RESEARCH ARTICLE

Maternal Serum Beta Human Chorionic Gonadotropin Level Estimation in Early Second Trimester as a Predictor for Pregnancy-induced Hypertension

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Abstract

Background and objectives: To date, pregnancy-induced hypertension (PIH) and its sequelae remains dreaded complication of pregnancy. Several tests have been proposed for the prediction of PIH but none has been accepted widely due to the controversial results. This study hypothesized that elevated levels of maternal serum beta human chorionic gonadotropin (β-HCG) during the early second trimester (13–20 weeks) predict PIH.

Materials and methods: The present 1-year prospective study was done in from January 2014 to December 2014 in the Department of Obstetrics and Gynecology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 300 pregnant women in early second trimester (gestational age 13–20 weeks) were enrolled. All the women were evaluated for serum β-HCG and followed till delivery, for the development of PIH.

Results: Maximum women (57%) were aged from 21 to 25 and the mean age was 23.42 ± 3.25 years. A total of 53.33% of the women were primigravida and most of the women had gestational age of 19 weeks (23.67%). The β-HCG levels of <30000 mIU/mL were noted in 46.33% of the women and mean β-HCG levels were 53338.50 ± 62109.39 mIU/mL and raised levels [rise of ≥2 multiple of median (MOM) β-HCG] was noted in 29% of the women. Out of 300 women, 25 (8.33%) women developed PIH of which 10 (40%) women had gestational hypertension, 9 (36%) developed mild preeclampsia, and 6 (24%) had severe preeclampsia. Significantly higher number of women with β-HCG MOM ≥2 were diagnosed with PIH ($p = 0.003$). The mean MOM of β-HCG was significantly high in women with PIH (2.41 ± 1.94 vs 1.62 ± 1.46; $p = 0.012$). Also significantly higher number of women with severe preeclampsia (83.33%), gestational hypertension (60%) had β-HCG levels of ≥2 MOM compared with women with mild preeclampsia (33.33%) ($p = 0.002$). There was significant rise in mean β-HCG MOM levels in women with mild preeclampsia, gestational hypertension, and severe preeclampsia compared with women who did not develop PIH ($p = 0.002$). The sensitivity of β-HCG considering a cut-off value of ≥2 MOM was 56% and specificity was 73.45%.

Conclusion and interpretation: There is strong association between elevated serum β-HCG levels of >2 MOM and development of PIH but it is not a good predictor of PIH due to low sensitivity (56%) and moderate specificity (73.45%).

Keywords: Beta human gonadotropin, Gestational hypertension, Pregnancy-induced hypertension.

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Introduction

Pregnancy-induced hypertension (PIH) is one of the common complication that causes the most detrimental effects to the maternal, fetal, and neonatal organs.[1]

Pregnancy-induced hypertension can be a major contributor to maternal morbidity and mortality as a immediate consequence of progression to eclampsia. The most common major obstetric complications include acute renal failure, disseminated intravascular coagulation, HELLP syndrome and pulmonary edema. Preeclampsia/eclampsia probably accounts for more than 50,000 maternal deaths worldwide each year.[2,3]

It is indeed a constant endeavor of obstetricians to predict the development of preeclampsia and if possible prevent its development. Prediction would identify those women who require more intensive monitoring, result in early recognition of PIH and permit intercession before life-threatening complications develop. In addition, early identification of women at risk might help select the patients most likely to benefit from any therapeutic measure. It could further help clarify pathogenic mechanisms and might ultimately lead to more specific, mechanistically based strategies for prevention and treatment.

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Variety of biological tests like provocative pressor tests were proposed, but these are cumbersome to perform, expensive, time consuming, invasive and low sensitivities and specificites.[4]

Biochemical tests like alpha fetoprotein, serum uric acid, microalbuminuria, calcium creatinine ratio, etc., were proposed

but these have less sensitivity and specificity with low positive predictive value (PPV).[4]

Biophysical markers such as uterine artery doppler velocimetry and pulse wave analysis have been proposed and these tests have a better sensitivity and specificity but needs expertise and are not available widely.[1]

Beta-human chorionic gonadotropin (β-HCG) is produced by placental trophoblasts and excreted directly into maternal circulation, its increased level is a sign of placental dysfunction. Its measurement is neither time consuming nor does it require expertise. This test is a widely available and easy to perform.

Association between elevated maternal serum HCG in second trimester and PIH has been hypothesized in few clinical studies[5–10] with good sensitivity and positive predictive value, necessitating the need for further studies for β-HCG as a marker for prediction of PIH.

This study is planned to determine whether elevated levels of maternal serum β-HCG during the early second trimester (13–20 weeks) can predict PIH.

Materials and Methods

This study was conducted in the Department of Obstetrics and Gynecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi.

Study Design

The study design was a prospective study.

Study Duration and Period

This study was conducted for period of 1 year from January 2014 to December 2014.

Place

The present study was done at Department of Obstetrics and Gynecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi, a teaching hospital attached to Jawaharlal Nehru Medical College, Belagavi, Karnataka.

Source of Data

Pregnant women in early second trimester (13–20 weeks) registered at Outpatient Antenatal Clinic, Department of Obstetrics and Gynecology, KLES Dr Prabhakar Kore Charitable Hospital and Medical Research Center, Belagavi, Karnataka were enrolled.

Sample Size

The study was comprised of 300 pregnant women in early second trimester (13–20 weeks).

Selection Criteria

Inclusion Criteria

- Normotensive patients in early second trimester (13–20 weeks) of pregnancy irrespective of parity were included in study.

Exclusion Criteria

Pregnant women with:

- Chronic hypertension.
- Preexisting renal diseases.
- Multiple pregnancy.
- Known case of diabetes mellitus.
- Molar pregnancy.
- Mother's with history of previous baby with Downs syndrome or pregnant women who are screened positive for Downs in present pregnancy.
- Abortion <20 weeks of gestation.
- Loss of antenatal follow up in KLE Dr Prabhakar Kore Charitable Hospital, Belagavi.

Method of Collection of Data

After the enrollment demographic data, obstetric history and current pregnancy details were obtained through an interview and noted. Gestational age was calculated from the reliable last menstrual period, and correlated with first trimester scan or early second trimester scan, if the last menstrual period was unknown than gestational age was calculated by either first trimester scan or early second trimester scan whichever was available. The data obtained was recorded on the predesigned and pretested proforma.

Estimation of Serum β-HCG

The serum β-HCG estimation was done by chemiluminescent immunometric assay (CLIA) method. The multiple of median (MOM) was calculated from the median of the diagnostic test employed for the current study for the HCG which being gestational age specific (PRISCA). The serum β-HCG was considered raised if levels were more than 2 MOM for the specific gestation age.[10] The cases were followed up in the antenatal clinic till delivery and observed for development of PIH.

Pregnancy-induced hypertension was defined as a systolic BP of 140 mm Hg or more OR a diastolic BP of 90 mm Hg or more OR both after 20 weeks of gestation. Proteinuria was defined as greater than or equal to 0.3 gm of protein in a 24-hour urine collection.[11]

Gestational hypertension defined as hypertension appearing for first time after 20 weeks of gestation with no proteinuria or any of severe features of preeclampsia and return of blood pressure to normal before 12 weeks postpartum.[11]

Mild preeclampsia was defined as hypertension developing after 20 weeks of gestation with systolic blood pressure less than 160 mm Hg and diastolic blood pressure less than 110 mm Hg accompanied by proteinuria of at least 300 mg/24-hour urine collection.[11]

Severe preeclampsia was defined by the presence of any of the below mentioned featues.[11]

- Hypertension—systolic >160 mm Hg or diastolic >110 mm Hg on two occasions at least 4 hours apart while the patient is on bed rest developing after 20 weeks gestation.
- Thrombocytopenia—platelet count <1,00,000.
- Impaired liver function test—elevated liver transaminases to twice the normal, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnosis or both.
- New development of renal insufficiency—serum creatinine >1.1 mg/dL OR doubling of serum creatinine in absence of renal disease.
- Pulmonary edema.
- New onset cerebral or visual disturbances.

Eclampsia was defined as preeclampsia that manifested with convulsions.[11]

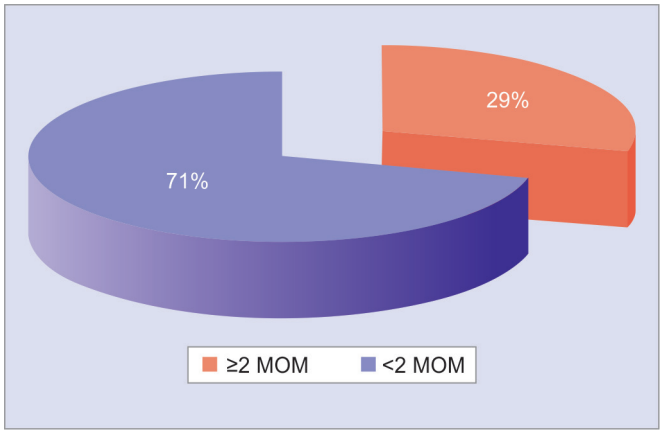

Fig. 1: Distribution of pregnant women according the β-HCG multiple of median

Statistical Analysis

The data obtained were coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data were expressed as rates, ratios, and proportions and continuous data were expressed as mean ± standard deviation (SD). Chi-square test or Fisher's exact test was used for the comparison of categorical data. Continuous data were compared using independent sample '*t*' test and in case of more than three means one way ANOVA was used. The rise in β-HCG levels was determined based on MOM. The accuracy of serum beta HCG levels in predicting PIH was found by calculating sensitivity, specificity, PPV, negative predictive value (NPV), and likelihood ratio.

A probability value ('*p*'-value) of less than or equal to 0.05 was considered as statistically significant.

Results

In the present study, maximum number of cases were aged between 21 and 25 years that is 171 women (57%), between 26 and 30 years 62 women (20.67%), below 20 years 59 women (19.67%), between 31 and 35 years 7 women (2.33%), and more than 35 years 1 women (0.33%). The mean age was 23.42 ± 3.25 years and median age was 23 years (range 18–38 years).

A total of 160 (53.33%) were primigravida, among the multigravida, there were 89 (26.97%) second gravida women, 38 (12.67%) third gravida, 10 (3.33%) fourth gravida, and 3 (1%) were fifth gravida pregnancy. Most of the women had gestational age of 19 weeks that is 71 (23.67%), followed by 13 weeks 51 women (17%), 18 weeks 50 women (16.67%), 14 weeks 37 women (12.33%), 17 weeks 36 women (12%), 15 weeks 27 women (9%), 16 weeks 27 women (9%), and one woman (0.33%) of 20 weeks gestation age.

A total of 139 (46.33%) women had β-HCG levels of <30000 mIU/mL followed by 69 (23%) women had values between 30000 and 59999 mIU/mL, 41 (13.67%) women had values between 60000 and 89999 mIU/mL and 51 (17%) women had absolute values of more than 90000 mIU/mL. The mean β-HCG levels were 53338.50 ± 62109.39 and median levels were found to be 33666 mIU/mL (range 470–586724). In present study, 25 (8.33%) women developed PIH.

Distribution of pregnant women according to β-HCG in MOM (Fig. 1) showed 29% of the total cases having values of more than 2 MOM.

A total of 10 women had gestational hypertension. Among them, 4 had β-HCG levels of 30000–59999 mIU/mL, 3 had ≥90000 mIU/mL, 2 had <30000 mIU/mL and 1 had 60000–89999 mIU/mL. However, this difference was statistically not significant ($p = 0.122$).

In this study, significantly higher number of women with β-HCG MOM ≥ 2 were diagnosed with PIH ([$p = 0.003$] Table 1).

Association of serum β-HCG levels (MOM) with severity of PIH (Table 2) showed that severe PIH was noted in 6 women, among them 5 (83.33%) had β-HCG levels of ≥2 MOM. Mild PIH was seen in 3 (33.33%) out of 9 women with >2 MOM. Also of the 10 women with gestational hypertension, 6 (60%) had β-HCG levels of ≥2 MOM. These observations were statistically significant ($p = 0.002$).

In the present study, the mean MOM of β-HCG was significantly high in women with PIH (2.41 ± 1.94 vs 1.62 ± 1.46; $p = 0.012$).

The mean β-HCG MOM levels were low in women who did not develop PIH (1.62 ± 1.47 mIU/mL) while there was significant rise in mean β-HCG MOM levels in women who developed mild PIH (1.65 ± 1.50 mIU/mL) and further rise was noted in women who developed mild and severe PIH (2.21 ± 1.30 and 3.92 ± 2.76 mIU/mL, respectively). This difference was statistically significant ($p = 0.002$).

No statistically significant association was found between absolute serum β-HCG levels and PIH (Table 3).

Table 1: Association of β-HCG MOM levels with development of PIH

	PIH					
	Yes		*No*		*Total*	
β-HCG levels (MOM)	*No.*	*%*	*No.*	*%*	*No.*	*%*
≥2	14	16.09	73	83.91	87	100.00
<2	11	5.16	202	94.84	213	100.00
Total	**25**	**8.33**	**275**	**91.67**	**300**	**100.00**

p-value = 0.003

Table 2: Association of serum β-HCG levels (MOM) with severity of PIH

	β-HCG levels (MOM)					
	≥2		*<2*		*Total*	
Severity	*No.*	*%*	*No.*	*%*	*No.*	*%*
Gestational HTN	6	60.00	4	40.00	10	100.00
Mild PIH	3	33.33	6	66.67	9	100.00
Severe PIH	5	83.33	1	16.67	6	100.00
Total	**14**	**66.00**	**11**	**44.00**	**25**	**100.00**

$p = 0.002$

Table 3: Association between absolute serum β-HCG levels and development of PIH

	PIH					
	No		*Yes*		*Total*	
β-HCG levels (mIU/mL)	*No.*	*%*	*No.*	*%*	*No.*	*%*
<30000	131	94.24	8	5.76	139	100.00
30000–59999	62	89.86	7	10.14	69	100.00
60000–89999	39	95.12	2	4.88	41	100.00
≥90000	43	84.31	8	15.69	51	100.00
Total	**275**	**91.67**	**25**	**8.33**	**300**	**100.00**

$p = 0.124$

Discussion

In the present study based on MOM, raised β-HCG levels (≥2 MOM) were noted 29% of the women and 71% of the women were found

to have β-HCG levels of <2. Similar results of serum β-HCG levels (MOM) have been reported in a study by Kaur et al.[10]

In the present study, of the 300 women studied, 25 (8.33%) of the women had PIH. Among them, 10 (46%) had gestational hypertension, 9 (36%) was mild PIH and 6 (24%) had severe PIH. The prevalence of PIH varies according to geographic regions of world.[12] In India, the incidence of PIH is more than 4% (41.2 per 1,000) reported in 2009.[13] The prevalence of PIH observed in the present study that is 8.3% was consistent with those of national levels and to the study done by Kaur et al. to assess the role of serum β-HCG levels in early pregnancy and development of PIH where authors reported 13% of the patients with PIH.[10]

Significantly higher number of women with ≥2 MOM β-HCG levels were diagnosed with PIH (16.03%) compared with women with <2 MOM β-HCG levels (5.16%) ($p = 0.003$). Further the mean MOM of β-HCG levels was significantly high in patients with PIH (2.41 ± 1.94) compared with those who did not develop PIH (1.62 ± 1.46) ($p = 0.012$). These findings suggest a significant relationship between elevated β-HCG levels and PIH that is, pregnant women with more than 2 MOM rise of β-HCG during the early second trimester are at increased risk of developing PIH.

A similar study by Kaur et al. from Jaipur also reported that, women with higher levels of β-HCG (>2 MOM) during the second trimester of pregnancy, developed PIH later in their pregnancy ($p = 0.001$).[10] In another study by Desai and Rao, out of 90 cases, 62 cases (68.9%) had PIH with β-HCG >2 MOM against 21 cases out of 130 (16.15%) with β-HCG value <2 MOM ($p = 0.001$).[6] Kabukcu et al. studied 610 pregnant women in second trimester, grouping them according to the MOM of β-HCG and found that women with elevated second trimester β-HCG levels (>2 MOM) are at increased risk of developing preeclampsia (odds ratio 5.93; 95% *CI* 1.97–15.88).[8]

In the present study, severe PIH was noted in six women. Among them five (83.33%) had β-HCG levels of ≥2 MOM. Mild PIH was seen in 3 (33.33%) out of 9 patients with >2 MOM. Also of the 10 women with gestational hypertension, 6 (60%) had β-HCG levels of ≥2 MOM. These observations were statistically significant ($p = 0.002$), these findings are in line with studies done by Kaur et al. and Jaiswal et al.[9,10]

In the present study, 51 women (17%) had β-HCG levels of >90000 and among them 8 (15.6%) developed PIH. In 251 women (83 %) with β-HCG levels of <100000, 17 (6.7%) developed PIH. This difference was statistically not significant ($p = 0.204$) suggesting lack of association between absolute β-HCG levels with PIH. This can be explained by the differences in gestation age at the time of enrolment into the study. However, the mean β-HCG MOM levels were significantly high in women who developed mild PIH (1.65 ± 1.50 mIU/mL), gestational hypertension (2.21 ± 1.30 mIU/mL) and severe PIH (2.21 ± 1.30 and 3.92 ± 2.76 mIU/mL) compared with women who did not develop PIH (1.62 ± 1.47 mIU/mL) ($p = 0.002$).

In the present study, accuracy of β-HCG in predicting PIH considering a cut off value of ≥2 MOM yielded sensitivity of 56%, specificity of 73.45%, PPV of 16.09%, and NPV of 94.84%. The positive likelihood ratio was 2.11 and negative likelihood ratio was 0.60.

Conclusion

Overall the present study showed strong relationship between developments of PIH with raised β-HCG levels expressed as ≥2 MOM during early second trimester with average accuracy for the prediction of PIH. Though the accuracy of β-HCG levels was moderate the estimation of β-HCG levels in early pregnancy, is simple test as compared with other predictor tests and raised β-HCG levels prompt suspicion of development of PIH in later half of pregnancy and provide basis for monitoring to obstetrician in clinical practice. The limitation of the study was small sample size and being the single center study the findings could not be generalized to the entire population. Hence, large scale multicentric studies are warranted to extend the role of β-HCG in prediction of PIH.

Ethical Approval

Prior to the commencement, ethical clearance was obtained from the Institutional Ethical committee, Jawaharlal Nehru Medical College, Belagavi.

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