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"Serum high sensitivity C-reactive Protein as predictor of Preeclampsia"

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Abstract:
Objective*: Estimation of high sensitivity C-reactive protein (hsCRP) in preeclamptic patients and to find out association between this biomarker and preeclampsia and also the role of this biomarker as predictor of the disease.*
Study-design & setting: *A case-control study was carried-out in the Dept. of Biochemistry in collaboration with Dept.of Obst & Gynae., Regional Institute of Medical Sciences (RIMS),Imphal (Manipur),India, from October 2011upto June 2013.*
Methods: *Data collected from 52 preeclamptic patients and 52 normal pregnant women in 3rd trimester admitted in antenatal ward and labour room, Dept. of Obst.& Gynae.,RIMS hospital. The blood samples were collected from the patients and analyzed for serum hsCRP level.*
Results: *The serum hsCRP level found significantly higher in preeclamptic cases than in normal controls. Mean± SD of hsCRP was 8.14±6.3 mg/L in the study group (cases) compared with 6.28±4.66 mg/L in control group. A significant positive correlation was found between serum hsCRP and preeaclampsia. Thus, the study showed a strong association of increased hsCRP level in preeclamptic patients.*
Conclusion: *Serum hsCRP may be feasible to be used as biomarker for identifying women at risk of preeclampsia.*
Key Words: *Blood pressure, hsCRP, preeclampsia.*

I. Introduction

Pre-eclampsia is a type of hypertensive disorder complicating pregnancy. It is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20th week in a previously normotensive and non-proteinuric patient.[1] The global incidence of preeclampsia has been estimated at 5- 14% of all pregnancies.[2, 3] The incidence of preeclampsia in the USA is 2-6% in healthy, nulliparous women.[4, 5, 6] Overall, 10–15% of maternal deaths are directly associated with pre-eclampsia and eclampsia.[7] WHO estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%)[8] In India the incidence of preeclampsia is reported to be 8-10% of the pregnancies.[9] The incidence in primigravidae is about 10% and in multigravidae about 5%.[1].

Its pathophysiology is poorly understood but numerous maternal, paternal and fetal factors have been implicated in its development. The factors currently considered include the followings [10]:

1) Maternal immunologic intolerance.
2) Abnormal placental implantation.
3) Genetic, nutritional and environmental factors.
4) Cardiovascular and inflammatory changes.

Among all these factors, though immunologic factors have long been considered to be key players in preeclampsia, the endothelial cell dysfunction and inflammation are considered to have a crucial role in pathophysiological mechanism of preeclampsia.[11]Currently endothelial dysfunction is most popularly hypothesized to be a central pathophysiological feature of preeclampsia leading to altered vascular reactivity, loss of vascular integrity and activation of the coagulation cascade.[10,11]

C-reactive protein (CRP) is a sensitive marker of systemic inflammation and is primarily synthesized in hepatocytes in response to infection and tissue injury,[12] which is stimulated by the release of proinflammatory cytokines. The present study was conducted to estimate hsCRP level in preeclamptic indigeneous Manipuri women and to find out any correlation between this parameter and the disease.

II. Materials And Methods

A case control study was conducted to evaluate the level of hsCRP level in preeclamptic patients and normal pregnant women in 3rd trimester admitted in the antenatal ward and labour room in the Dept. of Obstetrics and Gynaecology. It was done in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal, Manipur, India, from October 2011 upto June 2013 with approval of Institutional Ethics Committee. Diagnosis of preeclampsia was based on American College of Obstetrics and Gynaecology [13]: i) Systolic blood pressure >140 mmHg or a rise of at least 30 mmHg, ii) Diastolic blood pressure >90 mmHg or a rise of at least 15 mmHg (measured on two occasions at least 6 hours apart) and iii) Proteinuria of 300 mg or more in 24 hours urine collection or protein concentration of 1 gm/L (on two occasions of at least 6 hours apart), or $\geq 2^+$ in mild preeclampsia and $>3^+$ in severe preeclampsia by dipstick method.Those patients whose 24 hours urine sample examination revealed single plus (+) by dipstick method were categorised as normal patients, those who revealed two plus (++) or three plus (+++) were categorised as mild preeclampsia, and those who revealed more than three plus (+++) were categorised as severe preeclampsia. All the subjects had been divided into two groups: **Group-1(case group or study group):** Fifty two diagnosed preeclamptic patients in third trimester of pregnancy (29-40 weeks). **Group-2 (control group):** 52normal pregnant women of comparable gestational age. All the cases and controls in the study were subjected to detailed history regarding age, parity, gravida, height, pre-pregnancy weight, and weight at the time of blood collection was noted down, occupation, literacy, husband's occupation along with literacy, religion, race, socioeconomic status, family history of preeclampsia, past obstetric history, past medical history, smoking, medical disorders like hypertension and diabetes of first degree relatives, physical activity during pregnancy were taken. Systemic examination with special reference to oedema, blood pressure and gestational age was carried out. Patients who were overweight based on BMI, severe anaemic (< 6 gm %), suffering from any other known systemic or endocrine disorder, USG proven congenital abnormality or malformation of the foetus, unwilling to give consent and who were in labour pain and/or had premature rupture of membrane (PROM) were excluded from the study. 5 ml of venous blood was drawn from anterior cubital vein after an overnight fast, centrifuged for 10 minutes and analysed for total hsCRP. hsCRP estimation was carried out by high sensitivity C-reactive protein (hsCRP) ELISA kit. Statistical analysis was done and the data were processed through computer with statistical software using SPSS-16 version. Statistical formulae like (χ^2) - test, independent sample t-test, Pearson's correlation coefficient, degree of freedom (df) were used.

I. III. Results And Observations

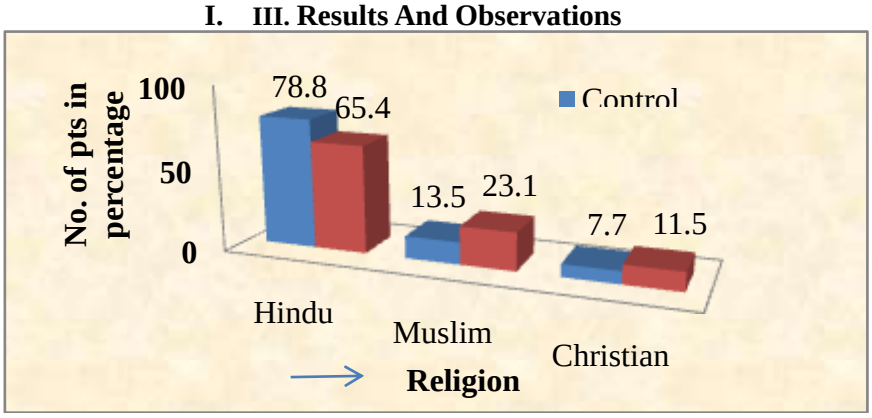

Fig. I shows distribution of cases and controls according to religion with majority of women in controls were (78.8%), Muslims and Christians patients were 13.5% and 7.7% respectively. In cases, Hindus were 65.4%,Muslims and Christians were 23.1% and 11.5% respectively with insignificant p-value.

TABLE 1: Distribution of cases and controls according to socioeconomic status

Socioeconomic status	Control group	Study group	Total
	Number (%)	Number (%)	Number (%)
Lowest (< 5)	0	0	0
Lower (5-10)	20 (38.5)	38 (73.1)	58 (55.8)
Lower middle (11-15)	30 (57.7)	13 (25.0)	43 (41.3)
Upper middle (16-25)	2 (3.8)	1 (1.9)	3 (2.9)
Upper / high (26-29)	0	0	0
Total	52 (100)	52 (100)	104 (100)

*Kuppuswamy's Socioeconomic Status Scale (2012).[14]

Table 1 shows majority of women in cases belonged to lower socioeconomic group (73.1%) followed by lower middle (25.0%) and upper middle class (1.9%) respectively. But in controls, maximum number of women belonged to lower middle class (57.7%) followed by lower (38.5%) and upper middle (3.8%) socioeconomic status respectively with statistically significant p-value.

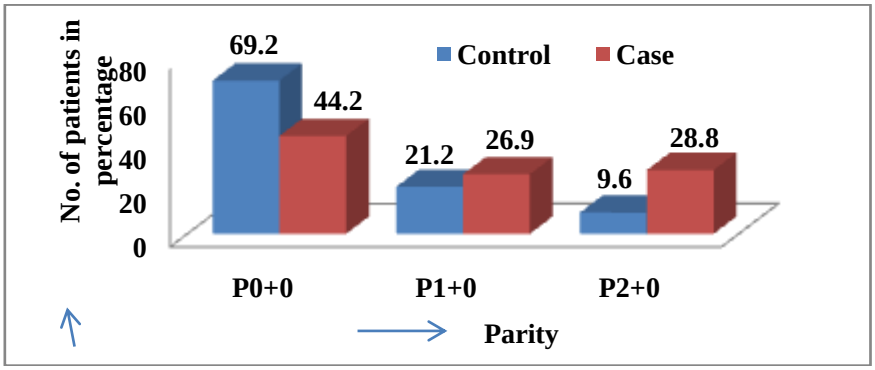

Fig. II. Distribution of cases and controls according to the parity where maximum number of cases occured in nulliparous with 69.2% in control group and 44.2% in cases with 21.2% and 26.9% in controls and cases respectively were in parity one and 9.6% and 28.8% in controls and cases respectively were in parity two with statistically significant p-value.

TABLE 2: Distribution of cases and controls according to age-group

Age (years)	Control group		Study group		Total	df	P-value
	Number (%)	Mean±SD(years)	Number (%)	Mean±SD (years)		2	0.001
18-25	27 (51.9)	25.96±3.89	12 (23.1)	29.42±5.10	39(37.5)		
26-30	20 (38.5)		18 (34.6)		38(36.5)		
31-35	5 (9.6)		22 (42.3)		27(26.0)		
Total	52 (100)		52 (100)		104		

Table 2 shows maximum no. of cases and controls belonged to age group of 31-35 years and 18-25 yrs with statistically significant p-value and mean value of age in controls was 25.96±3.89 yrs and in cases was 29.42±5.10 yrs which was statistically significant.

TABLE 3: Distribution of cases and controls according to mean±SD of weight and haemoglobin.

Parameter	Control group		Study group		t-value	df	p-value
	Numberof cases	Mean± SD	Number of cases	Mean± SD			
Weight (kg)	52	55.87±1.23	52	57.23±2.15	3.960	51	0.001
Hb (gm%)	52	11.44±1.39	52	11.32±1.21	0.456	51	0.644

Table 3 shows that mean weight of women in cases (57.23 ± 2.15 kg) was more compared with that of controls (55.87 ± 1.23 kg) with statistically significant (p = 0.001). Hb concentration was more in the controls (11.44 ± 1.39 gm %) compared with cases (11.32 ± 1.21 gm %) with (p = 0.644).

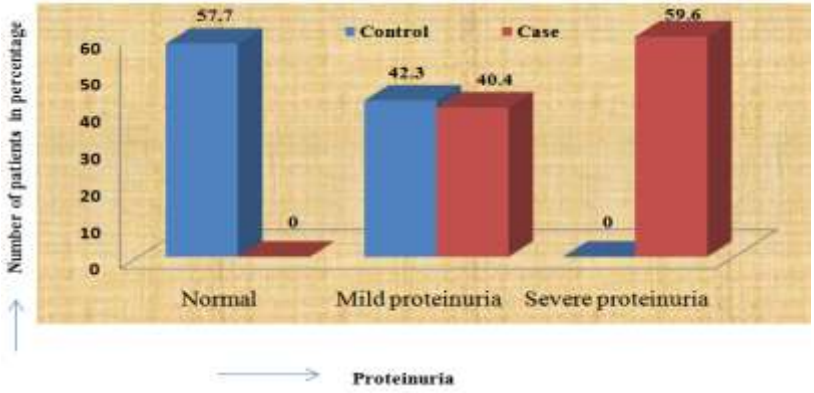

Fig.III. Comparison of proteinuria in cases and controls.

Fig. III shows that in cases maximum no. of patients had severe proteinuria i.e. >+++ (59.6%), and in controls maximum no. of patients had proteinuria of + (57.7%) which is considered as physiologically normal. But in both study and control groups mild proteinuria i.e. ++ or +++ was observed in 40.4% and 42.3% patients respectively with (p=0.001).

TABLE 4: Comparison of mean ± SD of blood pressure (mmHg) level between cases and controls

Parameter	Control group			Study group			t-value	df	p-value
	No. of patients	Mean ± SD (mmHg)	Median (mmHg)	No. of patients	Mean ±SD (mmHg)	Median (mmHg)			
Systolic BP	52	119.19± 10.36	120	52	163.04 ± 24.26	153	11.98	102	0.001
Diastolic BP	52	77.42 ± 7.37	80	52	104.19 ± 15.32	100	11.35	102	0.001

Table 4 shows mean ± SD of systolic and diastolic blood pressure levels in preeclamptic women were much higher than that of normal pregnant women with (p = 0.001).

TABLE 5: Distribution of frequency of hsCRP at different levels in cases and controls

Name of parameter	Range of parameter	**Study group**	**Control group**	**Total**	**Grandtotal**
		Number (%)	Number (%)	Number (%)	
hsCRP (mg/L)	< 0.068	0	0	0	104
	0.068-8.2	29 (55.8)	38 (73.1)	67 (64.4)	
	> 8.2	**23 (44.2)**	14(26.9)	37 (35.6)	

In Table 5, it is observed that hsCRP level was within normal range in 55.8% patients of cases and 73.1% patients of controls and was above the upper limit of normal range (i.e. >8.2 mg/L) in 44.2% patients of cases and 26.9% patients of controls. It is also found that not a single patient was there below the lower limits of hsCRP level in both of cases and controls.

TABLE 6: Relationship/comparison between mean value of hsCRP level in cases and controls

Parameters	Group	Mean±SD	Median	t-test	df	p-value
Serum hsCRP level (mg/L)	Study group	8.14±6.3	7.30	1.68	102	0.04
	Control	6.28±4.66	5.00			

Table 6 shows mean value of serum hsCRP level in cases was higher than that of controls with (p= 0.04) and mean value of hsCRP level in cases was very much near to upper limit of its normal range and mean value of hsCRP level always remained higher in cases and controls.

III. Discussion

The study shows that majority of patients belonged to Hindus. It may be due to the reason that the study was conducted in Hindu dominated area. Preeclampsia was more prevalent in the primigravidae and in the older age groups where mean age ± SD in years was 29.42±5.10. Women in the lower socioeconomic status had the highest frequency of preeclampsia (73.1%) followed by lower middle class (25.0%) and least patients in upper middle socioeconomic class (1.9%). This pattern was statistically significant (p= 0.002) when compared with control group. Our study findings were almost similar to the study of **Punam D et al** [15] where they showed maximum number of preeclamptic women belonged to lower socioeconomic status (56%) followed by middle class(23%) and higher status(21%) which was statistically significant . The body weight of preeclamptic patients (57.23±2.15 kg) were significantly higher than that of normal pregnant women (55.87±1.23 kg) of same gestational age. This finding was in agreement with that of **Rajkovic A et al**[16] where weights of the preeclamptic women were more than that of the normal pregnant controls. Haemoglobin level in case group was slightly lower (11.32±1.21 gm %) than controls (11.44±1.39 gm%) but it was statistically not significant. The cause may be due to variance in their dietary habits. Edema was significantly absent in majority (75%) of preeclamptic women. Edema was a common occurrence in women with normal pregnancy, and preeclampsia may occur in women with no edema. The use of edema as a defining criterion for preeclampsia is controversial, and most recent reports omit it from the definition. [17] Maximum number of patients with severe proteinuria (59.6%) was observed in cases. Mild proteinuria was observed in 40.4% and 42.3% patients respectively in both case and control groups .This difference was statistically significant (p=0.001). The triad of severe preeclampsia is often described as a combination of hypertension, edema and proteinuria. Proteinuria is the last sign to develop. [17,18] Mean ± SD of blood pressure (mmHg) was significantly higher in preeclampsia when compared with normal controls which was comparable to the findings of **Baksu A et al**[19] and **Powers RW et al** [20].

The level of serum hsCRP was higher in preeclamptic patients than the normal pregnant women and was significant (p=0.04). A positive correlation was found between serum hsCRP level and blood pressure but was not significant. In preeclampsia the level of CRP is increased. Native CRP is synthesized in a soluble form by hepatocytes and then secreted into the circulation. The production of CRP is induced by proinflammatory cytokines IL-1, IL-6 and IL-17 in the liver, although extra hepatic production can contribute to systemic concentrations. Cytokines exert their biological effects on CRP by signalling through their receptors on hepatic cells and activating different kinases and phosphatases, leading to the translocation of various transcription factors on the CRP gene promoter and the production of CRP. [21] In preeclampsia when there is endothelial cell injury, concentration doubles every 8 hours and peaks at 36-50 hours, although that depends on the stimulus and its severity. In response to an inflammatory insult, CRP concentration can increase above 500 mg/l and this amounts to as much as a 1000-fold or more concentration change [22,23] but if preeclampsia is accompanied by superimposed infection then the level of CRP increases more.

It is also observed that mean value of hsCRP was higher in both the study and control groups than their respective median values Though, the mean value in study group was within the normal range (0.068-8.2 mg/L), it was always higher than the mean value of the control group. In the study group, 44.2% women had hsCRP level more than upper limit of normal range. It is also found that in few preeclamptic patients (28.84%), the hsCRP value was >10 mg/L and in these study group the cause of increased hsCRP value may be superimposed infection along with preeclampsia which was latent or undiagnosed during taking of blood sample.

IV. Conclusion

The results of this study confirm the hypothesis that increased serum hsCRP level correlated with preeclampsia being indirect risk factor for placental vasculopathy predating clinical preeclampsia. Thus it can be concluded that increased serum hsCRP level can be used as biomarker for identifying women at risk of preeclampsia and its complications along with adverse effects. Several potential limitations of our study are worth mentioning. All the patients in study group were preeclamptic before the measurement of hsCRP levels, so it cannot be determined whether the observed elevation in hsCRP level preceded the development of preeclampsia. Increased hsCRP level in preeclamptic patients need to be confirmed in a designed strategy in which hsCRP level can be measured before the development of preeclampsia or early in pregnancy in order to identify and monitor the patients at risk of preeclampsia and thus to provide the best prenatal care for these women and their babies. However, further studies are required to determine whether genetic, nutritional defects or diseases related to hsCRP metabolism account for increased hsCRP level observed in pregnant women with preeclampsia.

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