Original Article

Prediction of Pregnancy-Induced Hypertension by Maternal Beta-hCG Levels in the Mid-Trimester of Pregnancy

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ABSTRACT

Objective: The study objective was to evaluate the association between mid-trimester Beta-hCG levels and the risk of PIH to assess its potential as a predictive marker.

Study Design: Prospective, observational study

Place and Duration of Study: This study was conducted at the Gynae and Obstet Department, Swat Medical College, Swat and Saidu Group of Teaching Hospitals, Swat from June 2022 to June 2023.

Methods: The study conducted on 130 pregnant women, divided into two groups: 65 with PIH and 65 Non PIH. Beta-hCG levels were measured between 13 and 20 weeks of gestation age. Demographic and clinical data, blood pressure (BP), BMI, family history of hypertension, and smoking status, were collected. 'Statistical analyses were performed with chi-square tests, independent t-tests, logistic regression, and ROC curve analysis to determine the predictive value of Beta-hCG'.

Results: The study revealed, no significant association was observed between Beta-hCG quartiles and PIH incidence. Whereas the 'ROC analysis showed an area under the curve (AUC)' of 0.524, indicating minimal 'predictive' ability, other factors, BMI, family history of hypertension, and smoking status had significant associations with PIH.

Conclusion: Only 'Beta-hCG levels' were not sufficient as an individual marker for PIH risk. The study suggests that a multifactorial approach, including both biomarkers and clinical factors, may provide accurate assessment for PIH risk. Further research is needed for comprehensive predictive models for PIH screening, particularly in resource-limited settings.

Key Words: Pregnancy-induced hypertension, Beta-hCG, predictive markers, maternal health

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INTRODUCTION

The pregnancy-induced hypertension (PIH) is a health issue affecting pregnant women worldwide, that is 'characterized by elevated BP that arises after 20 weeks of gestation' [1]. Globally, PIH affects about five to tenth percent of pregnancies, and is cause of mother and perinatal morbidity and mortality[2]. This makes women at risk of developing severe complications, preeclampsia and eclampsia, that are associated with adverse outcomes like, preterm birth, low birth weight, and, in severe cases, maternal and fetal death [3]. While developed countries have made significant advances in prenatal care and early detection, leading to lower the incidence and improved measure, but the burden remains increased in 'low-resource setting'. The effect of PIH on maternal and child health is particularly profound in these regions, where limited access to quality healthcare contributes to the persistence of complications.[4.]

In South Asia, including Pakistan, PIH remains a main challenge for maternal health[5]. Researches revealed that the prevalence of hypertensive disorders during pregnancy in Pakistan may be as high as 9-12%, noticeably higher than global averages[6]. This prevalence highlights the need for awareness, screening, and management strategies in the region[7]. Pakistan faces unique challenges in managing PIH due to discrepancies in healthcare access, socioeconomic factors, and differences in healthcare quality across urban and rural areas[8]. In addition, cultural barriers and a lack of awareness among pregnant women exacerbate the risk, often leading to late diagnosis and poor maternal outcomes. Addressing this issue requires a comprehensive approach that includes community-level

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education, improved access to healthcare services, and effective screening practices to detect PIH earlier.

Biomarkers, Beta-hCG 'beta-human chorionic gonadotropin' levels have emerged as possible marker for identifying pregnancies at higher risk of developing hypertensive disorders. Beta-hCG is a hormone produced by the placenta, important for maintaining early pregnancy, and its levels vary significantly throughout gestation. Studies advises that abnormal Beta-hCG 'levels may be associated with an elevated risk of PIH and related complications' as these levels reveal placental health and function[9]. Detecting deviations in Beta-hCG levels could help in early warning, allowing for proactive interventions to prevent the progression of PIH and mitigate its effects on mother and child. 'Although several studies have explored' this association, the predictive accuracy and practical application of the use of 'Beta-hCG' as a marker for predicting the risk of PIH remain under investigation[10].

The aims were to evaluate the relationship of Beta-hCG levels and the incidence of PIH among pregnant women in Pakistan. By examining Beta-hCG levels across different quartiles, this research seeks to identify whether variations in this hormone correlate with increased PIH risk. Findings from this study could contribute to establishing a cost-effective and accessible screening tool for PIH in Pakistan, particularly in resource-limited settings where advanced diagnostic options are scarce. If Beta-hCG levels prove to be a reliable marker for PIH risk, it could help healthcare providers implement preventive strategies earlier, ultimately reducing the 'burden of maternal and neonatal complications associated with hypertensive disorders in pregnancy'.

METHODS

The study design was prospective, observational study conducted at Swat Medical College and Saidu Group of Teaching Hospitals, Swat and aim was to analyze Beta-hCG levels in relation to PIH development with duration of 12 months from June 2022 to June 2023, allowing sufficient time for recruitment, follow-up, and data collection. Total130 pregnant women with purposive sampling method. The participants were equally divided into two groups: 65 women diagnosed with PIH and 65 women without PIH.

Ethical approval of study was obtained from 'Institutional Review Board (IRB)' of the College of Physicians and Surgeons Pakistan (CPSP) with the reference number CPSP/REU/OBG-2018-022-8930, ensuring adherence to ethical standards in all phases of the research. All participants provided written informed consent before enrollment, ensuring they understood the study's purpose, procedures, and any potential risks involved.

The inclusion criteria were: pregnant women during their 2nd trimester, in between 13 and 20 weeks of gestation, which aligns with the standard period for assessing Beta-hCG as a potential biomarker for hypertensive disorders, women aged 18 to 40 years, confirmed singleton pregnancies, and gestational age between 13 and 20 weeks at the time of recruitment. And exclusion criteria included women with pre-existing hypertension, renal or cardiovascular disease, multiple gestations, any known chronic illness that could influence Beta-hCG levels or blood pressure.

The data collection was categorized into two primary phases: baseline assessment and follow-up. At the baseline, demographic and clinical information, age, BMI, smoking status, and family history of hypertension was recorded for each participant. Blood samples were drawn to measure Beta-hCG levels using immunoassay techniques. These samples were processed at the Swat Medical College laboratory under strict protocols to ensure accuracy and reliability of the results.

The participants were then monitored throughout their pregnancies for the development of PIH. BP measurements were taken at each prenatal visit according to the guidelines provided by the American College of Obstetricians and Gynecologists (ACOG). PIH was detected based on a 'systolic diastolic blood pressure' (SBP) of 140 mmHg or above and/or a 'diastolic blood pressure' (DBP) of 90 mmHg or above after the between 13 and 20th weeks of gestation, in the presence of proteinuria or other symptoms indicative of preeclampsia.

The data was analyzed using SPSS 25. Descriptive statistics, including means, standard deviations, and percentages, were calculated for demographic and clinical characteristics. Beta-hCG levels were categorized into quartiles to assess the relationship between different levels and PIH incidence. 'The chi-square tests were used for categorical variables', while independent t-tests were performed to compare mean values of continuous variables between the PIH and non-PIH groups. The logistic regression was performed to evaluate the odds ratios for PIH associated with each quartile of Beta-hCG, adjusting for potential confounding factors, age, BMI, family history of hypertension, and smoking status. ROC curve analysis was conducted to assess the predictive accuracy of Beta-hCG levels for PIH, with the AUC reported. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the average Beta-hCG levels across four quartiles and the corresponding PIH incidence within each quartile. The mean Beta-hCG levels range from 97.78 IU/L in the second quartile to 124.86 IU/L in the third quartile. The highest PIH incidence rates are

found in the first and second quartiles, with 14.6% and 15.4% of cases, respectively. In the third and fourth quartiles, the incidence of PIH is slightly lower, at 10.0% in each.

Table No.1: Beta-hCG Levels and PIH Incidence

Beta-hCG Quartile	Average Beta-hCG (IU/L)	PIH Cases (n)	PIH Percentage (%)
Q1 (Lowest 25%)	101.69	19	14.6%
Q2 (25th - 50th %)	97.78	20	15.4%
Q3 (50th - 75th %)	124.86	13	10.0%
Q4 (Highest 25%)	115.02	13	10.0%

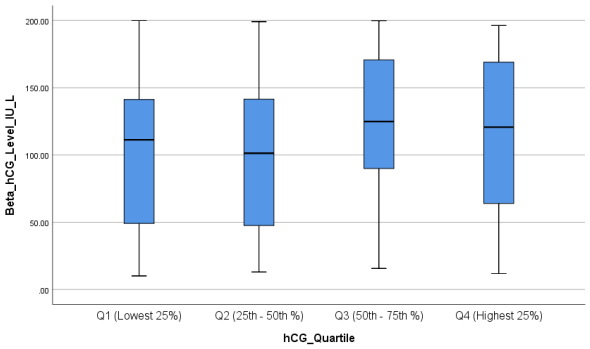

Figure 1: The box plot displays the **distribution of Beta-hCG levels** across four quartiles (Q1 to Q4), representing different percentile ranges. Median Beta-hCG levels are relatively similar across quartiles, with Q3 showing the most variation and Q2 the least. The whiskers illustrate the full range of values, with Q1 having a lower minimum and Q3 and Q4 showing higher maximum values. There are no apparent outliers, indicating a stable range within each group. Overall, the plot suggests minimal variation in Beta-hCG levels across quartiles.

Table 2 compares the demographics and lifestyle factors between groups. The 'PIH group' has a higher mean age of 29.77 years, while 26.83 years in the 'Non-PIH group', with a statistically significant difference (p = 0.008). A significant difference in BMI is also observed, with the 'PIH group' having an average BMI of 31.43 kg/m² versus 21.27 kg/m² in the Non-PIH group (p = 0.001). There is no statistically significant difference in gestational age at sampling between the groups (p = 0.384). For parity, the percentages of nulliparous and multiparous women are similar in both groups, with no significant differences (p = 0.596). However, family history of hypertension and smoking status are notably more common in the PIH group, with 33.1% of PIH cases reporting a family history of hypertension compared to 10.0% 'Non-PIH group', and 14.6% of the 'PIH group identified as smokers compared' to 2.3% in the 'Non-PIH group' (p = 0.001 for both).

Table 2: Demographics and Lifestyle Factors by PIH Status

Variable	PIH Group (n=65)	Non-PIH Group (n=65)	p-value
Age (years)	29.77	26.83	0.008
BMI (kg/m²)	31.43	21.27	0.001
Gestational Age at Sampling (weeks)	16.32	16.69	0.384
Nulliparous %	20.8%	23.1%	0.596
Multiparous %	29.2%	26.9%	0.596
Family History of Hypertension (%)	33.1%	10.0%	0.001
Smoking Status (%)	14.6%	2.3%	0.001

Table 3 provides a comparison of SBP and DB', uric acid levels, and 'proteinuria' between the groups. The PIH group shows significantly higher mean systolic and diastolic blood pressures, at 149.18 mmHg and 99.65 mmHg, respectively, compared to 118.71 mmHg and 77.68 mmHg in the Non-PIH group, with a p-value of 0.001 for both measurements. Uric acid levels are also elevated 'PIH group, with an average' of 7.92 mg/dL while, 4.01 mg/dL in the 'Non-PIH group' (p = 0.001). Proteinuria levels differ between groups as well, with the PIH group showing higher rates of moderate and severe proteinuria, while the Non-PIH group has higher rates of no or trace proteinuria (p = 0.001).

Table 3: Blood Pressure, Uric Acid, and Proteinuria by PIH Status

Measurement	PIH Group (n=65)	Non-PIH Group (n=65)	p-value
Systolic BP (mmHg)	149.18	118.71	0.001
Diastolic BP (mmHg)	99.65	77.68	0.001
Uric Acid (mg/dL)	7.92	4.01	0.001
Proteinuria Level			0.001
- Mild (%)	11.5%	12.3%	
- Moderate (%)	15.4%	0.0%	
- None (%)	0.0%	17.7%	
- Severe (%)	23.1%	0.0%	
- Trace (%)	0.0%	20.0%	

Table 4 summarizes gestational outcomes and maternal weight gain by PIH status. The preterm birth rate is 18.5% in the PIH group and 12.3% in the Non-PIH group, though this difference is not statistically significant (p = 0.128). APGAR scores at 1 minute and

5 minutes are significantly lower in the PIH group, with mean scores of 4.98 and 6.51, respectively, compared to 7.94 and 8.57 in the 'Non-PIH group' (p = 0.001 for both). Additionally, the PIH group has a lower average maternal weight gain of 7.42 kg, compared to 15.09 kg in the Non-PIH group, with a p-value of 0.001.

Table No.4: Gestational Outcomes and Maternal Weight Gain by PIH Status

Outcome	PIH Group (n=65)	Non-PIH Group (n=65)	p-value
Preterm Birth (%)	18.5%	12.3%	0.128
APGAR Score (1 min)	4.98	7.94	0.001
APGAR Score (5 min)	6.51	8.57	0.001
Maternal Weight Gain (kg)	7.42	15.09	0.001

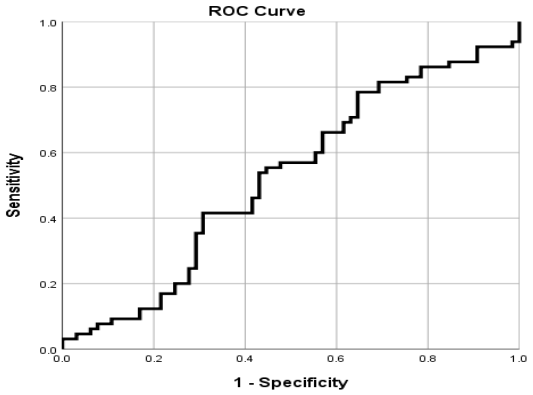

Figure No.2: The ROC curve shows the diagnostic performance of Beta-hCG levels for predicting PIH. The curve's proximity to the diagonal line (45-degree line) indicates limited predictive ability, with an area under the curve (AUC) of 0.524, suggesting minimal discrimination between cases with and without PIH. Sensitivity and specificity do not consistently improve, indicating that Beta-hCG levels are not a strong predictor of PIH in our study.

Table 5 presents a predictive analysis for PIH, including odds ratios and ROC analysis. The odds ratio for family history of hypertension (No vs. Yes) is 0.128, with a 95% confidence interval of 0.058 to 0.283, indicating a strong association with PIH. The ROC analysis for Beta-hCG levels yields AUC of 0.524, 'with a 95% confidence interval of' 0.507 to 0.541, suggesting limited predictive value for PIH. Adjusted odds ratios 'for family history of hypertension and smoking status' were 52.481 and 6.110, respectively, though the confidence intervals are extremely wide due to convergence issues in the logistic regression model.

Table No.5: Predictive Analysis for PIH

Analysis	Value	95% CI
Odds Ratio for Family History of Hypertension (No vs. Yes)	0.128	0.058 - 0.283
ROC (AUC) for Beta-hCG Levels	0.524	0.507 - 0.541
Adjusted Odds Ratio for Family History of Hypertension	52.481	(-14645.37, 14750.33)
Adjusted Odds Ratio for Smoking Status	6.110	(-9310.58, 9322.80)

DISCUSSION

This study examined the a'ssociation between Beta-hCG levels in mid-trimester and the risk of developing PIH' among pregnant women. Our findings showed no substantial difference in PIH incidence across Beta-hCG quartiles, suggesting that Beta-hCG levels in the second trimester may have limited predictive value for PIH. This aligns with some previous studies, while other research has shown conflicting results, emphasizing the complexity of predicting hypertensive disorders in pregnancy.

Previous studies have explored the Beta-hCG as a possible biomarker for hypertensive disorders during pregnancy, with mixed outcomes[11]. Research by Murmu et al. (2020) observed elevated Beta-hCG levels in women who later developed preeclampsia, suggesting a potential link between early placental dysfunction and hypertensive outcomes[10]. However, the predictive value was moderate, and Beta-hCG alone was not sufficient for reliable risk stratification. Similarly, a study by Chen et al. (2020) highlighted that while higher Beta-hCG levels were more common in pregnancies complicated by hypertensive disorders, this marker alone lacked specificity and was often inconsistent when evaluated independently of other clinical factors[12]. These findings resonate with our results, where Beta-hCG levels showed limited association with PIH, suggesting that this hormone may not act as a standalone predictor.

In contrast, some studies have shown a more considerable 'association between elevated Beta-hCG levels and PIH', especially in cases of severe preeclampsia[13]. Huma et al. (2022) reported that women with high Beta-hCG levels in early pregnancy had a higher risk of developing preeclampsia, supporting the hypothesis that elevated hormone levels may reflect placental stress or dysfunction[14]. However, our study did not observe a similar pattern, 'which could be attributed to differences in study design, sample size, and the population' under investigation.

Notably, our study was conducted in Pakistan, where genetic, environmental, and lifestyle factors may influence the incidence and expression of hypertensive disorders differently compared to other regions.

In addition to Beta-hCG, other biomarkers have been proposed as potential predictors of PIH, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), which reflect placental health and vascular adaptation. Studies including these biomarkers with Beta-hCG have shown improved predictive accuracy for hypertensive disorders, as they detect different aspects of placental function[15]. A study by Liu et al. (2021) report that combining Beta-hCG with PlGF considerably enhanced the detection rate for early-onset of preeclampsia[16]. This approach suggests that PIH may be best predicted by combination of biomarkers rather than depending on Beta-hCG only, emphasizing the need for integrated screening strategies.

Additionally, another important concern was the role of demographic and lifestyle factors in PIH risk. Our study revealed that age, BMI, smoking status, and family history of hypertension were significantly associated with PIH, that were in accordance with established risk factors reported in previous literature. A study by Wagata et al. (2020), Schenkelaars et al. (2021) and Zahra et al (2024) highlighted the impact of maternal age and obesity on hypertensive disorders, supporting the idea that demographic and clinical factors should be considered when determining risk of PIH[17-18]. 'These variables may interact with Beta-hCG levels, influencing the development of PIH in complex ways that single biomarker analysis cannot'.

Additionally, in terms of clinical implications, our study showed that Beta-hCG may not be sufficient as a only screening tool for PIH in the general population. The limited predictive accuracy of Beta-hCG, as observed in our study, highlight the need for a wider approach that associations biomarkers with demographic and clinical data. This approach could improve early detection and allow for targeted interventions in high-risk groups, eventually improving maternal and neonatal outcomes. Furthermore, this study highlights the importance of contextual factors, as the predictive value of Beta-hCG may differ by population, underlining the need for localized research that considers regional health profiles.

While Beta-hCG offers some insights into placental function, its efficacy in predicting PIH remains limited. The findings our study add to the growing body of literature suggesting that a sole biomarker approach may not be adequate for detecting PIH risk. Future research should focus on multi-biomarker models and consider adding demographic and lifestyle factors to improve screening accuracy. Moreover, large size studies in diverse populations are necessary to validate these findings and develop tailored screening strategies that support with the specific needs of different regions and healthcare settings.

CONCLUSION

The study observed the relationship between mid-trimester Beta-hCG levels and the development of PIH of pregnant women. Our findings showed that Beta-hCG levels alone may not serve as a reliable predictor of PIH, as no significant associations were found across different quartiles of the hormone.

The detected lack of strong correlation suggests that PIH risk assessment should consider a combination of biomarkers with demographic and lifestyle factors, age, BMI, family history of hypertension, and smoking status, that had significant associations with PIH in our study. By incorporating these varaibles, healthcare providers may achieve a more comprehensive approach to early PIH detection and management.

Author's Contribution:

Concept & Design of Study:	Hafiza Nida Mumtaz
Drafting:	Saima Ahmed, Asma Hameed
Data Analysis:	Sadaf Ali, Kiran Kalsoom
Revisiting Critically:	Hafiza Nida Mumtaz, Saima Ahmed
Final Approval of version:	By all above authors

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