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Original Research Article

An Analytical Case-Control Assessment of the Association between Elevated Maternal Serum β-hCG Levels and HDP

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Abstract

Aim: The objective of the present study was to determine the association between elevated maternal serum β-hCG levels and HDP.

Methods: This was a hospital based observational study conducted in the Department of Obstetrics and Gynecology, BMIMS, Pawapuri, Nalanda, Bihar, India over a period of 18 months after taking approval from the ethical committee. This study included 300 pregnant women, grouped into cases of 200 pregnant women with hypertensive disorders of pregnancy and control of 100 normotensive women. Serum β-hCG levels were measured and compared in both groups.

Results: Out of the 200 hypertensive women in the study group, there were 40 (20%) patients with gestational hypertension, 44 (22%) with non-severe preeclampsia, 80 (40%) with severe preeclampsia and 36 (18%) with antepartum eclampsia. The mean age of normotensive mothers in control group was 24.88 years and that of hypertensive mothers in the study group was 24.48 years. The difference in parity of mothers was statistically significant ($p<0.05$) with a greater number of primigravida in the study (hypertensive) group as compared to control (normotensive) women. The mean of SBP mothers with HDP was 150.70±18.72 mmHg and that of normotensive mothers was 110.40±10.15 mmHg which was statistically significant ($p<0.001$). The difference in gestational age between the two groups was statistically significant ($p<0.05$). Mean gestational age was 37.3±2.7 weeks in the normotensive group and 35.5±3.3 weeks in the hypertensive group.

Conclusion: As HDP cause significant maternal and fetal mortality and morbidity, early diagnosis may improve maternal and perinatal outcome by ensuring appropriate management. Serum β-hCG level was higher in hypertensive disorders of pregnancy when compared to normotensive women. The levels are also higher in severe preeclampsia patients when compared with non- severe preeclampsia; and in primigravid hypertensive women in comparison to multigravida hypertensive women.

Keywords: Eclampsia, Hypertensive disorders of pregnancy, Preeclampsia, Serum β-hCG

Introduction

Pregnancy is a physiological process but needs strict monitoring throughout gestational period to circumvent perilous complications like pregnancy induced hypertension (PIH), gestational diabetes etc. Pregnancy induced hypertension is defined as blood pressure ≥140/90 on two occasions, at least 6 hours apart and

proteinuria of ≥300mg/24 hours or ≥ 1+dipstick after 20 weeks of gestation in previous normotensive women.[1] Pregnancy induced hypertension (PIH) is the most common medical complication of pregnancy, whose incidence has continued to increase worldwide. It is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually[2,3] and risk is very high in Indian women.[4] WHO estimates that one woman die every minute due to the complications of hypertensive disorders of pregnancy (HDP).[5] Pregnancy induced hypertension is a disease influencing 5-10% of all pregnancies and PIH is identified in 3.9% of all pregnancies.[6]

Preeclampsia is characterized by hypertension in pregnancy along with proteinurea.[7] When there is onset of convulsions in cases of preeclampsia, it is termed as eclampsia. Hypertensive disorder of pregnancy is basically a microangiopathy with endothelial damage and hypoxic injury in the placenta.[8] It can be said that eclampsia also forms a part of the continuum of disease which starts from mild preeclampsia and progresses to severe preeclampsia and eclampsia. A normal pregnancy is characterized by trophoblastic invasion of spiral arterioles in 1st trimester as well as 2nd trimester. In the 1st trimester there is invasion of the decidual segment of spiral arterioles, whereas in the 2nd trimester there is invasion of myometrial segment of spiral arterioles by cytotrophoblast. As a result of this, the decidual as well as myometrial segment of the spiral arterioles lose their smooth muscle coat and become unresponsive to the effect of circulating pressor agents. In cases of preeclampsia, this 2nd wave of invasion fails to occur[9] and the spiral arterioles remain thick-walled and responsive to pressor substances, leading to a higher resistance in the placental bed.[10,11] This pathology ultimately leads to hypoxia in the placental bed,[12] leading to free radical-mediated injury in the vessels of placenta. This has multiple manifestations, namely maternal hypertension and fetal intrauterine growth restriction. Extreme cases progress to a microangiopathy called HELLP syndrome (hemolysis, elevated liver enzymes and low platelets).[13]

Various studies have shown that placental hypoxia might be responsible for increased hCG production. It was proved by in vitro trophoblastic cell culture that was grown under hypoxic conditions. Placental abnormalities like villitis, infarction, ischemic changes and intervillous thrombosis were also associated with increased serum β-hCG levels.[14] The impaired spiral artery vasculature and subsequent reduced blood flow in the placental villi were responsible for intrauterine growth restriction seen in severe forms of hypertensive disorders of pregnancy. As it is postulated that preeclampsia is a trophoblastic disorder and hCG is secreted from the trophoblasts, it has become essential to understand this disease, to investigate the pathologic and secretory reaction of the placenta.[15] Twin pregnancies and molar pregnancies produce higher levels of hCG and they are associated with higher incidence of preeclampsia than uncomplicated singleton pregnancies.[16,17]

The objective of the present study was to determine the association between elevated maternal serum β-hCG levels and HDP, the correlation between serum β-hCG level and severity of preeclampsia and to determine the value of serum β-hCG level as a diagnostic marker for early diagnosis of HDP.

Materials and Methods

This was a hospital based observational study conducted in the Department of Obstetrics and Gynecology, BMIMS, PAWAPURI, Nalanda, Bihar, India over a period of 18 months after taking approval from the ethical committee. This study

included 300 pregnant women, grouped into cases of 200 pregnant women with hypertensive disorders of pregnancy and control of 100 normotensive women. Serum β-hCG levels were measured and compared in both groups.

Inclusion criteria

Study group: This included 200 pregnant women with gestational age more than 20 weeks, fulfilling the criteria as any of the following three subgroups;

- Gestational hypertension: Pregnant women with gestational age more than 20 weeks with blood pressure, systolic ≥140 mmHg and diastolic ≥90 mmHg with no proteinuria.
- Preeclampsia (non-severe and severe): Pregnant women with gestational hypertension with proteinuria and imminent symptoms like headache, epigastric pain, thrombocytopenia, altered renal function test, elevated liver enzymes, pulmonary edema.
- Eclampsia: Preeclamptic women with convulsions.

Control group: This included 100 pregnant women with gestational age more than 20 weeks, who were normotensive with blood pressure, systolic <140 mmHg and diastolic <90 mmHg. **Exclusion criteria**

Pregnant women more than 20 weeks of gestation with

- Multiple pregnancies
- Gestational diabetes mellitus
- Medical disease like chronic hypertension, chronic renal disease, chronic liver disease, cardiac disease, SLE or hematological disorders.

A thorough evaluation was done including a detailed history, physical examination (general and systemic) to confirm the above-mentioned inclusion and exclusion criteria. A written informed consent was taken after explaining the procedure about measurement of blood pressure, taking of urine samples for proteinuria, collection of blood sample for serum β-hCG.

Measurement of blood pressure

Mercury sphygmomanometer was used to measure the blood pressure. An appropriate size cuff (length 1.5 times the upper arm circumference or a cuff with a bladder that encircles 80% or more of the arm) was used, with the patients in an upright position with their right arm supported in horizontal position at the level of the heart, after a 10 minute or longer rest period, and also when the patient is in left lateral recumbent position with the arm at the level of the heart. Diastolic blood pressure was determined by disappearance of sound (Korotkoff phase V) rather than by muffling of sound (Korotkoff phase IV) as it is more reproducible and shows better correlation with true diastolic blood pressure in pregnancy. Where KV is absent, KIV was accepted.

Assessment of proteinuria

Visual dipstick test was used to measure proteinuria.

Blood sample collection

Venous blood samples (about 3 ml) were collected in test tube with aseptic precautions. After 2 hours of collection, sample was centrifuged at 3000 rpm for 5 minutes. Serum was separated and collected in polythene tube with cork. The sera with no sign of hemolysis were used for the analysis of β-hCG. Biochemical analysis Serum β-hCG concentration was measured by solid-phase, two site chemiluminescence immunoassay (CLIA). Authors used fully automated enzyme amplified chemiluminescent immunoassay based Immulite 1000 analyser.

Statistical analysis

Proper template for data entry was generated on MS Excel and data was entered on this template. The data was compiled and subjected to analysis using statistical package for social sciences (SPSS) and interpreted according to the type of variables. The continuous variables

were analyzed in terms of mean and interpreted by Student's t-test. The discontinuous variables were described in terms of percentages and interpreted by $\chi 2$ (Chi-square) test. Data pertaining to β-hCG levels were analyzed using non-parametric tests - Mann Whitney U and Kruskal Wallis tests as the data was skewed and did not follow normal distribution. 5% level of significance ($p<0.05$) was considered for the study.

Results

Table 1: Patient details

Study group	N%
Gestational hypertension	40 (20)
Non- severe preeclampsia	44 (22)
Severe preeclampsia	80 (40)
Antepartum eclampsia	36 (18)

Out of the 200 hypertensive women in the study group, there were 40 (20%) patients with gestational hypertension, 44 (22%) with non-severe preeclampsia, 80 (40%) with severe preeclampsia and 36 (18%) with antepartum eclampsia. The mean age of normotensive mothers in control group was 24.88 years and that of hypertensive mothers in the study group was 24.48 years.

Table 2: Comparison between study group (hypertensive) and control (normotensive) mothers group in respect to parity and Systolic and diastolic blood pressure and proteinuria

Gravida	Normotensives (n=100)		Hypertensives (n=200)		Total (n=300)		Chi Sq.	P value
	N %		N %		N %			
Primi	45 (45)		112 (56)		157 (52.34)		4.3202	p=0.01
Multi	55 (55)		88 (44)		183 (47.66)			
Total	100		200		300			
Blood pressure								
	Mean	SD	Mean	SD				
SBP (mm Hg)	110.40	10.15	150.70	18.72			3.3456	p<0.001
DBP (mm Hg)	75.5	5.50	105.66	12.48				p<0.001
Proteinuria								
	No. %		No. %		No. %			
Absent	78 (78)		40 (20)		118 (39.34)		145.55	P < 0.001
Present	22 (22)		160 (80)		182 (60.66)			
Total	100		200		300			

The difference in parity of mothers was statistically significant ($p<0.05$) with a greater number of primigravida in the study (hypertensive) group as compared to control (normotensive) women. The mean of SBP mothers with HDP was 150.70±18.72 mmHg and that of normotensive mothers was 110.40±10.15 mmHg which was statistically significant ($p<0.001$). The mean DBP of hypertensive mothers was 105.66±12.48 mmHg and that of the normal mothers was 75.5±5.50 mmHg which was also statistically significant ($p<0.001$). It was observed that there was statistically significant difference ($p<0.001$) in the presence of proteinuria between the two groups.

Table 3: Distribution of cases according to gestational age

Gestational age	Normotensives (n=100)	Hypertensives (n=200)
20W OD-27W 6D	2 (2)	6 (3)
28W-31W 6 0D	3 (3)	12 (6)
32W-36W 6 OD	20 (20)	88 (44)
37W-40W 6 OD	70 (70)	96 (46)
41W OD & ABOVE	5 (5)	2 (1)
Mean±SD	37.3±2.7	35.5±3.3

The difference in gestational age between the two groups was statistically significant ($p<0.05$). Mean gestational age was 37.3±2.7 weeks in the normotensive group and 35.5±3.3 weeks in the hypertensive group.

Table 4: Comparison of serum β-hCG between non-severe preeclamptic and severe preeclamptic mothers

β-hCG (IU/L)	Non-severe preeclampsia(n=44)	Severe preeclampsia (n=80)	Mann Whitney U test value	Df	Significance
Mean	34422.32	60050.34			
SD	24987.74	2754.31	7.7845	145	p<0.001
Median	33456.5	67076			

The mean serum β-hCG level of severe preeclamptic mothers was higher than non-severe preeclamptic mothers.

Table 5: Comparison of serum levels of β-hCG in primigravida and multigravida women

Serum β- hCG (IU/L)	Primigravida (n=157)		Multigravida (n=143)	
	Normotensives (n=45)	Hypertensivs (n=112)	Normotensives (n=55)	Hypertensives (n=88)
Mean	18065.15	52820.15	17030.08	49050.1
SD	16740.90	29550.77	16590.06	30440
Median	13999.5	55350.6	10444	45026

Among primigravida, the difference in β-hCG levels between control (normotensives) and study (hypertensives) mothers was statistically significant ($p<0.001$). Similarly, among multigravida, the difference was statistically significant ($p<0.001$) with higher levels of β-hCG in hypertensive mothers. When comparing the β-hCG levels between primi and multigravid in control group (normotensives) there was no significant difference ($p>0.05$). There was statistically significant difference ($p<0.05$) between β-hCG levels of primi and multigravid of the study group (hypertensives) with higher levels in the primigravida patients.

Table 6: Comparison of serum β-hCG levels between different categories of hypertensive disorders of pregnancy

Serum β-hCG (IU/L)	Gestational hypertension (n=40)	Non-severe preeclampsia (n=44)	Severe preeclampsia(n=80)	Antepartum eclampsia (n=36)
Mean	20920.28	36520.36	60030.34	70250.46
SD	10690.29	23569.74	28720.31	23638.03
Median	19220	32420.5	67090	74130

It was seen that there was a significant difference between the different categories of HDP

($p<0.05$).

Discussion

Hypertensive disorders of pregnancy (HDP) remain one of the most intriguing unsolved problems in obstetrics. How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Although improvements in obstetrical and neonatal care have led to a reduction in morbidity and mortality from hypertensive disorders, our ability to predict the condition has not improved significantly. The prevalence of hypertensive disorders of pregnancy was 7.8%, with preeclampsia in 5.4% of the study population in India.[18] Approximately 1 in 2000 deliveries is complicated by eclampsia in developed countries whereas the incidence in developing countries is estimated around 1 in 100 to 1 in 1700 cases.[19,20]

Out of the 200 hypertensive women in the study group, there were 40 (20%) patients with gestational hypertension, 44 (22%) with non-severe preeclampsia, 80 (40%) with severe preeclampsia and 36 (18%) with antepartum eclampsia. The mean age of normotensive mothers in control group was 24.88 years and that of hypertensive mothers in the study group was 24.48 years. Studies by Begum Z et al, Basirat et al, Choudhury et al, also show similar results with no significant correlation of maternal age between the hypertensive and normotensive groups.[21-23] However, Mujawar et al, observed that maternal age was significantly different between the groups ($p<0.05$) with mean age of 26.4±4.48 years in the control group and 23.6±4.16 years in the preeclampsia group.[24]

The difference in parity of mothers was statistically significant ($p<0.05$) with a greater number of primigravida in the study (hypertensive) group as compared to control (normotensive) women. Similar results were seen in the study by Kaur G et al where the occurrence of PIH was more among primigravida with 17% developing PIH and 7.14% among multigravida but there was no statistically significant association.[25] The difference in gestational age between the two groups was statistically significant ($p<0.05$). Mean gestational age was 37.3±2.7 weeks in the normotensive group and 35.5±3.3 weeks in the hypertensive group. In a study by Al-bayati MM et al, it was observed that mean gestational age of normotensive mothers was 37.11±1.98 weeks and that of hypertensive mothers was 35.72±1.93 weeks and this was statistically significant ($p<0.001$).[26] The mean of SBP mothers with HDP was 150.70±18.72 mmHg and that of normotensive mothers was 110.40±10.15 mmHg which was statistically significant ($p<0.001$). The mean DBP of hypertensive mothers was 105.66±12.48 mmHg and that of the normal mothers was 75.5±5.50 mmHg which was also statistically significant ($p<0.001$) which was similar to findings in several other studies.[24-26]

The mean serum β-hCG level of severe preeclamptic mothers was higher than non-severe preeclamptic mothers. Similar results were noted in the studies by Begum Z et al, Mujawar et al with higher levels of serum β-hCG levels in the case group of preeclampsia.[21,24] Among primigravida, the difference in β-hCG levels between control (normotensives) and study (hypertensives) mothers was statistically significant ($p<0.001$). Similarly, among multigravida, the difference was statistically significant ($p<0.001$) with higher levels of β-hCG in hypertensive mothers. When comparing the β-hCG levels between primi and multigravid in control group (normotensives) there were no significant difference ($p>0.05$). There was statistically significant difference ($p<0.05$) between β-hCG levels of primi and multigravid of the study group (hypertensives) with higher levels in the primigravida patients. A study

by Mooney RA et al demonstrated a decrease in maternal serum hCG with increasing parity. The decrease in hCG was similar at each gestational week from 15-20. In contrast, MSAFP and MSAFP MoM were unaffected by parity.[27]

Singh A et al (2016) observed that serum βHCG was statistically significantly higher in pregnancy induced hypertensive subjects (41500 ± 14000 mIU /ml) as compared to healthy pregnant control subjects (22500± 4500 mIU /ml). Here, the increased βHCG secretion was due to abnormal placental invasion or placental immaturity.[28] In similar study, Nandini et al (2014) concluded that the serum βHCG level was significantly high in women developing PIH (65315 ± 10237 mIU /ml) than healthy pregnant control subjects (26088 ± 11391 mIU /ml) with $p<0.001$.[29]

Conclusion

As HDP cause significant maternal and fetal mortality and morbidity, early diagnosis may improve maternal and perinatal outcome by ensuring appropriate management. Serum β-hCG level was higher in hypertensive disorders of pregnancy when compared to normotensive women. The levels are also higher in severe preeclampsia patients when compared with non- severe preeclampsia; and in primigravid hypertensive women in comparison to multigravida hypertensive women. Therefore, estimation of the serum β-hCG levels may help in the early diagnosis of HDP and it may as well serve as an indicator of the severity of the disease. Hence further studies are required on a larger series of patients to confirm the significance of serum β-hCG as a screening test for HDP.

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