

Original Article

Diagnostic Accuracy of High β HCG (>2 MoM) Levels in Predicting Pregnancy Induced Hypertension

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Abstract

Objective: To determine the diagnostic accuracy of high β hCG (>2 MOM) levels in predicting pregnancy induced hypertension taking the development of PIH later in pregnancy as gold standard.

Methodology: The cross-sectional study was conducted in department of Obstetrics & Gynaecology, Sir Ganga Ram Hospital, Lahore, from 20th November 2018 to 19th May 2019. A total of 200 pregnant women, between 14 to 20 weeks of gestation were included. After informed consent blood sample of each woman was sent to the Institutional Pathology laboratory for measurement of serum β HCG levels by consultant pathologist. All women were followed till delivery for development of pregnancy induced hypertension by the researcher herself on regular basis and managed accordingly. Data was entered and analysed in SPSS version 20. The quantitative data like age, parity, gestational age, serum β HCG level, the mean and standard deviation was calculated. For qualitative variables percentage and frequency was used.

Results: Out of 200 enrolled patients 114 women had β HCG > 2 MOM. But 108 were True Positive and 06 were False Positive. Among rest of 86 patients with β HCG < 2 MOM, 09 (False Negative) had adverse maternal outcome whereas 77 (True Negative) had no PIH ($p=0.0001$). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of high β HCG (>2 MOM) levels in predicting pregnancy induced hypertension, taking development of PIH later in pregnancy as gold standard was 92.31%, 92.77%, 94.74%, 89.43% and 92.50% respectively.

Conclusion: This study concluded that diagnostic accuracy of raised β HCG (>2 MOM) levels in predicting pregnancy induced hypertension is quite high.

Keywords: β HCG, Pregnancy induced hypertension, Sensitivity.

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Introduction

Pregnancy associated hypertensive disorders and intrauterine growth restriction are common complications responsible for fetal, neonatal, and maternal morbidity.¹ Most current hypothesis regarding the pathophysiologic mechanisms of pregnancy-induced hypertension point to early placental abnormalities. The human placenta synthesizes steroid, protein, and glycoprotein hormones throughout gestation.² 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, it may be essential for the understanding of this disease, to investigate the pathologic and secretory reaction of the placenta.^{3,4}

Human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and uE3 levels in maternal serum have been used for Down syndrome screening for a long time and are commonly known as "the triple marker test". Fifty-six percent of fetal aneuploidy can be detected by a combination of

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abnormal serum levels of HCG and AFP.⁵ In 1992, the relationship between elevated HCG and non-genetic pregnancy complications was studied for the first time.⁶ After this report, many authors described that second trimester serum levels of HCG, AFP and uE3 may predict the development of pre-eclampsia later in pregnancy.⁷⁻⁸ In a study done by Chowdhary H et al⁹, it was seen that prevalence of pregnancy induced hypertension in 13.1% of women and also the sensitivity, specificity, positive predictive value and the negative predictive value for β HCG >2 MOM in predicting pregnancy induced hypertension were 83.3%, 96.9%, 80.0% and 97.5% respectively.

Many reasons have been given for suspecting role of HCG in predicting immunological conditions in obstetrics.¹⁰ Explanation to why HCG may rise in pre-eclampsia was given by Heinonen et al who said that this rise was probably a secretory response of trophoblasts to an immunological insult. Mid trimester is the time around which these changes that produce this response of β HCG levels are becoming overt. Therefore this period was decided upon for the study of β -HCG levels in pre-eclampsia. The study result was also supported by Desai et al.¹¹

Methodology

It was a cross-sectional study conducted in the department of Obstetrics & Gynaecology, unit 4, Sir Ganga Ram Hospital, Lahore. It was done from 20th November 2018 to 19th May 2019. Ethical approval was taken from concerned authority. The sample size of 200 cases was calculated with 95% confidence level, the prevalence of pregnancy-induced hypertension as 13.1% and 12% desired precision for the sensitivity of 83.3% and 3% desired precision for specificity of 96.9% of high β HCG levels in predicting pregnancy-induced hypertension.⁹ Non-probability, consecutive sampling technique was used. Total 200 women of ages between 18 to 40 years with a singleton pregnancy of cephalic presentation (assessed on USG) at gestational age of 13-20 weeks (assessed on LMP), presenting for routine antenatal followup in outdoor were included. Women with history of chronic hypertension, chronic liver disease (assessed on history and s/bilirubin >2 mg/dl), renal disease (assessed on history and s/creatinine >1.5 mg/dl), cardiac disease (assessed on history and medical

record) were excluded. A written informed consent was taken from all candidates. The blood sample of all women was sent to the institutional pathology laboratory for measurement of serum β HCG levels by a consultant pathologist (with at least 3 years of post-fellowship experience). All women were followed till delivery for development of pregnancy induced hypertension by the researcher herself on regular basis and managed accordingly.

Data was entered and analysed using SPSS-20. Descriptive statistics were applied to calculate mean and standard deviation for age, gestational age, parity and serum β HCG levels. Frequencies and percentages were calculated for h/o previous PIH (yes/no), high serum β HCG levels and pregnancy induced hypertension (yes/no). 2x2 contingency table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of high β HCG levels in predicting pregnancy induced hypertension. Stratification was done for age, gestational age, parity and h/o previous pre-eclampsia. Post-stratification chi square test was applied and p-value ≤ 0.05 was taken as significant. Diagnostic accuracy was also calculated.

Results

The age range in this study was from 18-40 years with a mean age of 27.69 ± 4.52 years. Majority of the patients 146 (73.0%) were between 18-30 years of age. Mean gestational age was 16.82 ± 1.90 weeks. Mean parity was 2.62 ± 0.88 . The distribution of patients according to h/o previous pre-eclampsia is shown in Table I. Mean β HCG levels were 3.33 ± 1.72 MOM.

Table I: Demographic Distribution of the Patients (n=200)

Characteristics	
Age (years)	Mean \pm SD = 27.69 ± 4.52 years
18-30 years	146 (73%)
31-40 years	54 (27%)
Parity	Mean \pm SD = 2.62 ± 0.88
Primiparas	90 (45%)
Multiparas	110 (55%)
Gestational Age (weeks)	Mean \pm SD = 16.82 ± 1.90 weeks
14-16 weeks	84 (42%)
17-20 weeks	116 (58%)
H/O previous PIH	
Yes	51 (25.5%)
No	149 (74.5%)

Table II: Diagnostic accuracy of high β HCG (>2 MOM) levels in predicting pregnancy induced hypertension (N=200)

	Development of PIH later	No development of PIH later	P- value	Sensitivity	Specificity	PPV	Diagnostic accuracy
Positive result	108 (TP)*	06 (FP)***	0.0001	92.31%	92.77%	94.74%	92.50%
Negative result	09 (FN)**	77 (TN)****					
Stratification of diagnostic accuracy with respect to no h/o previous pre-eclampsia (n=149)							
Positive result	75 (TP)	06 (FP)	0.001	93.75%	91.30%	92.59%	92.62%
Negative result	05 (FN)	63 (TN)					
Stratification of diagnostic accuracy with respect to h/o previous pre-eclampsia (n=51).							
Positive result	33 (TP)	00 (FP)	0.001	87.30%	95.74%	96.49%	90.91%
Negative result	04 (FN)	14 (TN)					
Stratification of diagnostic accuracy with respect to age 18-30 years (n=146).							
Positive result	77(TP)	05(FP)	0.001	92.77%	92.06%	93.90%	92.47%
Negative result	06 (FN)	58 (TN)					
Stratification of diagnostic accuracy with respect to age 31-40 years (n=54)							
Positive result	31(TP)	01(FP)	0.001	91.18%	95.0%	96.88%	92.59%
Negative result	03(FN)	19(TN)					
Stratification of diagnostic accuracy with respect to gestational age 13-16 weeks (n=84)							
Positive result	45 (TP)	02 (FP)	0.001	93.75%	94.44%	95.74%	94.05%
Negative result	03 (FN)	34 (TN)					
Stratification of diagnostic accuracy with respect to parity ≤ 2 (n=90)							
Positive result	53 (TP)	04 (FP)	0.001	98.15%	88.89%	92.98%	94.44%
Negative result	01 (FN)	32 (TN)					
Stratification of diagnostic accuracy with respect to parity > 2 (n=110)							
Positive result	55 (TP)	02 (FP)	0.001	87.30%	95.74%	96.49%	84.91%
Negative result	08 (FN)	45 (TN)					

*-TP=True positive **-FP=False positive ***-FN=False negative ****-TN=True negative

In this study, 108 were True Positive and 06 were False Positive. Among 86, β HCG negative patients, 09 (False Negative) had adverse maternal outcomes whereas 77 (True Negative) had no PIH ($p=0.0001$). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of high β HCG (>2 MOM) levels in predicting pregnancy induced hypertension, taking development of PIH later in pregnancy as gold standard was 92.31%, 92.77%, 94.74%, 89.43% and 92.50% respectively. (Table II)

Discussion

Pregnancy induced hypertension (PIH) is a unique disease seen only in pregnancy affecting 12–15 % of all pregnant women. Despite improvement in maternal and neonatal care, PIH and its sequelae are still a dreaded complication of pregnancy. If the prediction of PIH becomes possible, prevention will follow naturally. Several tests have been proposed but none has been accepted widely due to their low predictive value. The abnormal placentation has been considered as one of the initial event in the disease process. Hsu et al¹² hypothesized that during mid-trimester,

immunological changes occur in the trophoblasts, resulting in secretory response, which is seen as a rise in the β HCG levels.

A study conducted by Chowdhary H et al⁹, it was seen that prevalence of pregnancy induced hypertension in 13.1% of women and also the sensitivity, specificity, positive predictive value and the negative predictive value for β HCG >2 MOM in predicting pregnancy induced hypertension were 83.3%, 96.9%, 80.0% and 97.5% respectively. These results are similar as the current study.

Another study with same conclusion as this study was done by Kabukcu et al¹³ in 610 pregnant women. These women were in second trimester and they were grouped according to the multiple of median (MOM) of β HCG and found that women with elevated second trimester human chorionic gonadotropin levels (>2 MOM) were at increased risk for preeclampsia (Odds ratio 5.93, 95 % confidence interval 1.97 to 15.88).

A study by Pankaj Desai et al¹⁴ 62 cases out of 90 (68.9%) with values of β -HCG >2MOM developed pregnancy induced hypertension against 21 cases out of 130 (16.15%), having a β -HCG value <2 MOM. The difference was statistically significant (p

value <.001).

But a study by Sebire et al¹⁵ concluded that maternal serum-free β -hCG concentration at 10-14 weeks, as distinct from the findings in the second trimester, was not significantly different between normotensive women and those that subsequently develop pre-eclampsia. This difference may be due to difference in ethnicity.

In another study by Ashour et al¹⁶, in the overall population the β -HCG levels >2 MOM, during second trimester were significantly associated with development of pregnancy induced hypertension. They concluded that with the use of β -HCG value of 2 MOM as a cut off, its sensitivity as a screening test for pregnancy induced hypertension was 15.6%, the specificity was 90%, and the positive predictive value was 12.8%. These results are lower than our study may be due to difference in patient number and gestation.

A relationship between the two variables was observed in a study, conducted in China on 142 normotensive and 43 preeclamptic women ($r = 0.677$, $p < 0.05$). The authors of the study concluded that the β -HCG level might reflect the degree of disordered activity of placental trophoblast in pregnancy induced hypertension (PIH) and could be utilized as a marker in determining PIH.¹⁷ In another study, conducted on 32 women with PIH and 17 normotensive pregnant women, the relationship between Endothelin (ET) and HCG with preeclampsia was studied. The study concluded that ET and HCG are higher in women with PIH than those in normotensive subjects. Therefore, their increases suggest a functional disorder in placental cells, which may result from damage to the endothelial cells.¹⁸

Another study supporting our results was conducted in Istanbul, Turkey, in 2004, which compared β -HCG levels in 80 women suffering from mild preeclampsia, severe preeclampsia, superimposed hypertension and chronic hypertension with 25 normotensive pregnant women. The β -HCG level was reported to be 17000 mIU/mL in mild preeclamptic women, 49000 mIU/mL in severe preeclamptic women, about 41000 mIU/mL in women with superimposed hypertension, 12558 mIU/mL in women with chronic hypertension and 9647 mIU/mL in normotensive women. The results indicated that

the β -hCG level in women with severe preeclampsia was significantly more than those in other groups ($p < 0.001$).¹⁹

In a study conducted to test the hypothesis that women with high serum β -HCG levels and lipid profile in early second trimester have risk of developing pregnancy-induced hypertension, the serum β HCG level increased very significantly in those women who developed PIH. It was also found that for every 1,000 mIU/ml increase in serum β -HCG, the chance of developing PIH was 10.7%.²⁰ In another study 68.9 % of pregnant women with elevated HCG (>2MOM) developed pregnancy induced hypertension.²¹

Roiz-Hernandez et al²², showed that with a cut off value of 2 MOM for β HCG in multipara and primigravida during second trimester, area below the curve was 0.96 and 0.95, respectively, sensitivity was 88.5 and 100 %, respectively, the positive predictive value was 0.46 and 0.25, respectively, and the negative predictive values were 0.99 and 1.0. In a study, out of 90 women, 81 women were followed till term and 12 (14.8%) cases developed gestational hypertension. β HCG levels (Mean \pm SD) were higher (69808.66 \pm 54764.7 vs. 38126.49 \pm 97419.2; $p = 32726$ mIU/ml) has a sensitivity of 75%, specificity of 72.5% and accuracy of 72.8%.²³

Conclusion

This study concluded that diagnostic accuracy of raised β HCG (>2 MOM) levels in predicting pregnancy induced hypertension is quite high.

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