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Evaluating the Link Between Beta hCG and Pre-eclampsia in the Second Trimester: A Prospective Study

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Abstract

Pregnancy induced hypertension *(PIH)* is a type of hypertension that occurs during pregnancy, affecting 6-10% of pregnancies. The study aimed to evaluate the role of Beta Human Chorionic Gonadotropin (β-hCG) levels in second trimester in predicting the on set of pre-eclampsia. The study population included 120 pregnant women in their second trimester who were normotensive and non-proteinuric, selected using consecutive sampling. The blood pressure of the participants was monitored, and the occurrence of pre-eclampsia, method of delivery, gestational age, and fetal outcome were documented. The level of Beta *HCG* was measured using the *ELISA* method, and the results were statistically analyzed. Among a total of 120 pregnant women were analyzed, with 21.5% having hypertension in pregnancy. The results showed a relationship between maternal serum β-hCG levels and the development of Pregnancy Induced Hypertension *(PIH)*, but the sensitivity was only 25% with a specificity of 75.93%. The study found that β-hCG *MOM* levels alone are not a highly reliable predictor for *PIH*, with the model having limited ability to differentiate between women who develop *PIH* and those who don't. The study also showed a strong statistical association between gestational age and *NICU* admission as potential risk factors for the development of *PIH*. In conclusion, β-hCG levels may have some utility in predicting *PIH*, but further studies are needed to determine the most effective markers and understand the underlying mechanisms.

Keywords: Pregnancy induced hypertension *(PIH)*; Pre-eclampsia; Beta hCG.

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INTRODUCTION

Pregnancy induced hypertension *(PIH)* is a unique disease characterized by high blood pressure during pregnancy.[1] About 6 to 10% of pregnancies are complicated by *PIH*. Pre-existing hypertension, gestational hypertension with pre-eclampsia, pre-existing hypertension plus superimposed gestational hypertension with proteinuria, and unclassifiable hypertension are the four conditions that the Canadian Hypertension Society defines as *PIH*.[2,3]

Preeclampsia is traditionally defined by the American College of Obstetrics and Gynecology *(ACOG)* as the presence of hypertension and proteinuria after 20 weeks of pregnancy in a patient who was previously normotensive.[4]

The development of preeclampsia risk factors has been extensively researched. Pre-eclampsia history, chronic hypertension, pregestational diabetes mellitus, antiphospholipid syndrome, and obesity are a few examples of major risk factors.[4,5]

Pre-eclampsia is still regarded as a terrifying pregnancy complication, despite advancements in maternal and neonatal care. Numerous tests have been widely proposed, but very few of them have been adopted due to their poor predictability. One of the early stages in the development of the disease has been thought to be the abnormal placentation. It is believed that during the middle of the third trimester, the conceptus experiences immunological changes that cause a secretory response that is used to predict preeclamptic status.[6]

PE has been dubbed the "disease of theories" and was first mentioned by the ancient Egyptians 3000 years ago as a condition connected to pregnancy.[5]

The "two stage theory" is currently the most widely accepted explanation for how preeclampsia develops. Reduced placental perfusion is thought to be the first stage of the illness, followed by generalized maternal endothelium dysfunction. Poor placentation as a result of impaired trophoblast invasion into the lumen and walls of spiral arteries is the primary cause of decreased placental perfusion. Antiangiogenic factors that are over produced by the poorly perfused placenta and then transferred to the mother's circulation are likely what damage the endothelium.[5,6]

By binding to the proteins vascular endothelial growth factor *(VEGF)* and transforming growth factor *(TGF)-1*, which are necessary to maintain normal endothelium function, respectively, these factors, which include soluble fms like tyrosine kinase 1 *(sFlt1)* and soluble endoglin *(sEng)*, contribute to endothelium damage and dysfunction.[6,7]

Methodologies like genomics, proteomics, and metabolomics have become more accessible for clinical research over the past ten years. Several new pathways and factors have been described using these techniques in the quest to understand the etiology of *PE*. Many of the etiological factors mentioned have been tested as biochemical markers for *PE* prediction and diagnosis because they can be measured in maternal blood. These include serum/plasma markers for inflammatory markers, placenta derived factors, hemolysis, renal dysfunction, endothelial dysfunction, metabolic status, and oxidative stress.[5]

There are a few maternal clinical traits that have been identified as *PE* risk factors. The glycoprotein hormone β-hCG, which is produced by trophoblast cells, is frequently used to identify pregnancies, ectopic pregnancies, and hydatidiform moles. Between 10 and 12 weeks into a typical pregnancy, the level of β-hCG peaks and then gradually declines. Serum β-hCG levels may change as a result of abnormal placental formation or function.[8-10]

It is important to investigate the connection between hCG levels in the blood and pre -eclampsia, as changes in *hCG* levels may indicate the placenta's response to pre-eclampsia. With this understanding, we under took this study to determine if *hCG* levels can predict the on set of pre-eclampsia.

METHODS

The study was conducted in the Department of Obstetrics and Gynaecology at Bharati Hospital, Pune over a period of 2 years from October 2020 to October 2022. The study design was a prospective observational (analytical) longitudinal study. The study population included women in their second trimester of pregnancy who were normotensive and non-proteinuric. The sample size for the study was 130 subjects and was obtained using consecutive sampling of women attending the antenatal *OPD* who matched the inclusion and exclusion criteria. The study participants were selected based on specific inclusion and exclusion criteria. Inclusion criteria included pregnant women who were attending the antenatal outpatient department *(OPD)* at the tertiary centre and were normotensive and non-proteinuric. Exclusion criteria included women with multiple pregnancies, congenital malformations, molar pregnancy, a history of Downs syndrome, and chronic hypertension.

The sampling strategy followed in the study involved enrolling consecutive pregnant women who met the inclusion and exclusion criteria and visited the antenatal *OPD* at Bharati Hospital until the required sample size was reached. The level of maternal serum Beta human chorionic gonadotropin was measured during the 18th to 20th week of pregnancy. The blood samples were collected from the participants for Beta *HCG* analysis using the *ELISA* method. Data analysis was performed by

calculating the Multiples of Median *(MoM)*. The blood pressure of the participants was recorded at every visit, and the cases were monitored until delivery, with or without the development of pre -eclampsia. The occurrence of pre-eclampsia, the method of delivery, the gestational age at delivery, and the fetal outcome in terms of birth weight and fetal growth restriction were also documented.

The statistical analysis was performed using *SPSS* (Statistical Package for Social Sciences) version 26.0 software. Descriptive statistics were used to represent continuous variables, while categorical variables were shown through frequency and percentages. Group comparisons were made by using the Chi square test for categorical variables, such as the severity and out come categories. For continuous variables with normal distribution, the Student T test was used, while the Mann-Whitney U-test was used for continuous variables with abnormal distribution. Through out the results, a 5% level of significance was employed, with all results presented with 95% confidence. *AP* value less than 0.05 was considered significant.

RESULTS

A total of 120 pregnant women with a mean age of 27.16 ± 4.58 years and a mean gestational age of 19.60 ± 2.05 weeks were included in the study. Out of 120, 12 developed *PIH*, and 108 were with out *PIH*. There were significant differences in pulse rate, systolic blood pressure, diastolic blood pressure, and weight between the two groups, with those who developed *PIH* having higher pulse rate, systolic blood pressure, diastolic blood pressure, and lower weight compared to those who did not. However, there was no significant difference in age and Beta *HCG* levels between the two groups. (Table 1)

Table 1: Descriptive statistics between the groups

	Development of PIH				
	Yes		No		P value
	Mean	SD	Mean	SD	
Age	29.25	4.56	26.93	4.56	0.0972
Pulse (BPM)	84.08	5.47	88.82	7.39	0.0333*
Systolic BP	122.00	18.99	112.09	10.61	0.0060*
Diastolic BP	82.50	12.88	74.30	8.93	0.0048*
Weight (KG)	2.19	0.63	2.75	0.49	0.0004*
Beta HCG	21751.04	20650.81	21609.80	17403.75	0.9792

The presence of comorbidities between the groups, i.e., *PIH* and no *PIH*, was compared and shown in table 4 and presented graphically. We found a significant difference in the distribution of patients on the basis of comorbidities, with a significantly ($p<0.0001$) higher number of patients in the PIH group having comorbidities.

The table presents data on the relationship between maternal serum Beta *hCG* Multiples of Median *(MOM)* and the development of Pregnancy Induced Hypertension *(PIH)*. It shows the number (N) and percentage (%) of women who did or did not develop *PIH* for *MOM* values less than 2 and greater than 2. The total number of subjects for each *MOM* value is also shown. The P value for the relationship between *MOM* and *PIH* is also presented, with a P value of 0.999 for *MOM* values less than 2 and no significant relationship between *MOM* and *PIH* (P value not significant).The sensitivity of serum β-hCG was 25%, the specificity was 75.93%, the positive predictive value was 10.34%, the negative predictive value was 90.11%, and the accuracy was 70.83%.

Table 2: Association between β-hCG (MOM) and PIH.

Beta hCG MOM	PIH		No PIH		Total	P value
	N	%	N	%		
<2	9	9.89	82	90.11	91	0.999
>2	3	10.34	26	89.66	29	

The receiver operating characteristics *(ROC)* curve analysis revealed the area under the *ROC* curve of 0.529 ± 0.0998 and cut off value of ≤7896.54 with sensitivity of 33.33%, specificity of 80.56%,

positive and negative likelihood ration were 1.71 and 0.83, respectively. The *ROC* curve analysis outcomes are shown in table 3 and graph presents the *ROC* curve for beta *HCG*.

The receiver operating characteristic *(ROC)* curve analysis for Beta *hCG MOM* levels in predicting the development of *PIH*, gave *AUC* of 0.529. This means that the *ROC* curve has a moderate predictive ability, with standard error of 0.0998. The cut -off value used for this analysis was ≤7896.54. The sensitivity of the model was 33.33, which means that 33.33% of the positive cases were correctly classified by the model. The specificity of the model was 80.56, which means that 80.56% of the negative cases were correctly classified by the model. The positive likelihood ratio was 1.71, which means that the likelihood of *PIH* is 1.71 times higher in subjects with a positive test result compared to subjects with a negative test result. The negative likelihood ratio was 0.83, which means that the likelihood of no *PIH* is 0.83 times higher in subjects with a negative test result compared to subjects with a positive test result. (Fig. 1)

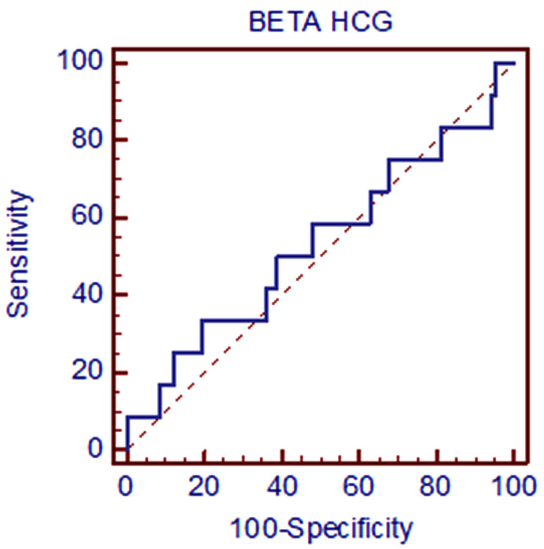

Fig. 1: ROC curve analysis of beta hCG for prediction of PIH

According to the table 3 among individuals without *PIH*, majority of patients 84 (77.8%) had no associated comorbidity reported. Other comorbidities, such as anemia, hypothyroidism, and obesity, were present in only a small number of individuals (0.9% to 3.7%).

Table 3: Distribution of associated comorbidities in no. PIH group

	No PIH	
	Frequency	**Percent**
Anemia	2	0.9
Beta thalassemia	1	0.9
Hypothyroid	4	3.7
IUI conception	1	0.9
None	84	77.8
Obesity	1	0.9
OS stitch in-situ	2	1.9
Overt DM	1	0.9
Rh incompatibility	2	1.9
Total	108	100.0

According to the Table 4, the most common comorbidity among individuals with *PIH* was *IVF* conception, which was present in 4 people (33.3% of the total). Other comorbidities, such as anemia, chronic hypertension with previous *LSCS*, elderly Primi, and obesity with chronic hypertension, are present in only a small number of individuals (8.3% each).

Table 4: Distribution of associated comorbidities in PIH group

	Frequency	**Percent**
Anemia	1	8.3
Chronic HTN with previous LSCS	1	8.3
Elderly Primi	1	8.3
IVF conception	4	33.3
None	1	8.3
Obesity with chronic HTN	1	8.3
Overt DM	1	8.3
Low pappa	1	8.3
Teen pregnancy	1	8.3
Total	12	100.0

Table 5 presents the results of a study examining the relationship between various factors and the development of pregnancy-induced hypertension *(PIH)*. The factors studied include delivered gestational age, type of delivery, live/still birth, and *NICU* admission.

For delivered gestational age, 5 individuals who developed *PIH* had preterm delivery while 7 had term delivery. On the other hand, 4 individuals who did not develop *PIH* had preterm delivery while 104 had term delivery. The p-value of 0.0004,

indicated a strong statistical association between delivered gestational age and the development of *PIH*.

For type of delivery, 2 individuals who developed *PIH* had full term vaginal delivery *(FTVD)* while 9 had lower segment caesarean section *(LSCS)* and 1 had preterm vaginal delivery *(PTVD)*. On the other hand, 34 individuals who did not develop *PIH* had *FTVD* while 70 had *LSCS* and 4 had *PTVD*. There wasno statistical (p=0.4686) association between the two variables.

For live/still birth, 1 individual who developed *PIH* had a fresh still birth while 11 had a live birth. On the other hand, 1 individual who did not develop *PIH* had a fresh still birth while 107 had a live birth. The p-value for the association between live/still birth and the development of *PIH* is 0.1907, indicating a weak statistical association between the two variables.

For *NICU* admission, 3 individuals who developed *PIH* were admitted to the *NICU* while 9 were not. On the other hand, 5 individuals who did not develop *PIH* were admitted to the *NICU* while 103 were not. The p-value for the association between *NICU* admission and the development of *PIH* is 0.0325, indicating a moderate statistical association between the two variables. This suggests that individuals who were admitted to the *NICU* are more likely to develop *PIH* compared to individuals who were not.

Table 5: Comparison of PIH and type of delivery

		Development of PIH				P value
		Yes		No		
		N	%	N	%	
Delivered gestational age	Preterm	5	41.7	4	3.7	0.0004*
	Term	7	58.3	104	96.3	
Type of delivery	FTVD	2	16.7	34	31.5	
	LSCS	9	75.0	70	64.8	0.4686
	PTVD	1	8.3	4	3.7	
Live/ Still Birth	Fresh still birth	1	8.3	1	0.9	0.1907
	Live	11	91.7	107	99.1	
NICI admission	Yes	3	25.0	5	4.6	0.0325
	No	9	75.0	103	95.4	

DISCUSSION

Pregnancy complications like hypertension can cause health problems for women and their unborn children. Pre-eclampsia and chronic hypertension with superimposed pre-eclampsia are severe forms of hypertensive disorders during pregnancy, with hypertension being the key factor.[4,11] Preeclampsia can lead to multiple health issues, including proteinuria, hematologic abnormalities, and organ dysfunction such as renal, cardiac, pulmonary, hepatic, and neurological problems, as well as fetal growth restriction, still birth, and maternal death. The severe pregnancy complication affects 5-7% of women world wide, leading to high morbidity and mortality and contributing to maternal morbidity, mortality, cesarean sections, *NICU* admissions, and prematurity.[12,13]

The primary cause of preeclampsia is believed to be in sufficient trophoblast invasion into the maternal spiral arteries, reducing placental blood flow and leading to trophoblast apoptosis and pro-inflammatory cytokine production, with recent studies also suggesting a potential role for the placenta in its pathophysiology.[14,15]

With the goal of improving maternal and fetal outcomes, researchers have been searching for reliable markers for the early prediction of pre-eclampsia. One such marker is beta Human Chorionic Gonadotropin (β-hCG).[16,17] The current study aimed to evaluate the role of β-hCG levels in predicting the onset of pre-eclampsia. A total of 120 pregnant women were analyzed, with an average age of 27.16 ± 4.58 years and an average gestational age of 19.60 ± 2.05 weeks. Out of the 120 women, 12 developed *PIH*, and the remaining 108 women were normotensive. The two groups were similar in demographics and clinical characteristics, with the exception of higher systolic and diastolic blood pressure in the *PIH* group.

In this study, the prevalence of hypertension in

pregnancy was 21.5 percent, with the normotensive group being in the majority. The mean ages of the hypertensive and normotensive groups were found to be similar, with slight differences in some studies.[18,19]

The syncytiotrophoblast in the placenta produces *hCG* (human chorionic gonadotrophin). During the first trimester, maternal *hCG* levels are high and decrease rapidly after. High levels of *hCG* have been linked to pregnancy disorders such as pre-eclampsia, placental abruptions, intrauterine death, and growth retardation.[14,20-22]

A study by Kaur G et al.[9] found that out of 178 cases, 154 had low *hCG* levels and 24 had high hCG levels. The study showed that there was a higher chance of developing *PIH* (pregnancy-induced hypertension) in cases with high *hCG* levels compared to those with low *hCG* levels. The positive predictive value of high *hCG* levels for *PIH* was 83.33%, with a specificity of 97.44% and sensitivity of 90.91%.

The two studies concluded that higher *hCG* levels are associated with a higher incidence of *PIH* (pregnancy induced hypertension). The sensitivity and specificity for *hCG* levels as a predictor of *PIH* were found to be in the range of 72.5% to 96%, and 72.8% to 76%, respectively.[23,24]

The results of this study demonstrate the relationship between maternal serum Beta *hCG* levels and the development of Pregnancy Induced Hypertension *(PIH)*. The data shows that the relationship between maternal serum Beta *hCG* Multiples of Median *(MOM)* with values greater than and less than 2, and *PIH* was not significant. This suggests that higher maternal serum Beta *hCG* levels do not appear to be a risk factor for *PIH*. However, the sensitivity of serum Beta *hCG* in predicting *PIH* was only 25%, with a specificity of 75.93%. This means that while serum Beta *hCG* levels may be useful in identifying some cases of *PIH*, there is a significant number of cases that will not be identified using this marker.

In contrast according to a study by Jindal N[25], the severity of pre-eclampsia was found to be associated with higher levels of the *hCG* hormone in the mother's blood in pre-eclampsia cases compared to healthy controls. Similarly, another study by Begum Z et al.[26] from Dhaka found that there was a significant increase in *hCG* levels in women with severe pre-eclampsia compared to those with mild, moderate, or normal pregnancy.

Present study suggest that Beta *hCG MOM* levels alone are not a highly reliable predictor for the development of *PIH*. For beta *hCG*, *AUC* of 0.529 and the moderate standard error of 0.0998 indicate that the model has a limited ability to differentiate between women who develop *PIH* and those who do not. The sensitivity and specificity of the model were also moderate, with 33.33% and 80.56% respectively. This suggests that this model has low ability to correctly identify women who will develop *PIH*. However, the positive likelihood ratio of 1.71 and the negative likelihood ratio of 0.83 suggest that Beta *hCG MOM* levels can provide some level of information about the likelihood of *PIH*.

According to a study by Keikkala E et al.[7], the ability of *hCG* to predict pre-eclampsia was found to have an *AUC* (area under the curve) value of 0.594. This value is similar to the results of the current study being conducted.

In terms of comorbidities, the majority of individuals without *PIH* (77.8%) had no associated comorbidity. Meanwhile, among individuals with *PIH*, the most common comorbidity was *IVF* conception, which was present in 33.3% of individuals. This information can be useful in understanding the potential risk factors for *PIH* and the factors that may increase an individual's risk for developing *PIH*. Further research is needed to fully understand the relationship between comorbidities and *PIH*.

It is conceivable that preeclampsia has a direct impact on the out comes for newborns. However, analyses must take into account the fact that pre -eclamptic women have a higher risk of giving birth prematurely, which is also linked to higher neonatal morbidity, in order to estimate the direct effect of preeclampsia on neonatal morbidity. Because pre-eclampsia can only be treated by delivery and preterm birth may be necessary to safeguard the mother's health or avoid still birth, this risk may also be correlated with the severity of the disease. In actuality, pre-eclampsia is linked to more than 20% of preterm births that have a medical indication.[28,29]

The results of this study suggest that there is a strong statistical association between delivered gestational age and the development of *PIH*. Women who had preterm delivery were more likely to develop *PIH* compared to those who had term delivery. Additionally, the results showed a moderate statistical association between *NICU* admission and the development of *PIH*, indicating that the women with *PIH*, are more prone for *NICU* admission of their children compared to those who were not. However, there was no significant association between type of delivery and live/

still birth and the development of *PIH* was noted. Comorbidities were present in only a small number of individuals both with and without *PIH*. *IVF* conception was the most common comorbidity among individuals with *PIH*, while the majority of individuals without *PIH* had no reported comorbidity.

In conclusion, while Beta *hCG MOM* level alone is not a highly reliable predictor of *PIH*. While maternal serum Beta *hCG* levels may have some utility in predicting *PIH*, they should not be relied upon as the sole indicator of *PIH*. Further studies are needed to determine the utility of Beta *hCG MOM* levels in predicting *PIH* and to improve the accuracy of the model, and to determine the most effective markers for predicting *PIH*, and to understand the underlying mechanisms that contribute to this condition. This study also highlights the importance of considering gestational age and *NICU* admission as potential risk factors for the development of *PIH*.

CONCLUSION

Second trimester serum beta *hCG* levels showed no role in prediction of pre-eclampsia in our study. It may have a positive role in prediction of pre eclampsia if coupled double marker test or quadruple marker test. Our study was intended to become simpler using a single marker and avoiding other markers, but has shown no significance.

So, beta *hCG* with other serum markers in second trimester have greater part in prediction of pre eclampsia. We need more researches and larger study to demonstrate that positive role of serum beta *hCG* as single investigation.

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