Study of Correlation Between Mid Trimester Serum Beta Human Chorionic Gonadotropin Levels and Prediction of Hypertensive Disorders of Pregnancy

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ABSTRACT

Introduction: Hypertensive disorders of pregnancy (HDP) are among the commonest medical disorders during pregnancy constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide**.** In view of increased maternal and foetal morbidity and mortality associated with HDP and lack of definite predictive test for early identification of the woman at the risk of HDP, this study was undertaken to correlate the raised serum beta hCG measured in early second trimester with prediction of HDP.

Material and Methods: The study group consisted of A total of 150 pregnant women attending Maharaja Agrasen hospital OPD/IPD during their second trimester (14-20 weeks) of pregnancy from Dec 2016 to Nov 2017.

Results: Out of 146 cases studied, 129 cases remained normotensive and 17 cases developed HDP. Out of 17 cases, 8 cases had mild HDPs and 9 cases had severe HDPs. We observed that serum β hCG levels for those women (Group A) who developed HDPs were significantly higher than normotensive group (B). By using β hCG value of 2 MoM as a cut off, its sensitivity as a screening test for HDP was 58.8%, the specificity was 96.9%, and the positive and negative predictive values were 71.43% and 94.70 respectively.

Conclusion: My study showed that raised mid trimester serum β hCG value can be used for prediction of Hypertensive disorder of pregnancy before its clinical outset as well as drawing special attention and care of cases having raised β hCG value from initial phase to prevent both maternal and fetal morbidity and mortality resulting from HDP. Our study also revealed correlation between raised mid trimester serum β HCG value and severity of HDP.

Keywords: HDP, Hypertension, Pregnancy, Mid Trimester Serum β HCG

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are among the commonest medical disorders during pregnancy constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide.[1-4] HDP complicate up to 5-10% of all pregnancies.[5] It accounts for 10-15% of maternal deaths specially in the developing world.[6] The spectrum of disease ranges from mildly elevated blood pressures with minimal clinical significance to severe hypertension and multi-organ dysfunction. Besides perinatal death, HDP lead to preterm delivery, fetal intrauterine growth restriction, low birth weight. HDP can also trigger some severe forms of maternal complications, such as cardiovascular and cerebrovascular diseases, liver and kidney failure, placental abruption, disseminated intravascular coagulation (DIC) and HELLP syndrome.

Hypertension in pregnancy is defined as a systolic BP of 140 mmHg and higher, and a diastolic BP of 90 mmHg and higher. Severe pregnancy hypertension is defined as SBP ≥160 mmHg or a DBP ≥110 mmHg. The systolic value was reduced from 170 mmHg by most international societies after recognition that a SBP≥160 mmHg is associated with an increased risk of stroke in pregnancy.

Hypertensive disorders during pregnancy are classified into four categories, as recommended by the National High Blood Pressure Education Program (2000) Working Group on High Blood Pressure in Pregnancy[7]:

Gestational hypertension (transient hypertension of pregnancy)
Preeclampsia-eclampsia
Preeclampsia superimposed on chronic hypertension
Chronic hypertension

The human chorionic gonadotropin (hCG) is a glycoprotein composed of two non covalently linked subunits, α and β, and is produced during pregnancy by the developing embryo and later by the syncytio trophoblast of the placenta mainly.[8] Its plasma half life is 36 hours. High β hCG production in early second trimester when definitive placental development occurs may be used as a predictive marker as placenta is the known primary trigger of gestational hypertension/ pre-eclampsia. In pre-eclampsia the rise of blood pressure is due to vasoconstriction and impaired angiogenesis leading to hypoxia and hyperplasia of trophoblastic cells which causes hyper secretion of placental hormone ultimately leading to high level of circulating β-hCG.[9-12] Moreover, conditions like twins, molar pregnancies which are associated with elevated hCG levels also carry an increased risk of gestational hypertension/preeclampsia.

Estimation of serum β hCG titres are especially helpful in

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How to cite this article: Seema Kumari. Study of correlation between mid trimester serum beta human chorionic gonadotropin levels and prediction of hypertensive disorders of pregnancy. International Journal of Contemporary Medical Research 2019;6(9):I9-I12.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.9.42

the diagnosis and management of trophoblastic disease and ectopic pregnancies.[13] Other clinical conditions associated with increased secretion of β hCG are Down syndrome, neural tube defects, fetal aneuploidy and multiple gestation.

In view of increased maternal and foetal morbidity and mortality associated with HDP and lack of definite predictive test for early identification of the woman at the risk of HDP, this study was undertaken to correlate the raised serum beta hCG measured in early second trimester with prediction of HDP. It will help us in taking timely preventive and curative measures to counter these complication particularly in Indian scenario.

Study aimed to evaluate raised mid trimester serum β-hCG as a predictive test in HDP but also correlate it with severity of HDP.

MATERIAL AND METHODS

The study was conducted at Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi. Woman with singleton pregnancy visiting Obs and Gynae OPD/IPD of the hospital during their second trimester (14-20 weeks) of pregnancy were enrolled in the study. The study design was prospective observational study and sample size was 150.

Inclusion Criteria: All pregnant women in their second trimester (14 - 20 weeks) above 18 years and below 40 years of age with informed consent having singleton pregnancy confirmed by ultrasonography and who were previously normo tensive and non proteinuric.

Exclusion Criteria: All pregnant woman having age less than 18 and more than 40 years, multiple pregnancy, episode of Chronic Hypertension, Gestational trophoblastic diseases in present or previous pregnancy, Down syndrome/any congenital anomalies, Pregnancy associated with Germ cell tumors.

Methodology: Diagnostic criteria for Gestational Hypertension was new onset of hypertension (≥140 mmHg systolic and/or ≥90 mmHg diastolic) after 20 weeks gestation without Proteinuria and signs of end organ dysfunction.

Diagnostic criteria for Pre-eclampsia (revised ISSHP, 2014) was Hypertension after 20 weeks gestation and the coexistence of one or more of the following new-onset conditions:

1. Proteinuria (spot urine protein/creatinine >30 mg/mmol [0.3 g/mg] or >300 mg/day or at least 1 g/L[‘2 + ’] on dipstick testing).
2. Other maternal organ dysfunction: renal insufficiency (creatinine >90 umol/L; 1.02 mg/dL), liver involvement (elevated transaminases – at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurological complications (eclampsia, altered mental status, blindness, stroke,or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata), haematological complications (thrombocytopenia,, DIC, haemolysis).
3. Uteroplacental dysfunction (foetal growth restriction)

Diagnostic criteria for Eclampsia was Pre-eclampsia associated with convulsion.

- Routine antenatal investigation including triple or quadruple test for Down syndrome were done for subjects. special investigation like LFT,KFT, repeat CBC and coagulation profile, Urinary albumin, 24 hour Urinary protein estimation, blood sugar and fundus examination were carried out in woman who developed gestational hypertension/preeclampsia/eclampsia.
- Serum beta hCG value in ng/ml and Multiple of median (MoM) were obtained from triple or quadruple marker test done for screening of Down syndrome.
- β hCG was considered raised if levels are more than 2 MoM. The cut off value of β hCG was calculated by ROC method for HDP.
- Subjects were followed for every three weeks interval till 28 weeks and then for 2 week interval upto 37 weeks then weekly till delivery. At each visit, BP was measured for assessing the development of HDP. Patient showing HDP was followed more frequently depending on severity and test for protein urea, LFT and KFT done and admitted indoor as applicable.
- At the end of the study, subjects were divided into two groups depending on the evolution of pregnancy
  - Group A - who developed HDP.
  - Group B - who did not develop HDP and had Physiological evolution of pregnancy.
- Group A was divided further into two group i.e. Group A1 and Group A2 based on features of severity.
- Result was analysed and β hCG level in both the group was compared. If value was higher in group A and the difference of β hCG level between group A and B was statistically significant then it was concluded that mid trimester β hCG level level is a good predictor of development of HDP.
- Result were analyzed also for correlation between mid trimester serum β hCG and severity of HDP.

RESULTS

The mean age of normotensive group was 27.86+/-3.71, whereas in Mild HDP and Severe HDP group was 29.87+/-4.63 and 29.11+/-4.40. There was statistically no significant difference between age of three groups (table-1). The three groups were comparable regarding age as shown in figure-1. Corrected Chi-square (χ^2) test (χ^2 =13.28; p=0.10 NS-Not Significant) showed that there was no significant association between age and cases of the three groups (p=0.10). Thus the cases of the three groups were more or less equally distributed over age. One ANOVA showed that there was no significant difference between the mean age of the cases of the three groups ($F_{2,143}$=2.11;p=0.12). Thus the cases of the two groups were age matched.

One ANOVA showed that there was significant difference between the mean level of βhCG MOM of the cases of the three groups ($F_{2,143}$=99.90;p<0.0001). As per CD the mean level of βhCG MOM of the cases with Severe HDP was significantly higher than that of the cases with mild HDP and

Groups	Mean ± SD	Range	Median	P value
Normotensive (B)	27.86±3.71	19-37	28	0.10
Mild HDP (A1)	29.87±4.63	21-38	30	
Severe HDP (A2)	29.11±4.40	24-39	29	

Table-1: Mean Age of the three groups (Normotensive, Mild HDP and severe HDP)

Level of βhCG MOM	Normotensive (n=129)	Mild HDP (n=8)	Severe HDP (n=9)
Mean±s.d.	0.82±0.42	1.38±0.52	2.90±0.53
Median	0.72	1.57	2.68
Range	0.21 - 1.91	0.44 - 2.19	2.16 - 3.70

Table-2: Distribution of level of βhCG MOM of the cases of the three groups

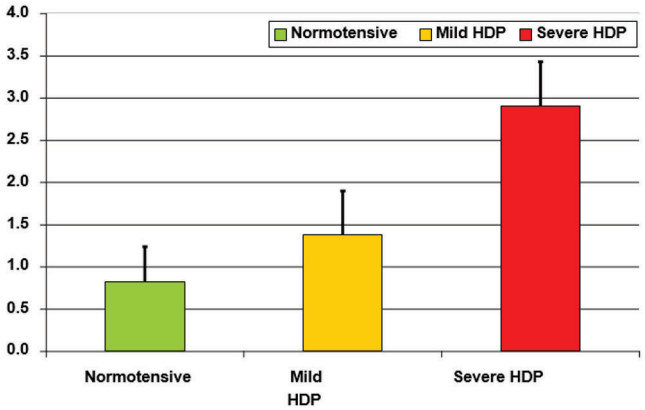

Figure-1: Mean level of beta hCG MOM

normotensive cases (p<0.001) (table-2).

Also the mean level of βhCG MOM of the cases with mild HDP was significantly higher than that of the normotensive cases (p<0.01). Spearman's Correlation co-efficient showed that there was significant positive correlation between level of βhCG and HDP of the cases (ρ (rho)= 0.607;p<0.0001). Thus proportion of HDP increased with the increase in level of βhCG.

DISCUSSION

Hypertensive disorders of pregnancy (HDP) is a major challenge in overcoming pregnancy complications that are responsible for poor maternal and prenatal outcome in developed as well as underdeveloped countries of the world. These disorders comprise of chronic hypertension, gestational hypertension, preeclampsia and eclampsia.

The spectrum of HDP ranges from mildly elevated blood pressures with minimal clinical significance to severe hypertension and multi-organ dysfunction. In my study, 150 cases were initially enrolled. However, only 146 cases (97.3%) could be evaluated for the final results. The 4 cases were lost to follow up.

These cases were divided into two groups:

- Group A - who developed HDP.
- Group B - who remained normotensive

Group A was divided further into two group i.e. Group A1 and Group A2 based on features of severity. Cases in Group A1 were mild hypertensive and A2 were severe hypertensive. The mean age of the cases for my study was 27.86 (Group B normotensive) 29.87 (Group A1, mild hypertensive) and 29.11 (Group A2, severe hypertensive). There was no statistically significant correlation found between the age and the occurrence of HDP which was in concordant with the results of study conducted by Vishal Sharma et al (2016)[14], who observed that there was no statistically significant difference between age of subjects and HDP. 76.34% of the patients in my study were between 21 and 30 years of age thus rendering a very young population morbid and at risk of mortality.

In the present study, the increasing β-hCG levels (in ng/ml) showed a direct association with the HDP. The mean value of b HCG was 10.12 ng/ml(group B), 13.85 ng/ml (group A1) and 24.83 ng/ml (group B). There was significant difference between the mean level of β-hCG of the patients of the three groups, a p value of <.01, which is statistically significant. Spearman's Correlation co-efficient showed that there was significant positive correlation between level of β-hCG and HDP of the patients (ρ (rho)= 0.607;p<0.0001). Thus proportion of HDP increased with the increase in level of βhCG.

In another prospective observational cohort study conducted by Heena Chaudhary et al[15], Pregnant women with high β-hCG levels in second trimester have significantly higher risk for development of gestational hypertension. Similar results have been shown by Roiz-Hernández et al[16] that measuring levels of β-hCG during the second trimester of pregnancy is useful in clinical practice to identify pregnant women who will develop pre-eclampsia. Gurmandeep Kaur et al[17] also found out in their study that the serum β-hCG estimation at mid trimester is a good predictor of HDP and higher levels of β-hCG are associated with increased severity of HDP. However, Morssink et al[18], Pouta et al[19] and Muthulakshmi D et al[20] did not find any correlation between serum β-hCG and HDP in their study.

CONCLUSION

In my study, 150 cases were initially enrolled. However, only 146 cases (97.3%) could be evaluated for the final results. The 4 cases were lost to follow up. Out of 146 cases studied, 129 cases remained normotensive and 17 cases developed HDP. Out of 17 cases, 8 cases had mild HDPs and 9 cases had severe HDPs. The mean age of the cases for my study was 27.86(Group B normotensive) 29.87 (Group A1, mild hypertensive) and 29.11 (Group A2, severe hypertensive). There was no statistically significant correlation found between the age and the occurrence of HDP. The finding in my study reinforces the association between elevated ß hCG concentrations and placental damage in early pregnancy. Elevated maternal serum β-hCG levels identify a subgroup of pre-eclamptic patients who needs intensive observation. Our finding shows that in both forms of HDP(mild and severe forms), serum β-hCG is raised, this elevation was higher in severe than in mild form. Our results indicate the

association between high β-hCG levels in second trimesters of pregnancy and the development of HDP. β-hCG, being a product of trophoblast cells, might be a marker for the evaluation of placental turnover.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 06-08-2019; **Accepted:** 06-09-2019; **Published:** 28-09-2019