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To study serum βhCG in early second trimester as predicator of gestational hypertension and Preeclampsia

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Abstract:

Context: - Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. It has been estimated that preeclampsia complicates 2–8% of pregnancies globally. Beta human chorionic gonadotropin (βhCG) is secreted mainly from placenta and it is elevated in mid trimester in patients who develop PIH later on.11,12 Keeping in view the present study was planned to estimate serum βhCG during 14-20 weeks of pregnancy with the aim to investigate the role of serum βhCG level as predictors of gestational hypertension and preeclampsia.

Objectives: To investigate the role of serum βhCG at 14-20 weeks of gestation as predictors for the development of gestational hypertension and preeclampsia & to access Accuracy of serum βhCG in predicting gestational hypertension and preeclampsia at different values of βhCG

Material & Methods: A prospective cohort study was conducted in the Department of Obstetrics and Gynaecology in collaboration with Department of Clinical Biochemistry and Laboratory Medicine of VMMC and Safdarjung Hospital, New Delhi. The study group included 150 pregnant women attending the ANC OPD; the sample size was calculated assuming alpha to be 0.05 and power of study to be 90%. For the analysis, the study group (n=150) was divided into 2 groups on the basis of the subsequent development of hypertension (with and without proteinuria). Cases(n=20): Women who subsequently developed gestational hypertension or preeclampsia were included in the case group and were labelled as the hypertensive group. Controls (n=130): Women who remained normotensive till delivery were included in the control group and were labelled as normotensive group. The obstetrical examination was done at every visit to note fetal growth and wellbeing. Besides routine antenatal investigations, βhCG profile was done between 14-20 weeks of gestation from the central hospital laboratory. All the women were monitored for the development of gestational hypertension /preeclampsia and were followed up till delivery.

Results & Conclusion: Serum βhCG at 14-20 weeks of gestation is a good predictor for the subsequent development of hypertension (PE/GH) in pregnancy. At an acceptable sensitivity of 85%, the value of βhCG obtained from ROC curve is 57,226 mIU/ml. The accuracy of this value in predicting hypertension is 96.67%.

Keywords:

Serum βhCG, Gestational hypertension, pre-eclampsia

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Introduction

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. It has been estimated that preeclampsia complicates 2–8% of pregnancies globally.1

Gestational hypertension is defined as a Systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure2. i.e. High blood pressure that develops after 20 weeks of pregnancy, without any accompanying signs of organ damage or excessive protein in the urine.

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria3.

i.e a more serious condition characterized by high blood pressure and other signs of organ damage, such as protein in the urine, liver problems, kidney problems, or other signs of organ dysfunction.
Preeclampsia is a systemic disease characterized by endothelial injury. Although overt illness appears in the third trimester, there are multiple indicators that the disease process begins early in pregnancy. Second trimester changes in several maternal serum factors are among the frequent precursors of clinical symptoms.4-7 Hypertension and proteinuria are the simple clinical criteria for the diagnosis of preeclampsia but the pathophysiological mechanism that leads to this disorder are by all very diverse.8

A variety of biochemical and biophysical markers have been proposed for the purpose of predicting preeclampsia development later in pregnancy. Various tests used in literature are Roll over test at 28-30 weeks, isometric exercises and angiotensin 2 infusion. The sensitivity of these tests' ranges from 55-70% and approximately 85% of specificity.9

The non-invasive biomarkers have been proposed to predict the development of hypertensive disorders (with or without proteinuria). Amongst these are angiogenic factors like vascular endothelial growth factor (VEGF), placental growth factor (PlGF), fms like tyrosine kinase (flt)-1, soluble Endoglin(Eng), P selectin, a disintegrin and metalloprotease 12 (ADAM 12), a membrane bound zinc dependent protease, placental protein -13(PP -13), tumor necrosis factor stimulated gene 14 (PTX 3), pregnancy associated plasma protein A (PAPP-A) which have limited clinical utility.10 The role of serum βhCG in the prediction of development of hypertensive disorders (with or without proteinuria) has also been evaluated by various studies.11-13 Placenta is the known primary trigger of pregnancy induced hypertension (PIH). Women with PIH (with or without proteinuria) have hyper placentosis or an abnormal placentation.
Beta human chorionic gonadotropin (βhCG) is secreted mainly from placenta and it is elevated in mid trimester in patients who develop PIH later on.11,12 Keeping in view the present study was planned to estimate serum βhCG during 14-20 weeks of pregnancy with the aim to investigate the role of serum βhCG level as predictors of gestational hypertension and preeclampsia.

Aims and objectives:

1. To investigate the role of serum βhCG at 14-20 weeks of gestation as predictors for the development of gestational hypertension and preeclampsia.
2. To access Accuracy of serum βhCG in predicting gestational hypertension and preeclampsia at different values of βhCG

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Material and methods:

A prospective cohort study was conducted in the Department of Obstetrics and Gynaecology in collaboration with Department of Clinical Biochemistry and Laboratory Medicine of VMMC and Safdarjung Hospital, New Delhi. Before starting the study, permission was taken from the ethical committee of the hospital. The study group included 150 pregnant women attending the ANC OPD; the sample size was calculated assuming alpha to be 0.05 and power of study to be 90%. A total of 150 pregnant women who were willing to participate in study and who planned to deliver at Safdarjung Hospital were included in the study. The women were recruited as per the inclusion and exclusion criteria and were followed till delivery.

Inclusion criteria:

1. Singleton pregnancy
2. Gestational age between 14-20 weeks
3. Women sure of last menstrual period (LMP)
4. History of previous regular menstrual cycles

Exclusion criteria:

1. Gestational age <14 and >20 weeks
2. Multiple pregnancy
3. Women not sure of LMP
4. History of previous irregular cycles
5. Any gross congenital abnormality in fetus
6. Women with chronic medical disease like hypertension, diabetes, thyroid disease, heart disease and collagen disorders

For the analysis, the study group (n=150) was divided into 2 groups on the basis of the subsequent development of hypertension (with and without proteinuria).

Cases(n=20): Women who subsequently developed gestational hypertension or preeclampsia were included in the case group and were labelled as the hypertensive group.

Controls (n=130): Women who remained normotensive till delivery were included in the control group and were labelled as normotensive group.

Before starting the study, an informed consent was obtained from all the women who participated in study. A detailed history regarding age, parity, menstrual cycles and period of gestation, pre-pregnancy weight, any chronic medical and surgical history and family history was taken at first visit. Complete physical examination including height, weight, blood pressure, pedal oedema and systemic examination was done. The obstetrical examination was done at every visit to note fetal growth and wellbeing. Besides routine antenatal investigations, βhCG profile was done between 14-20 weeks of gestation from the central hospital laboratory. All the women were monitored for the development of gestational hypertension /preeclampsia and were followed up till delivery.

Case definition:

Gestational hypertension refers to BP ≥ 140/90 mmHg for the first time in pregnancy without proteinuria, after 20 weeks of gestation.9

Preeclampsia is characterized by BP ≥140/90 mmHg and proteinuria ≥300mg / 24 hour or ≥1+ dipstick that develop after 20 weeks of gestation.9

Sample collection and procedure

βhCG: 2ml of blood in plain vial was taken and allowed to clot. The centrifugation of the sample was done and serum was separated. Sample was stored at 2-8°C for not more than 5 days. Before testing, the sample was brought down to room temperature at 20-27°C and assay was done with Microplate Immuno- enzyme- metric method.

Statistical analysis

The descriptive statistics in term of mean, S.D., range (min, max) of all the parameters of interest was calculated for hypertensive and for nomotensive groups separately and p value <0.05 was set as level of significance. The difference of various parameters between the two groups was tested by chi square test. The Receiver Operating Characteristic Curve (ROC) curve was used to choose the cut off value of β hCG and lipid profile. The logistic regression model was used for causal effect relationship. The effects of these predictors were measured in terms of odds ratio (OR) and its confidence limits (C.I.).

Results and Discussion:

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In the present study, out of 150 antenatal women, 20 women developed hypertension (with or without proteinuria) till delivery and 130 remained normotensive. Among 20 hypertensive women, 13 developed preeclampsia while 7 developed gestational hypertension. In Our study shows that majority (60%) of hypertensive and 56.7% of normotensive women were multipara while 40% of hypertensive and 43.8% of normotensive women were primipara. The association was not statistically significant. These results are in consistent with other studies done by Setareh et al.14 However ,the present observation is in contrast with study done by Vidyabati et al which showed that the risk of developing hypertension was higher in primiparas as compared to multiparous women.11 The incidence of preeclampsia in nulliparous population ranges from 3-10 % , while in multiparous it is comparatively less, but variable ; The difference of parity in different studies can be because of difference in race and ethinicity.9

The Mean ± SD of SBP in the hypertensive group at delivery was 148.00 ± 13.88 and in normotensive group, it was 118.96 ± 7.59 mm Hg. The difference was statistically significant (p-value <0.001). In the study by Vidyabati et al, the mean SBP was 165.52 mm Hg and DBP 98.66 mmHg, at delivery among hypertensive women.12

In the hypertensive group, the Mean ± SD of DBP at delivery was 96.95 ± 8.80, while in normotensive group, it was 78.82 ± 3.65 mm Hg. The difference was statistically significant (p-value <0.001).

Table 1: Comparison of Mean ± SD of Serum βhCG between hypertensive and normotensive group.

Variable	HYPERTENSIVE (PE/GH) (n = 20) Mean ± SD	NORMOTENSIVE (n=130) Mean ± SD	p -value
Serum βhCG	80661.65 ± 24007.68	25104.38 ± 11550.00	0.000

In the hypertensive group, the Mean ± SD of Serum βhCG was 80661.65 ± 24007.68; in the normotensive group it was 25104.38 ± 11550.00 mIU/ml. The difference was statistically significant (p-value <0.001).

Table 2: Distribution of Serum βhCG between hypertensive and normotensive group.

βhCG (mIU/ml)	HYPERTENSIVE (PE/GH) (n = 20)		NORMOTENSIVE (n = 130)	
	No.	percentage	No.	percentage
<10,000	0	0%	5	3.9%
10-30,000	0	0%	94	72.3%
30,001-50,000	2	10%	28	21.5%
50,001-70,000	6	30%	2	1.5%
70,001-90,000	6	30%	0	0%
90,001-1,10,000	2	10%	1	0.8%

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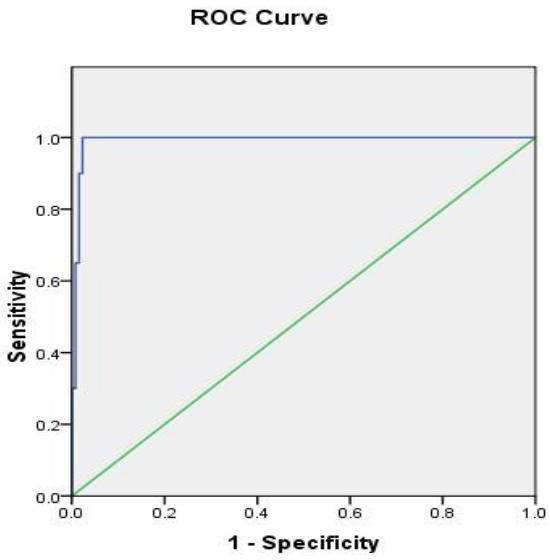
1,10,01-1,30,000	**4**	**20%**	**0**	**0%**

In the present study, majority (72.3%) of the normotensive women had βhCG between 10,000 to 30,000 mIU/ml, while all of the hypertensive women had βhCG above 30,000 mIU/ml. At a cut off of 30,001 mIU/ml, there were 100% true positives and 23.8% false positives, giving a sensitivity of 100% and specificity of 77%. Thus, with this value as cut off, we would not be missing out any women who would subsequently develop hypertension; however, we would have to unnecessarily follow 23.8% women, who would remain normotensive. When a cut off of 50,001 mIU/ml was chosen, there were 90% true positives and 2.3% false positives, making the sensitivity of 90% and specificity of 97.7%. If the value of β hCG was chosen as 57,226 mIU/ml from ROC at 85% sensitivity, the accuracy of β hCG in predicting development of hypertension was approximately 96%. An Indian study by Vidyabati et al also reported that pregnant women having serum βhCG level around 45,000 mIU/ml in the early second trimester of pregnancy would develop PIH. The percentage detection of PIH using βhCG as marker was 72.41%.12 The association of βhCG with blood pressure was statistically significant (p-value <0.001).

The cut off value of β hCG in our study for the prediction of development of hypertension was taken from Receiver Operating Characteristic curve (ROC Curve). Figure 1

Figure 1: ROC Curve of Serum βhCG



Area Under the Curve

Test Result Variable(s): hCG

			Asymptotic 95% Confidence Interval	
Area	**Std. Errora**	**Asymptotic Sig.b**	**Lower Bound**	**Upper Bound**

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.991	.006	.000	.000	1.000

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

ROC defined the sensitivity and 1- specificity for each value of βhCG.

Table 3: Accuracy of β hCG in predicting hypertension at different values of β hCG

β hCG mIU/ml	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
57,226	85	97.3	90.48	97.67	96.67
62,735	70	98.5	87.5	95.52	94.67

When the cut off value of β hCG was chosen at 57,226 from ROC, the sensitivity of β hCG in predicting the development of hypertension was 85%, specificity was 97.3%, positive predictive value was (PPV) 90.48%, negative predictive value (NPV) was 97.67%. The accuracy of this value in the prediction of development of hypertension was 96.67%.

When the cut off value of β hCG was chosen at 62,735, the sensitivity was 70%, specificity was 98.5%, PPV was 87.5, NPV was 95.52%. The accuracy of this value in the prediction of development of hypertension was 94. 67%.

Table: -4 Crude Odd's Ratio for Serum βhCG

variable	Cut off	p value	OR	95% C. I.
Serum βhCG (mIU/ml)	57,226	< 0.001	362.667	56.494-2328.169

In the present study, crude odd's ratio of βhCG was 362.667, taking a cut- off of 57,226 mIU/ml, ie. in women with βhCG >57,226 mIU/ml, there was 362.667 times chances of developing hypertension. Another study reported that, with 1000 mIU/ml increase in serum βhCG, the chances of a pregnant woman developing PIH increased by 10.7%.11 According to Sorenson et al, risk ratios increased between the control group and the study group, which they took as hCG levels of 2.0 to 3.99 multiples of median The women with elevated hCG levels were almost 7 times more likely to develop proteinuric PIH than were women with normal levels (adjusted risk ratio 6.9 ,95% CI of 2.0 to 23.2 (s) and 1.7 times more likely to have PIH without proteinuria.11 The study by Davidson et al reported that the MoM of serum hCG was significantly elevated in those women who later developed pre-eclampsia (a 24% increase in these women compared with the controls) but not in women who developed non proteinuric hypertension .15

From the above studies, it was evident that there is an association between βhCG and the development of hypertension in pregnancy (PE/GH). There is

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general agreement that the placenta remains the main source of βhCG in patients with preeclampsia, but whether the cause of high circulating levels of hormone is placental overproduction is still debated. Some advocate that hCG secretion may be increased as a consequence of abnormal placental invasion or placental immaturity.16 It may also be linked to the trophoblast response to hypoxia with the development of a hypersecretory state .17 A role for placental factors is further supported by the findings of increased lipid peroxidation and oxidation stress in placentas of women with pre-eclampsia.9 Placenta is the known primary trigger of PIH ; women with PIH have hyperplacentosis or an abnormal placentation, hence βhCG is secreted in abundance from these placentae and these changes start early in pregnancy .12 PIH is not a disease of late pregnancy or of hypertensive origin but instead a progressive systemic disease shown by some studies.11 It was shown that elevated serum βhCG levels in severely preeclamptic women might reflect a significantly pathologic change and secretory reaction of the placenta.18

Table 5: Findings of Multiple Logistic Regression Model

variable	OR	p value	95% C. I.
Serum βhCG	320.312	<0.001	28.895- 3550.735

By applying Multiple Logistic Regression, only Serum βhCG came out to be a significant predictor for developing hypertension. Odds Ratio of Serum βhCG was 320.312 with 95% C.I. 28.895-3550.735.

Conclusion:

- Serum βhCG at 14-20 weeks of gestation is a good predictor for the subsequent development of hypertension (PE/GH) in pregnancy.
- At an acceptable sensitivity of 85%, the value of βhCG obtained from ROC curve is 57,226 mIU/ml. The accuracy of this value in predicting hypertension is 96.67%.

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