjects had values below the cut-off value and 32% had above it. On comparison of the mean values of ß-hCG between the PIH and the normotensive women significant difference was noted. (P-value<0.001). When the value ß-hCG in relation to the SBP/DBP measured at the time of booking and at the time of delivery was analysed, good correlation was observed between ß-hCG and SBP/DBP taken at delivery. (P-value <0,001). In the present study the ß-hCG had a sensitivity of 73% and a specificity of 100% which is comparable to the study done by Aparna Rajesh which had a sensitivity of 75%. The positive predictive value for the study was 100% whereas the negative predictive value was 89%.

CONCLUSION

The present study shows that the midtrimester ß-hCG measurement helps in the prediction of the PIH and it is a good candidate test to be used as a predictor of PIH. The study sample being 150 is small to draw generalized conclusions hence requires further validation by large scale trials. For any test to be a good screening test, it must have good sensitivity, specificity and positive predictive value. The sensitivity in the present study was 73% but with a specificity of 100%. In view of varied results in different studies conducted elsewhere, addition of other predictors of PIH like the lipid profile, AFP, uterine artery Doppler along with the estimation of ß-hCG, may provide better prediction with better accuracy.

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