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Gynaecology

SECOND TRIMESTER BETA HCG ESTIMATION FOR PREDICTION OF HYPERTENSIVE DISORDER

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ABSTRACT

BACKGROUND: Gestational hypertension is the development of hypertension in a pregnant woman after 20 weeks of gestation. Women with high serum beta-HCG levels in early pregnancy are at higher risk of developing hypertensive disorder.

AIM: The present study aims to find the relationship between serum Beta-HCG levels at mid trimester (13-20 weeks) and development of hypertensive disorder.

MATERIAL AND METHODS: Serum beta-HCG estimation was done by CLIA method in 110 women between 13 to 20 weeks of gestation, selected randomly for this study from June 2017 to May 2018. Multiple of median (MOM) was calculated from the median of the diagnostic test, Diagnostic Products Corporation, U.S, Immulite 2000- HCG, for that weeks of pregnancy. Cases were followed till delivery for the development of hypertension and results analysed statistically with Chi-square test.

RESULT: Out of 110 cases, 94 (85.5 %) were finally evaluated in which 84 cases (89.4%), had Beta- HCG levels, <2MOM, whereas 10 cases (10.6%), had values >2 MOM. Out of 84 cases with Beta-HCG levels < 2 MOM, only 2 cases (2.1%) developed hypertension. The remaining cases, 82 (87.42%), were normotensive and out of 10 cases with Beta-HCG values >2MOM, 8 cases (8.5%) developed hypertensive disorder, and only 2 cases (2.1%) were normotensive. The p value for this parameter when calculated for the development of pregnancy induced hypertension, came out to be <.001, which is highly significant.

CONCLUSION: The study concluded that the serum beta HCG estimation at mid trimester (13–20 weeks) is a good predictor of development of hypertensive disorder.

KEYWORDS : Gestational hypertension, Human Chorionic Gonadotrophin (HCG), multiple of median (MOM)

INTRODUCTION

Hypertensive disorders are the most common medical problem encountered in pregnancy and remains an important cause of feto-maternal morbidity and mortality (1). It complicates almost 5-10% of all pregnancies (2). The spectrum of disease ranges from mildly elevated blood pressures with minimal clinical significance to severe hypertension and multi-organ dysfunction(3).

Pregnancies complicated by hypertension are associated with increased risk of adverse fetal, neonatal and maternal outcomes such as preterm birth, intrauterine growth restriction (IUGR) , perinatal death, acute renal or hepatic failure, antepartum hemorrhage, postpartum haemorrhage and maternal death(1).

Its pathophysiology remains unclear, despite the progress made in the past decades (1). Therefore, it is still a challenge to obtain an accurate prediction of women who are at risk of developing hypertensive disorders of pregnancy. It is indeed a constant endeavour of every obstetricians to identify the risk involved in pregnancy and if possible its prediction. If prediction becomes possible, prevention will follow naturally. Placental function changes in the form of increased serum beta HCG has been documented and several prospective studies indicates changes in the hormone which may be present before the clinical diagnosis of preeclampsia. Physiological concentration of HCG, which is a glycoprotein expressed in trophoblast and various malignant tumors, significantly increased in *in vitro* capillary formation and migration of endothelial cells in a dose dependent manner and has novel function in uterine adaptation to early pregnancy (Zygmunt *et al*). Because the possible role of HCG in pathophysiology of hypertensive disorders in pregnancy is not well understood and changes in its level can reflect the placental reaction, we are promoted to determine correlation of serum concentration of beta HCG and hypertension in pregnancy. Many reasons have been postulated for suspecting the role of HCG in predicting immunological conditions in obstetrics (Sayeed et al 1984).In a multicenter study, approximately 30% of hypertensive disorders of pregnancy were due to chronic hypertension while 70% of the cases were diagnosed as gestational hypertension / preeclampsia (4).

Treating the hypertension does not alter the progression of disease. However it has been shown that early treatment decreases not only the frequency of hypertensive crisis, but also the rate of neonatal complications. So, early prediction and diagnosis can lead to a reduction in feto-maternal mortality and morbidity.

AIMS

To predict hypertensive disorder of pregnancy, severity and associated other risk factors by studying maternal serum beta HCG levels in second trimester (13-20 weeks).

MATERIALS AND METHODS

The prospective cohort study was conducted at Gauhati Medical College and Hospital, Guwahati at the department of Obstetrics and Gynaecology, over a period of one year, from June 2017 to May 2018. The study population was pregnant patient attending antenatal OPD of Gauhati Medical College and Hospital in their 2nd trimester over the specified period, with selective samples of 110 subjects.

INCLUSION CRITERIA: All pregnant women in their second trimester (13-20 weeks of gestation) at or above 18 years and below 40 years of age, with a singleton pregnancy, irrespective of parity who was previously normotensive and non-proteinuric .

EXCLUSION CRITERIA: cases with multiple pregnancy**,** chronic hypertension , present or previous history of gestational trophoblastic disease, others like germ cell tumor, Down's syndrome were excluded from the study.

COLLECTION OF BLOOD SAMPLE: About 3ml of venous blood was collected from each subject with their consent during their ANC visit. The blood was allowed to clot and the serum was separated by centrifugation and stored at -20°c until determination of β-HCG level.

BETA-HCG ESTIMATION: The beta- HCG estimation in maternal serum was done by chemiluminescent immunometric assay (CLIA) method with the help of VITROS 5600 Immunodiagnostic products.

COMPARISON: Multiple of median (MOM) was calculated from the median of the diagnostic test employed for the current study (Diagnostic Products Corporation, U.S, Immulite 2000- HCG) having the central 95% values accuracy.

STATISTICAL ANALYSIS: All the continuous variables were shown in terms of descriptive statistics and categorical variables with frequency and percentages. The standard statistical tests like chi-square test and Fischer's exact test were used to see the association. All the results were discussed on 5% level of significance i.e. p value <0.05 was considered significant.

ETHICAL CONSIDERATION: The research proposal was approved and ethically cleared by the Ethical Committee .

METHODOLOGY Initially, a structured interviewer administered questionnaire was filled for all the patients after recruitment to obtain information on age, educational status, occupation, ethnic group, gestational age, weight, height and so body mass index (BMI), obstetric history regarding parity and history of hypertension during previous pregnancy if any and cell phone number. General, obstetrical and systemic examinations were done and all the relevant informations were recorded. Gestational age was calculated from the reliable menstrual history dates and early ultrasonographical measurement of fetal crown-rump length. Anomaly scan was advised to all except those who already did it. Blood sampling was done for beta-HCG estimation and was sent to CCL.

Subsequently, all the subjects in the study group were examined once in a month till 28 weeks, at least once in fortnight till 36 weeks and thereafter weekly till delivery.

At every check-up, blood pressure was measured by Richter's mercury sphygmomanometer, with a properly sized cuff and the patient in a seated position.

Cases were considered to be hypertensive in case of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions at least six hours apart. This way cases were followed up till delivery.

- For the purpose of study, hypertensive cases were divided in two groups based on the severity of the disease:

a) MILD DISEASE: Included all cases of mild gestational hypertension & mild preeclampsia

b) SEVERE DISEASE: Included all cases of severe gestational hypertension, severe preeclampsia and eclampsia.

RESULT

TABLE 1: DISTRIBUTION OF CASES ACCORDING TO OUTCOME OF PREGNANCY AFTER RECRUITMENT:

Total No. Of Cases Recruited	Missed Abortion	Spontaneous Abortion	Lost To Follow Up	Congenital Malformation	No. Of Cases Followed Till Delivery
110	4(3.7%)	2(1.8%)	8(7.2%)	2(1.8%)	94(85.5%)

TABLE 2: DISTRIBUTION OF CASES ACCORDING TO HYPERTENSIVE STATUS AND HCG LEVELS:

Hcg Levels (mom)	Number Of Cases (%)	Without Hypertension (%)	With Hypertension (%)
<2	84 (89.4)	82 (87.3%)	2 (2.1%)
>2	10 (10.6)	2 (2.1%)	8 (8.5%)
TOTAL	94 (100)	84 (89.4)	10 (10.6)
CHI-SQUARE= 56.632		DEGREE OF FREEDOM=1	P-VALUE= <0.001

TABLE 3: RELATION OF BETA HCG LEVELS (ABSOLUTE) AND HYPERTENSION

Beta-hcg Levels (miu/l)	No. Of Cases	Normotensive (%)	Hypertensive Cases (%)
<20,000	13	13 (15.5)	0
20,000-30,000	23	23 (27.4)	0
30,000-40,000	30	30 (35.7)	0
40,000-50,000	15	12 (14.3)	3 (30)
50,000-60,000	6	5 (5.9)	1 (10)
60,000-70,000	2	0	2 (20)
70,000- 80,000	4	1 (1.2)	3 (30)
>80,000	1	0	1 (10)
TOTAL	94	84 (100)	10 (100)
P VALUE= <0.001			

TABLE 4: RELATION OF SERUM BETA HCG (ABSOLUTE) LEVELS WITH SEVERITY OF HYPERTENSION :

BETA HCG LEVELS	MILD HTN	SEVERE HTN	TOTAL
<80,000	6	3	9
>80,000	0	1	1
CHI-SQUARE= 1.667		DEGREE OF FREEDOM= 1	P VALUE= 0.197

Table 2 depicts relation of occurrence of hypertension in relation to serum beta HCG whereas table 3 & 4 depicts relation of absolute levels of serum beta HCG with hypertension.

TABLE 5: PERIOD OF ONSET OF HYPERTENSION IN RELATION TO SERUM BETA HCG LEVELS :

	BETA HCG > 2 MOM		BETA HCG < 2 MOM	
Weeks	Number	Percentage	Number	Percentage
28-32 weeks	0	0	0	0
32-36 weeks	4	50	1	50
>36 weeks	4	50	1	50

This table depicts period of onset of hypertension in relation to serum beta HCG which failed to show any association.

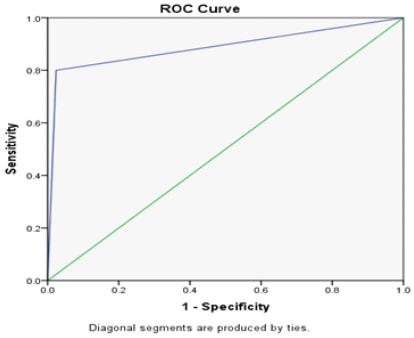
TABLE 6: BETA HCG (MOM) AS A PREDICTOR OF GESTATIONAL HYPERTENSION :

Hypertension	Hcg>2 Mom	Hcg≤2 Mom	Sensitivity	Specificity	PPV	NPV
YES	8 (TP)	2 (FP)	80%	97.62%	80%	97.6%
NO	2 (FN)	82 (TN)				
TOTAL	10	84				

TP: True positive; FP: False positive; FN: False negative; TN: True negative

PPV: Positive predictive value; NPV: Negative predictive value

RECEIVER OPERATING CHARACTERISTICS CURVE



Sensitivity of second trimester beta HCG as predictor of gestational hypertension is 80% whereas specificity is 97.6%. Positive predictive value also found to be 80%.

TABLE 7: GESTATIONAL AGE OF DELIVERY (FOR THOSE WHO DEVELOPED HYPERTENSION)

GESTATIONAL AGE (WEEKS)	NUMBER	PERCENTAGE
< 34	0	0
34- 37	6	60
>37	4	40
TOTAL	10	100

60% of the hypertensive cases delivered at or before 37 weeks.

TABLE 8: DISTRIBUTION OF CASES ACCORDING TO MODE OF DELIVERY

MODE	NUMBER	PERCENTAGE
VAGINAL DELIVERY	4	40
CESAREAN SECTION	6	60

Out of 10 hypertensive cases, 4 cases delivered vaginally whereas 6 cases delivered by caesarean section.

DISCUSSION

In our study, women with higher levels of beta HCG (>2 MOM) during the second trimester of pregnancy, developed hypertension later in their pregnancy. Out of total 94 cases evaluated, 84 cases (89.4%) had beta HCG levels < 2MOM, whereas 10 cases (10.6%) had beta-HCG levels > 2MOM (Table 6). Out of total cases with beta HCG levels < 2 MOM, only 2 cases (5.7%) developed hypertension whereas out of 10 cases with beta HCG values >2MOM, 8 cases (71.4%) developed hypertension with p value <0.001 which was statistically significant. Similar to our findings, **Sharma V *et al*** (5) in their study observed that out of 387 cases with beta-HCG levels <2MOM, only 6 cases (1.56%) developed pregnancy induced hypertension and out of 60 cases with beta-HCG values >2MOM, 49 cases (81.67%) developed pregnancy induced hypertension (p<0.001). Present findings are also consistent with the findings of **Kaur G *et al*** (6). . In another study by **Desai and Rao (7), Hernandez R *et al*** (8) and **Soundararajan P *et al*** (9) reported similar findings.

Statistically, no difference could be found and any association of early onset gestational hypertension in cases with raised serum beta HCG (Table 5) , which was in contrast to the study done by **Priya K *et al*** (10) which showed cases with beta HCG > 2 MOM had early onset gestational hypertension with the statistically significant result.

According to our study, beta HCG (MOM) is a good predictor of hypertensive disorder in pregnancy with sensitivity 80 %, specificity 97.6 % and the positive predictive value of 50 % (Table 6). **Roiz-Hernandez *et al*** (8), showed that with a cut off value of 2 MOM for beta 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 the study of **Pankaj Desai (7)**, they concluded that the use of beta-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%. The increasing Beta-HCG levels (in mIU/ml) showed a direct association with the severity of pregnancy induced hypertension.

In the present study, we observed that the higher absolute levels of beta HCG correlates with occurrence of gestational hypertension (Table 2 & 3). Out of 94 pregnant women, 10 women who developed gestational hypertension were having higher absolute levels of beta HCG. However, in the present study the increasing beta HCG levels (in mIU/ml) failed to show a direct association with the severity of PIH with p value 0.197 (Table 4) with contrast to the results shown in study by **Jaiswar *et al*** (11) in which the author concluded that there was a positive correlation between the absolute beta HCG levels and the severity of PIH. **Zhonghua *et al*** (12) and **Basirat Z *et al*** (13) reported similar findings.

CONCLUSION

The study of estimation of serum beta-HCG at mid trimester for the prediction of hypertensive disorder, is the ability of the predicting the same in non- invasive way which is one of the important achievement of modern obstetrics. Hypertensive disorder being one of the most common cause of maternal mortality and morbidity, prediction and prevention of the disease at the earliest is of utmost importance. Out of all prediction tests, serum beta HCG estimation at 2nd trimester can be singled out for screening of cases, especially those are at high risk e.g., primigravida, teenage pregnancy, cases with previous history of gestational hypertension etc. This test has proved to be reliable, easily reproducible, non-invasive, relatively cost effective and a test which can easily be performed as out patient basis.

Thus, the current study can be concluded as, the beta HCG estimation at mid-trimester can be used as a good predictive test for the development of hypertensive disorder, as early as before 20 weeks with fair sensitivity, good specificity and good positive predictive value.

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