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Original Research Article

Association of biochemical markers with time of onset and severity of hypertensive disorder of pregnancy

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ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP) are a common cause of morbidity and mortality. Inflammation is considered as one of the etiologic factors along with a complex interplay of multiple genetic, nutritional and other environmental agents. This study was undertaken to find association of biochemical markers with severity and time of onset of HDP.
Methods: Institutional review board and ethics committee approval was taken prior to the study. History and examination was done. Blood pressure was recorded at each antenatal visit. Blood samples were taken for the study of biochemical markers-hsCRP and interleukin 6 levels. Data was analyzed. P value <0.05 was taken as significant.
Results: Of the 80 women, 27.5% had early onset HDP. 72.5% had severe HDP. Inflammatory indices were altered as compared to the range of normal pregnant women. Mean IL-6 and hsCRP levels were found to be raised but no statistically significant association was observed between IL-6 levels or hs-CRP levels and time of onset of HDP (p value = 1 and 0.5859 respectively and severity of onset of HDP (p value = 0.197 and 0.453 respectively).
Conclusions: Biochemical indices, IL-6 and hs-CRP levels were elevated in women with HDP, indicative of increased inflammation.

Keywords: Hypertensive disorders of pregnancy, hs- CRP, Inflammatory markers, Interleukin 6

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) affects up to 10 percent of pregnancies globally.[1] It's prevalence in India is 6.9%.[2] The onset of HDP maybe early (<34 weeks) or late (>34 weeks) and it may be mild or severe; depending upon the blood pressure and presence of associated symptoms.

The pathophysiology of HDP is not clear. Inflammation has been proposed as one of them. Haematological, cytokine and coagulation profiles in pregnant women with HDP differ from those in normotensive pregnant women.[3]

Excess oxidative stress results from interactions between pre-existing maternal co-morbidities such as obesity, diabetes and hyperlipidaemia, leading to increased production of inflammatory factors causing hypertension. One of these is C-reactive protein (CRP).[4]

In HDP, there is limited invasion of the spiral arteries to only the superficial layers of the deciduae. The failure of trophoblast invasion results in reduced uterine perfusion pressure and placental ischaemia. The poorly perfused and hypoxic placenta releases increased amounts of vasoactive factors like tyrosine kinase-1 (sFMS-t), interleukin and possibly the angiotensin 2 type 1 receptor auto antibodies which link placental ischaemia with cardiovascular and renal dysfunction symptoms in these disorders.

Inflammation and hypercoagulability occur as a result of endothelial dysfunction, which thus results in the activation of coagulation factors.[5]

Coagulative dysfunction also causes release of proteases that bind to the protease activator receptors which in turn induce interleukin 6 (IL-6) production. The role of IL-6 is to induce the differentiation and growth of pro inflammatory factors.

HDP is a highly complex syndrome with interplay of multiple genetic, nutritional and other environmental factors. Haematological and cytokine parameters vary in different populations and therefore, it is justified to extrapolate the findings from European or American studies to our population. This study was undertaken to find if an association exists between the biochemical indices and time of onset and severity of HDP in our population.

METHODS

This was a hospital based descriptive study conducted in the Department of Obstetrics and Gynaecology at a teaching hospital, from July 2021 to June 2022. Institutional review board and ethics committee approval was taken prior to the study.

Inclusion criteria

Women aged 18-35 years, admitted to the labour room with a singleton live pregnancy after 20 weeks period of gestation, with a blood pressure equal or more than 140/90 mm Hg, developing after 20 weeks period of gestation were selected.

Exclusion criteria

Women with multiple pregnancy, premature rupture of membranes, fever, chorioamnionitis, and history of blood transfusion in current pregnancy were excluded from the study. Women with severe liver/cardiac/renal disease, obesity, malignancy, hypo or hyperthyroidism or history of polycystic ovarian syndrome were excluded. Women with severe hematological disease, history of inflammatory diseases like rheumatoid arthritis and chronic obstructive lung disease were also excluded.

Sample size calculation

Sample size was calculated at 95% confidence interval assuming standard deviation of 0.45 pg/ml for IL-6 among patients of hypertensive disorders of pregnancy as found in the article of Kong et al.[4] At the absolute allowable error (precision) of 0.1 pg/ml minimum 78 HDP patients were required as sample size for this study which was rounded off to 80 women with HDP.

Written informed consent of all enrolled was taken. After a detailed history, examination was done. Blood pressure was recorded with an automated sphygmomanometer. HDP was diagnosed when a woman with no previous history had developed hypertension - systolic (≥140 mm of Hg) and/or diastolic ≥90 mm of Hg) after 20 weeks of gestation. HDP was labelled as mild (blood pressure less than or equal to 159/99 mm of Hg) or severe (blood pressure more than or equal to 160/100 mm of Hg). It was also classified as early onset (<34 weeks) or late onset (>34 weeks) HDP.

Plasma levels of IL-6 were determined from EDTA plasma using enzyme-linked immunosorbent assays and hs-CRP levels were determined through immunological transmission turbidimetry. Urine was evaluated for proteinuria by the dipstick method.

Statistical analysis

Data was recorded in a pre-structured proforma and statistical analysis done. P value <0.05 was taken as significant. Medcalc 16.4 version software was used for all statistical calculations.

RESULTS

The study was conducted on 80 women with HDP. The mean age of the women included in the study was 24.76 years, 44.54% were educated more than secondary level. Most women belonged to middle and lower socioeconomic class. In the study, most women were from the urban area (76.55%). There was no difference in the socio-demographic profile of women with mild or severe and early or late onset HDP. They were grouped as early or late onset HDP and as mild or severe HDP. 72.5% women had late onset HDP, 55 had severe HDP. Biochemical indices evaluated were interleukin 6 and hsCRP.

Table 1: Association of interleukin 6 levels with time of onset of HDP.

Biochemical marker	Range (Total =80) (ng/ml)	Early onset (<34 weeks) N=22	Late onset (>34 weeks N=58	X^2, Df, p value
Interleukin 6 levels	0-4.25	5	13	X^2=0.327, Df=3, p value=1.00
	4.26- 9	6	15	
	9.1-25	4	17	
	>25	7	13	
Mean±SD	28.41± 11.63	32.80±42.93	27.4±34.22	

The mean interleukin 6 level in women with HDP was 28.41±11.63 ng/ml which was higher than interleukin 6 levels given for normotensive women. Though the mean IL-6 levels in early onset HDP was higher than those with late onset HDP, but this was not found to be statistically significant (Table 1).

Another biochemical marker studied was serum hsCRP. The mean HsCRP levels in the hypertensive women was 13.81±4.71ng/ml which was also higher than given for normotensive women. Furthermore the mean HsCRP in early onset group was higher than late onset group but was not statistically significant (Table 2).

Table 2: Association of Hs-CRP levels with time of onset of HDP.

Biochemical marker	Range (N=80) (ng/ml)	Early onset (<34 weeks) N=22	Late onset (>34 weeks) N=58	X^2, Df p value
Hs-CRP levels	0-3.27	12	27	X^2 = 1.9351 Df = 3 p value = 0.5859
	3.27-6.36	5	22	
	6.36-12.17	3	5	
	12.17-140.24	2	4	
Mean levels±SD	13.81±4.71	14.00±17.11	12.56±15.44	

Table 3: Association of interleukin 6 levels with severity of HDP.

Biochemical marker	Range (N=80) (ng/ml)	Mild HDP N=25	Severe HDP N=55	X^2, Df p value
Interleukin 6 levels	0-4.25	7	11	X^2=5.341 Df=3 p value=0.197
	4.26-9	7	14	
	9.1-25	8	13	
	>r25	3	17	
Mean interleukin 6 levels ±SD	28.41±11.63	22.39±24.64	27.04±35.33	

Values were compared between women with mild and severe disease. Mean IL-6 levels in the group with mild HDP was lower than of those with severe HDP (Table 3).

The mean levels of hsCRP also were lower in the mild HDP group than those with severe HDP. The levels of IL-6 and hsCRP did not show any statistically significant difference between mild and severe HDP (p value =0.453) (Table 4).

Table 4: Association of Hs-CRP levels with severity of HDP.

Biochemical marker	Range (N=80) (ng/ml)	Mild HDP (N=25)	Severe HDP (N=55)	X^2, Df p value
Hs-CRP levels	0-3.27	15	24	X^2=2.621 Df=3 p value=0.453
	3.27-6.36	7	20	
	6.36-12.17	1	7	
	12.17-140	2	4	
Mean±SD	13.81±4.71	12.09±12.03	14.54±15.55	

DISCUSSION

Out of the 80 women studied, 72.5% women had late onset HDP. The IL-6 and hsCRP values in patients with HDP were higher than in normal pregnancy.

Luppi et al reported that the spontaneous intracellular synthesis of IL-1,IL-6 and IL-8 in monocytes of pre-eclamptic women was higher than in normal pregnant and suggested that this was due to the systemic maternal inflammatory response.[6] Kucuk et al studied the serum and umbilical blood samples of antenatal women and found no significant difference in maternal and umbilical cord serum IL-6 levels between early- and late-onset HDP groups.[7] Xiao et al also found higher levels of IL-6 but no difference in it's levels between early onset and late onset preeclampsia.[8] Kong et al and Gencheva et al also found statistically significant higher levels of hs-CRP in patients with HDP than those in normal pregnant women.[4,9]

In the present study, there was no significant difference between the interleukin 6 levels or HsCRP levels in mild and severe HDP.

The expressions of interleukin 6 and hs-CRP in HDP patients with favourable pregnancy were lower than those with adverse pregnancy outcome ($p<0.05$) and these had a linearly positive correlation with systolic blood pressure in HDP patients.[6]

Xiao et al found higher levels of IL-6 in severe HDP but not in mild cases.[8] Page et al and Tosun et al showed that maternal serum levels of IL-6 and TNF-alpha were significantly increased in pre-eclamptic patients, higher levels are found in patients with severe compared to mild preeclampsia.[10,11] Though Ovayolu et al found no difference between the inflammatory markers concentrations in patients with mild and severe HDP.[12]

All these results suggest the overall excessive maternal response due to inflammation. IL-6 enhances endothelial cell permeability by altering the ultrastructural distribution of tight junctions and inhibits vascular prostacyclin production by down regulating cyclooxygenase expression. It can also induce aberrant angiogenesis.

The plasma of women with HDP contain elevated levels of placental debris, reactive oxygen species and augmented levels of pro inflammatory cytokines. These inflammatory mediators promote systemic vascular damage particularly in the kidney that results in the characteristic proteinuria and hypertension of the maternal syndrome of preeclampsia.[13]

Systemic arteriolar spasms in HDP causes injury and activation of endothelial cells, which causes placental ischemia and hypoxia. A series of cytotoxic factors are released into the maternal body and lead to increased intravascular permeability. Excessive coagulation substances are released, which in turn lead to elevated blood hs-CRP level.[14]

However studies by Chen et al and Joshi et al report that most patients with normal hsCRP levels presented with mild HDP while a greater fraction of patients with raised hsCRP levels presented with severe HDP.[14,15]

The study shows that the various biochemical indices are altered in women with HDP as compared to the range of normal pregnant women, indicative of increased inflammation in these women. No significant association was seen with the time of onset or severity of HDP. This suggests that it is the onset of the inflammatory process which triggers the abnormalities in the parameters rather than the time of onset or severity of HDP.

Potential diagnostic value of hs-CRP for HDP was analyzed by using ROC curve analysis. Results showed that hs-CRP had high predictive value for HDP with an AUC of 0.943 and 95% confidence interval (CI), suggesting that hs-CRP can be used as a potential diagnostic tool for prediction of HDP.[14]

This study has few limitations. The study was performed in a single centre which is a tertiary care referral centre, thus it is not reflective of the whole population.

CONCLUSION

Based on these findings, we recommend performing simple inexpensive laboratory tests measuring inflammatory markers in all antenatal women. This would help in easy, early and accurate detection of inflammation. Closer monitoring of the women with raised markers could be done for development of HDP. Thus, their management could then be initiated early and further progression of HDP and maternal and foetal morbidity due to it could be prevented.

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