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Original Research Article

Correlation of levels of early second trimester beta-human chorionic gonadotropin levels with severity of preeclampsia

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ABSTRACT

Background: Hypertensive disorders in pregnancy remains a leading cause of maternal morbidity and mortality all over the world as per World Health Organization (WHO), affecting 5-10% of all pregnant women. Screening women at an early stage and preventing complications are corner stone in the management of pre-eclampsia. Several studies have proven the reliability of beta-human chorionic gonadotropin (β-hCG) as predictor of preeclampsia. In this study we aim to find the correlation of increasing levels of β-hCG with severity of preeclampsia.
Methods: In this study serum β-hCG estimation was done in 200 pregnant women between 13 and 20 weeks of gestation, selected randomly over a period of 1 year attending antenatal clinic by quantitative determination of β-hCG by electro-chemiluminescence immunoassay. Multiple of median (MOM) is calculated from charts of norms available. They were followed till delivery for development of pre-eclampsia. The following patients were followed up till delivery. Blood parameters, blood pressure readings, were done at 34 weeks for every patient and maternal complications were noted and results were analysed statistically.
Results: The incidence of preeclampsia in this study population was 8% (16 out of 200). This study found a significant correlation between increasing levels of MOM's of β-hCG with the severity of preeclampsia.
Conclusions: In this study, there was significant association between MOM values of β-hCG with the parameters defining severity of preeclampsia. The results of our study show β-hCG to be not only a reliable marker for prediction of preeclampsia, but also its severity.

Keywords: β-hCG, Preeclampsia, Pregnancy induced hypertension, HDP

INTRODUCTION

Hypertensive disorders in pregnancy remains a leading cause of maternal morbidity and mortality all over the world as per World Health Organization (WHO). Pregnancy induced hypertension (PIH) is a unique disease seen only in pregnancy affecting 5-10% of all pregnant women.[1] In spite of improvement in maternal and neonatal care, PIH and its sequelae are dreaded complication of pregnancy. Maternal complications are preeclampsia, eclampsia, disseminated intravascular coagulation, intracranial bleed, pulmonary oedema, renal failure, heart failure, abruption placentae, and death.[2-4,6] It also carry risk factors for foetus, preterm birth and low birth weight, intrauterine growth restriction (IUGR) thereby increasing perinatal mortality and morbidity.[5]

Preeclampsia

New onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy in previously normotensive women and the coexistence of 1 or more of the following new-onset conditions

Proteinuria (urine protein: creatinine ratio ≥0.3, ≥300 mg/24 hours or dipstick 1+ persistent

Other maternal organ dysfunction: renal insufficiency (creatinine >1.1 mg/dl or doubling of baseline), liver involvement (serum transaminase levels twice normal), cerebral symptoms (headache, visual disturbances and convulsions), thrombocytopenia (platelets <100,000/µl), and pulmonary edema.

Severe preeclampsia

Preeclampsia with severe hypertension (blood pressure ≥160 mmHg systolic or ≥110 mm diastolic).

In normal pregnancy uterine spiral arterioles undergo extensive remodeling as they are invaded by endovascular trophoblasts which transform them into low resistance high flow system.[7] So far abnormal or defective placentation due to faulty endovascular trophoblastic remodellingis considered to be one of the main cardinal etiology, some have even postulated the theory of immunological origin.[8,9]

Beta-human chorionic gonadotropin (β-hCG) is a glycoprotein, almost solely produced by syncytiotrophoblast of the placenta, pregnant women with high serum β-hCG levels in early pregnancy are at higher risk of developing PIH and its correlation with raised levels.[10-12] Several studies have proven the role of β-hCG as a very good predictor of preeclampsia. Aim of our study is to investigate the association of increasing levels of early 2nd trimester serum β-hCG with severity of preeclampsia.

METHODS

This study is aprospective observational hospital-based study which was conducted at a tertiary care hospital for a period of 1 year. The sampling technique was purposive sampling 200 pregnant women attending antenatal clinic in early 2nd trimester of pregnancy and who meet inclusion criteria were randomly selected and recruited in this study after taking proper consent.

Inclusion criteria

All pregnant women attending antenatal clinic during 13th-20th of gestation with normal blood pressure fulfilling exclusion criteria.

Exclusion criteria

All non-pregnant women having chronic hypertension (HTN), renal disease, gestational diabetes mellitus (GDM), cardiovascular disease, any other medical disorder, multiple pregnancy, obese pregnant women, anomalous fetus diagnosed by ultrasonography (USG), previous molar pregnancy, and previous preeclampsia or eclampsia were excluded.

Maternal serum β-hCG was done between 13th to 20thweek of pregnancy. Serum β-hCG was done using electro-chemiluminescence immunoassay (ECLIA) method. The level of β-hCG was then divided by the median concentration of β-hCG for the given week of pregnancy to generate a multiple of the median value (MOM). β-hCG levels were considered raised if the levels will be ≥2 multiple of median (MOM). The patients with raised β-hCG were subjected to detailed history, physical examination and laboratory investigations and management was done as per hospital protocol. The parameters used for correlation of severity of preeclampsia were systolic and diastolic blood pressure, serum creatinine levels, liver enzymes, platelet counts, serum uric acid were measured at 34 weeks of gestation and maternal complications were noted as patients were followed up till delivery. For the comparative study the MOM values were divided into 4 categories: 1: MOM <2, 2: MOM 2-2.9, 3: MOM 3-3.9, and 4: MOM ≥4.

Statistical analysis

Statistical tests were performed using the available version of statistical package for the social sciences (SPSS) software version 20. Mean and standard deviation were reported for continuous variables and no and % were reported for categorical variables. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant. Receiver operating characteristic (ROC) curve analysis is done to establish the cut offs for MOM β-hCG (13-20 weeks) for development of preeclampsia and sensitivity, specificity, positive predictive value, and negative predictive value.

RESULTS

This is a hospital OPD based prospective study. 200 pregnant women attending antenatal OPD were randomly selected (fulfilling inclusion and exclusion criteria). Antenatal patients were registered and serum β-hCG was done by ECLIA method during 13-20 weeks of gestation.

Out of 200 pregnant women 16 developed preeclampsia. The incidence of preeclampsia in the study population is 8%., as shown in Table 1.

Table 1: Incidence of preeclampsia in the study population.

Preeclampsia	Number	Percentage
Developed yes	16	8
Developed no	184	92

Table 2 showing comparison of increasing value of MOM MS β-hCG with development of preeclampsia. 1 case had MOM value ≥4 and developed preeclampsia. 3 cases had MOM 3-3.9 and all developed preeclampsia. Out of 13 cases having MOM 2-2.9, 7 developed preeclampsia. 183 cases had MOM <2 and only 5 developed preeclampsia.

Table 3 showing comparison of serum urea and creatinine with MOM value. Serum urea has mean standard deviation (40.34±9.06), (41±6.48), (41±10.58), (52±0) with increasing MOM value, <2, 2-2.9, 3-3.9, >4 respectively. It was statistically not significant (p=0.625).

Serum creatinine has mean standard deviation (0.71±0.15), (0.79±016), (0.9±0.1), (1.1±0) with increasing MOM value, <2, 2-2.9, 3-3.9, >4 respectively. It was statistically significant (p=0.003).

Platelet count has mean standard deviation (2.79±0.68), (2.12±0.72), (1.4±0.17), (1.6±0) with increasing MOM value, <2, 2-2.9, 3-3.9, >4 respectively. It was statistically significant (p<0.001).

Systolic blood pressure (SBP) had mean standard deviation (117.5±8.08), (129.33±15.55), (146±3.46) with increasing MOM value, <2, 2-2.9, 3-3.9 respectively. It was statistically significant (p<0.001). Diastolic blood pressure (DBP) had mean standard deviation (77.03±5.46), (83.5±8.4), (91.33±2.31) with increasing MOM value, <2, 2-2.9, 3-3.9 respectively. It was statistically significant (p<0.001).

Serum uric acid done at 34 weeks of pregnancy have mean standard deviation (4.08±0.71), (4.42±0.89), (5.53±1.04) and (5.0±0) with increasing MOM value, <2, 2-2.9, 3-3.9, >4 respectively. It was statistically significant (p=0.003).

Table 5 shows comparison the incidence of maternal complications, 11 cases of preeclampsia had MOM value ≥2. Frequency of eclampsia, oliguria/anuria, abruption, heart failure and maternal death are 3, 6, 1, 1, and 0 respectively in the study population.1 case had MOM ≥4, and had 3 complications, eclampsia, oliguria/anuria, heart failure. 3 cases had MOM 3-3.9, and frequency of eclampsia, oliguria/anuria, abruption was 2, 3 and 1 respectively.13 cases had MOM 2-2.9, frequency of eclampsia, oliguria/anuria, abruption was 0, 2 and 0 respectively. 183 cases had MOM <2 and only 1 patient had oliguria/anuria with no other complications in this group. Thus, table shows that with increasing MOM value maternal complications increases.

Table 6 and Figure 1 shows that the sensitivity, specificity, positive predictive value and negative predictive value of MOM value of β-hCG are 68.75, 97.28, 68.75 and 97.28 respectively. According to ROC curve of MOM value of maternal β-hCG.

Diagnostic accuracy of β-hCG is 95.00.

Cut off MOM β-hCG is 2.08.

Table 2: Comparison of MOM value of MS β-hCG with development of preeclampsia.

MOM MS β-hCG (IU/ml) (13-20 weeks)	Developed preeclampsia		Total	P value	Significance
	No	Yes			
<2	178 (96.74)	5 (31.25)	183 (91.5)	<0.001	Significant
2-2.9	6 (3.26)	7 (43.75)	13 (6.5)		
3-3.9	0 (0)	3 (18.75)	3 (1.5)		
≥4	0 (0)	1 (6.25)	1 (0.5)		
Total	184 (100)	16 (100)	200 (100)		

Table 3: Comparison of serum urea and serum creatinine level, platelet count, systolic blood pressure, diastolic blood pressure and serum uric acid at 34 weeks with MOM value.

Parameters	MOM β-hCG (IU/ml) (13-20 weeks) (mean±SD)				P value	Significance
	<2 (N=183)	2-2.9 (N=13)	3-3.9	≥4		
Serum urea (mg/dl)	40.34±9.06	41±6.48	41±10.58	52±0	0.625	Not significant
Serum creatinine	0.71±0.15	0.79±0.16	0.9±0.1	1.1±0	0.003	Significant
Platelet count (×10^5 ml)	2.79±0.68	2.12±0.72	1.4±0.17	1.6±0	<0.001	Significant
SBP (mm Hg) 34 weeks	116.91±6.07	127.38±9.47	133.33±9.45	144±0	<0.001	Significant
DBP (mm Hg) 34 weeks	76.69±5.36	84.92±5.51	88.67±2.31	90±0	<0.001	Significant
Serum uric acid (mg/dl)	4.08±0.71	4.42±0.89	5.53±1.04	5.0±0	0.003	Significant

Table 4: Comparison of serum liver enzymes level with MOM value.

Serum liver enzymes	MOM β hCG (IU/ml) (13-20 weeks)				Total	P value	Significance
	<2	2-2.9	3-3.9	≥4			
Normal	143 (78.14)	8 (61.54)	0 (0)	0 (0)	151 (75.5)	<0.001	Significant
Normal to twice normal	30 (16.39)	0 (0)	0 (0)	0 (0)	30 (15)		
More than twice of normal	10 (5.46)	5 (38.46)	3 (100)	1 (100)	19 (9.5)		
Total	183 (100)	13 (100)	3 (100)	1 (100)	200 (100)		

Table 5: Comparison of maternal complications between mothers preceded by raised MOM (≥2) and mothers not preceded by raised MOM (<2).

Maternal complications	Mom <2	MOM >2			Total	P value	Significance
		2-2.9	3-3.9	≥4			
Eclampsia	0	0	2	1	3	0.000	Significant
Oliguria/anuria	1	2	3	1	6	0.000	Significant
Abruption	0	0	1	0	1	0.001	Significant
Heart failure	0	0	0	1	1	0.001	Significant
Maternal death	0	0	0	0	0	NA	NA
Total no. of patient according to MOM	183	13	3	1			

Table 6: Sensitivity, specificity and predictive values of β-hCG in prediction of development of preeclampsia.

Anthropometric indicator	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
MOM msβ-hCG (IU/ml) (13-20 weeks)	11	179	5	5	68.75	97.28	68.75	97.28	95.00

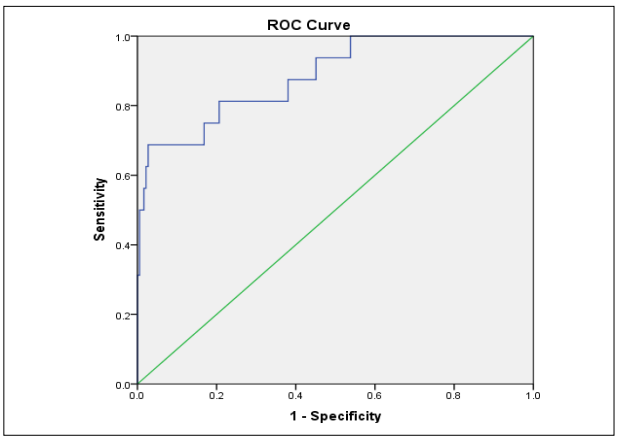

Figure 1: ROC curve of MOM value of maternal β-hCG.
Cut off MOM β-hCG=2.08; AUC of the ROC curve=0.886

DISCUSSION

Preeclampsia is a specific disorder of pregnancy and is a major cause of maternal and perinatal morbidity and mortality worldwide. The overall aim of this study was to correlate the values of β-HCG with severity of preeclampsia.

In this study, 16 out of the total 200 patients developed preeclampsia. Thus, incidence was 8%. Consistent with previous studies, that stated incidence of 2-8%.[13-15]

In the study, as shown in Table 2 MOM value ≥2 of β-hCG (13-20 weeks) was found in 17 (8.5%) mothers out of 200. 11 (5.5%) out of 17 mothers having MOM value ≥2 developed preeclampsia (SBP≥140, DBP≥90, dipstick≥1+), with p value <0.001, and found significant. Out of 183 patients not preceded by raised MOM value (<2) 5 (2.5%) patients developed preeclampsia.

One patient had MOM value >4, and 3 had MOM (3-3.9). All the 4 patients had preeclampsia while out of 13 having MOM (2-2.9), 7 developed preeclampsia. 1 patient having MOM >4 had severe preeclampsia (BP≥160/110 mm of Hg, dipstick 2+). 3 patients having MOM value >3 also had higher blood pressure and more dipstick values. Increasing blood pressure association was found with higher MOM values for all weeks of pregnancy after 20 weeks with p<0.001.

A study was conducted in department of obstetrics and gynaecology, SMS Medical College, Jaipur from July 2008 to August 2009 on 200 pregnant, normotensive, nonproteinuric women selected randomly between the gestational age 13–20 weeks attending the ANC clinics.[16] Out of 200 cases, 178 (89%) were finally evaluated. Of whom 22 (12.36%) cases developed PIH. β-hCG levels were considered raised if the levels were >2 MOM. 20 (83.33%) out of 24 cases with β-hCG levels >2 MOM developed PIH against 2 (1.2%) cases out of 154 having β-hCG levels ≤2 MOM (p value <0.001). Also, higher levels of β-hCG are associated with increased severity of PIH (p value <0.01). The sensitivity was 90.91%, specificity was 97.44% and positive predictive value was 83.33% The association of MOM of β-hCG with preeclampsia was also found significant by Rao. In this study by Desai and Rao, 62 cases out of 90 (68.9%) with values of β-hCG >2 MOM developed PIH against 21 cases out of 130 (16.15%), having a β-hCG value <2 MOM.[17] The difference was statistically significant (p value <0.001).

In Tables 3 and 4 from the comparisons of all blood parameter like serum urea, serum creatinine, liver enzymes, platelet count, it was found that severity of complications are higher with increasing MOM value. Both the comparison shows of SBP and DBP values shows that severity of blood pressure is increasing with MOM value. In a study done in MGM Medical College, Indore, they also found p value of <0.001 both SBP and DBP was

found increasing with higher MOM value.[15] Maternal complications shows that with increasing MOM value maternal complications increases.

This significant association was also found in study conducted in department of obstetrics and gynaecology, SMS Medical College, Jaipur, where higher levels of β-hCG are associated with increased severity of PIH (p value <0.01).[16] Roiz-Hernandez et al, and Kabukcu et al also found the same association.[18,19] Similar results were shown in study by Jaiswar et al in which the author concluded that there was a positive correlation between β-hCG and severity of PIH.[20]

Sensitivity, specificity, positive predictive value and negative predictive value of MOM value of β-hCG are 68.75, 97.28, 68.75 and 97.28 according to ROC curve of MOM value of maternal β-hCG. Diagnostic accuracy of β-hCG is 95.00. Cut off MOM β-hCG is 2.08. In a study conducted in department of obstetrics and gynaecology, SMS Medical College, Jaipur, the sensitivity was 90.91%, specificity was 97.44% and positive predictive value was 83.33%.[16]

Roiz-Hernandez et al, showed that with a cut off value of 2 MOM for β-hCG in multipara and primigravida during second trimester, 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.[18]

Limitations

This study was based on only one parameter i.e. MOM value β-hCG in early 2nd trimester and its prediction in mothers developing preeclampsia during later month of pregnancy. But there are several other biochemical and biophysical markers in early 2nd trimester which can also predict preeclampsia either alone or in combinations. This study could have combined with one or more than one marker for better prediction. Other biochemical markers are serum AFP, serum PAPP-A, serum Inhibin-A. Biophysical markers like Doppler ultrasound of uterine artery, as there are studies shown that pulsatility index (PI), resistance index (RI) and persistent diastolic notching till 2nd trimester can also predict poor placental implantation and preeclampsia.

CONCLUSION

In this study, 16 cases (8%) had developed preeclampsia. On comparing severity of preeclampsia, SBP, DBP, severity was found higher in cases with higher values of 2nd trimester β-hCG. Thus, β-hCG has strong association with the severity of preeclampsia. Mothers having higher level of β-hCG had suffered more degree of complications. Thus, 2nd trimester β-hCG levels not only is a good predictor of preeclampsia, it also serves as a great tool for determining the severity of preeclampsia.

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