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SERUM CONCENTRATIONS OF C-REACTIVE PROTEIN AND URIC ACID CORRELATE WITH SEVERITY OF PRE-ECLAMPSIA.

Biochemistry

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ABSTRACT

Pre-eclampsia can have profound adverse effects on pregnant women and fetus. Monitoring of this disorder with serum markers is desirable to reduce the effects on fetomaternal health. In a cross-sectional study, we tried to assess the significance of serum CRP (C-reactive protein) and uric acid levels in normotensive pregnancies and preeclamptic women. Fifty preeclamptic (25 mild, 25 severe) and 50 normotensive pregnant women in their third trimester were included. Both the markers were significantly higher in preeclamptics than normotensive pregnancies and in severe than mild preeclamptics. In preeclamptics, significant positive correlations were found between CRP/blood pressure, uric acid/blood pressure and CRP/uric acid. We suggest that serum concentrations of CRP and uric acid correlate with severity of pre-eclampsia and can be used for monitoring this disorder.

KEYWORDS

Pre-eclampsia, Severity, CRP, Uric acid.

INTRODUCTION:

Pre-eclampsia/eclampsia is one of the commonest causes of high maternal and infant mortality and morbidity rate.[1] Pre-eclampsia develops after 20 weeks of gestation, and is characterized by hypertension, proteinuria and edema. The condition is termed eclampsia when it is complicated by convulsions. Pre-eclampsia can also manifest as HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. How pregnancy instigates hypertension remains unclear till now.[2]

According to various studies performed across different parts of the world, the incidence of hypertensive disorders in pregnancy is variable, being higher in developing countries than in the developed ones. There is wide variation in the burden of the problem across the world, with incidences ranging from as low as 0.49 per 1000 maternities in some developed countries to as high as 16.5% in some developing ones.[3-11]

Significant impact of hypertensive disorders of pregnancy upon fetomaternal health has prompted several authors to evaluate serum levels of various substances in these disorders.[7,12-22] These observations have tried to address the relevance of such markers in the pathobiology, diagnosis, assessment of severity and determination of prognosis of pregnancy induced hypertension.

C-reactive protein (CRP) derives its name from its ability to precipitate the C-polysaccharide of *Streptococcus pneumoniae*. It was the first acute-phase reactant to be described and is widely used as a marker for systemic inflammation and tissue damage.[23-24] Evidences suggest that CRP plays an important role in the characteristic inflammatory response of pre-eclampsia and its pathogenesis; thus it has emerged as a potential biomarker in this disorder.[25-29] However, routinely available standard assays for CRP might fail to detect low-grade inflammation (lower detection limit of 3–8 mg/L).[30-31] With the advent of high-sensitivity methods, serum CRP levels as low as 0.1 mg/L can be detected in clinical laboratories with 100-fold higher sensitivity than standard assays.[31-32] CRP measured by such techniques is referred to as high-sensitivity CRP (hs-CRP). It has been used to establish low-grade inflammation in several disorders such as cardiovascular disorders, diabetes mellitus and bronchial asthma.[23,33]

Serum uric acid level is another analyte which has been studied in hypertensive disorders of pregnancy.[13-14,18,21-22] Its concentration is raised in pre-eclampsia owing to increased tubular reabsorption or reduction in glomerular filtration rate in addition to the increased oxidative stress which stimulates placental urate production.[1]

Pre-eclampsia is not an infrequent disorder in North-East India. In this study, we tried to evaluate the association of serum CRP and uric acid levels with the severity of pre-eclampsia, thereby further detailing the role of endothelial cell dysfunction and inflammatory processes in determining the severity and progression of the disease. No such study had ever been undertaken in this region of India to the best of our knowledge.

MATERIALS AND METHODS:

The study was conducted in Department of Biochemistry and Department of Obstetrics/Gynaecology, Assam Medical College and Hospital, Dibrugarh, India. Pre-eclampsia was defined by the following standard criteria: blood pressure $\geq$ 140/90 mm Hg, proteinuria $\geq$ 300 mg/24 hours or $\geq$ 1+ by dipstick method and edema. The cases comprised of 50 pre-eclamptic patients in their 3rd trimester, who were further classified into two groups: 25 mild (blood pressure $\geq$ 140/90 mm Hg but < 160/110 mm Hg) and 25 severe pre-eclamptics (blood pressure $\geq$ 160/110 mmHg). Fifty age matched normotensive pregnant women in their 3rd trimester were used as controls. Informed consent was taken from all participants. Patients with history of essential hypertension, renal disease, collagen vascular disease, diabetes mellitus, severe anemia, hydatidiform mole, multiple pregnancy and inflammatory diseases were excluded.

Three mL of blood sample was collected from each woman for analysis. For estimation of hs-CRP, 10µL of serum was used whereas 20µL of serum was used for uric acid measurement. Serum hs-CRP concentration was estimated by particle enhanced turbidimetric immunoassay (PETIA) technique (Dimension RxL Max autoanalyzer, Siemens), whereas uric acid concentration was estimated by uricase method using semiautoanalyzer Microlab 300, Merck. Data was analysed by stata 12, presented as mean ± SD/median (range). Continuous variables following normal distribution were compared among the groups by one way ANOVA followed by post hoc comparison using Bonferroni test. On the other hand, data not following normal distribution were compared by Kruskal-Wallis test, followed by multiple comparison using Dunn-Bonferroni test. Correlation between the variables was assessed by Spearman correlation coefficient. P value of less than 0.05 was considered as statistically significant.

RESULTS:

Most of the pre-eclamptic patients were from tea estates (21/50, i.e., 42%) followed by rural areas (17/50, i.e., 34%) and urban areas (12/50, i.e., 24%). Relevant clinical and biochemical parameters of the study groups including age distribution are presented in table 1.

Table 1: Clinical and biochemical parameters of normotensive pregnant women and pre-eclamptic patients.

Parameter	Normotensive pregnant women (n=50)	Mild pre-eclamptic patients (n=25)	Severe pre-eclamptic patients (n=25)	P1	P2	P3
Age (years)	24.32 + 3.78	23.84 + 3.95	24.84 + 4.76	1.000	1.000	1.000
Gestational age at sampling (weeks)	36.86 + 1.62	36.4 + 1.78	37.1 + 1.77	0.814	1.000	0.350
SBP (mmHg)	115.96 + 8.75	151.04 + 5.30	179.84 + 13.25	<0.001	<0.001	<0.001
DBP (mmHg)	75.8 + 5.75	94.08 + 3.29	112.96 + 3.61	<0.001	<0.001	<0.001
Serum hs-CRP (mg/dl)	0.38 (0.24-0.54)	0.97 (0.48-2.79)	3.12 (0.53-5.25)	<0.001	<0.001	0.009
Serum uric acid (mg/dl)	4.01 + 0.35	4.51 + 0.69	6.62 + 0.83	0.003	<0.001	<0.001

[All data represented as mean $\pm$ SD except hs-CRP which is presented as median (range)].

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hs-CRP: High sensitivity C-reactive protein.

P_1: p value (comparing normotensive pregnant women and mild pre-eclamptic patients).
P_2: p value (comparing normotensive pregnant women and severe pre-eclamptic patients).
P_3: p value (comparing mild and severe pre-eclamptic patients).

Serum hs-CRP and uric acid concentrations were found to be significantly higher in both mild and severe pre-eclamptic patients than in normotensive pregnancies. Additionally, serum concentrations of both these parameters were significantly higher in severe pre-eclamptics than the mild ones (Table 1).

Significant positive correlation was found between systolic blood pressure (SBP) and diastolic blood pressure (DBP) with both serum hs-CRP and uric acid levels in mild as well as severe pre-eclamptic patients (Table 2). In normotensive pregnancies, there was negligible correlation between SBP/uric acid, DBP/uric acid and DBP/hs-CRP (r=0.0479, 0.0124 and 0.0009 respectively) and no correlation was observed between SBP/hs-CRP (data not included). We also noted significant positive correlation between serum hs-CRP and uric acid levels in both mild and severe pre-eclamptics (Table 2), but no such correlation was found in normotensive pregnancies (data not included).

Table 2: Correlation of serum hs-crp and uric acid with systolic and diastolic blood pressures and with each other in mild and severe preeclamptic patients.

Parameter	Mild pre-eclamptic patients (n=25)	Severe pre-eclamptic patients (n=25)
hs-CRP and SBP	r=0.59, p <0.01	r= 0.48, p <0.05
hs-CRP and DBP	r=0.61, p <0.01	r= 0.77, p <0.001
Serum uric acid and SBP	r=0.65, p <0.001	r=0.54, p <0.01
Serum uric acid and DBP	r=0.73, p <0.001	r=0.75, p <0.001
hs-CRP and serum uric acid	r=0.89, p <0.001	r=0.82, p <0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-CRP: High sensitivity C-reactive protein.

DISCUSSION:

The etiology of pre-eclampsia remains unsolved in spite of many years of scientific research.[2] Endothelial dysfunction has emerged as the leading pathogenic event in pre-eclampsia. Redman and colleagues suggested that endothelial dysfunction in this disorder is a part of a generalized systemic inflammatory response.[34] CRP is an inflammatory marker, which activates the classical complement pathway and helps in the phagocytosis of particulate antigens. It is also responsible for the clearance of damaged cell membranes and nuclear antigens released from apoptotic and necrotic cells.[35] There is a fair amount of evidence now that apart from being an inflammatory marker, CRP also participates in the development of inflammation by modulating endothelial function.[36-38]

In our study, serum hs-CRP concentrations were found to be significantly higher in pre-eclamptic patients than normotensive pregnant women. Moreover, its concentrations were significantly higher in severe pre-eclamptics than women with mild pre-eclampsia. Similar observations were reported in various other studies on pre-eclampsia.[12,16-17,39-40] Pro-inflammatory markers may rise not only in pre-eclampsia but in normal pregnancy too. It has been suggested that a reduction in plasma volume is another contributing factor causing significant elevation of serum CRP in pre-eclamptics, who already have a more severe inflammatory reaction than normotensive women.[34-35]

We also found significant positive correlation between serum hs-CRP concentrations and blood pressure (systolic and diastolic) in both mild and severe pre-eclamptic patients, similar to observations by Kumru and colleagues.[16] Correlation of CRP level and hypertension has been reviewed by Hage, who mentioned that in hypertensive individuals, CRP levels associate with vascular stiffness, atherosclerosis, development of end-organ damage and cardiovascular events.[41]

The hyperuricemia in pre-eclampsia is due to renal dysfunction, mainly as a result of reduced renal clearance.[19] The formation of uric acid is associated with generation of reactive oxygen species. Moreover in pre-eclampsia, implantation may be superficial resulting in a hypoxic maternal-fetal interface. This leads to increased turnover of trophoblastic tissue that contributes to increased production of uric acid and free radicals in pre-eclampsia. In our study, serum uric acid concentrations were found to be significantly higher in pre-eclamptics than normotensive pregnancies and in the severely affected ones than those with mild pre-eclampsia. Similar observations were made in several other studies.[18, 22] In addition, we found significant positive correlation between serum uric acid concentration and blood pressure (systolic and diastolic) in both mild and severe pre-eclamptic patients. This finding is at par to those noted in other research.[14, 19] On the contrary, Manjareeka and Nanda observed that elevated levels of uric acid did not correlate with the raised systolic and diastolic blood pressure in pre-eclamptics.[21] In another study, uric acid level was seen to be an unreliable indicator for development of hypertension.[42] Though the latter was a longitudinal study as opposed to the cross sectional design of our study, the relation between serum uric acid levels and blood pressure in pre-eclampsia remains debatable. In pre-eclampsia, the ongoing oxidative stress and renal dysfunction may further contribute to development of hypertension and hyperuricemia. As indicated by CRP levels, the inflammation is less severe in normotensive pregnancies than pre-eclamptics and in mild pre-eclamptics than the severely affected ones. Significant elevation of blood pressure as well as serum uric acid levels in pre-eclamptics as compared to normotensive pregnancies and in severe pre-eclampsia as compared to mild pre-eclampsia correlates with the severity of inflammation. Our study suggests that the serum concentration of CRP tends to increase as pre-eclampsia progresses from mild to severe, supporting the role of inflammation in the pathogenesis of the disease.

Additionally, we noted significant positive correlation between hs-CRP and uric acid levels in mild and severe pre-eclamptics but not in normotensive pregnancies. Similar findings were reported in measurements on women with pre-eclampsia in few other studies.[43, 44] These observations suggest an inter-relationship between the inflammatory state and renal dysfunction in pre-eclampsia, likely representing widespread endothelial injury.

CONCLUSION:

Our findings indicate that serum concentrations of CRP and uric acid correlate with the severity of pre-eclampsia and thus they can be used for monitoring the disease. However, this study is limited by the fact that there was only a single point determination of the parameters in women in their 3rd trimester, thereby precluding the assessment of serial measurements from early pregnancy. Such a design would have helped to determine optimal cut offs for these parameters to identify those at risk of developing pre-eclampsia later in pregnancy. Larger prospective studies are required to explore the role of these serum markers in assessing the progression of the disease and to determine

whether these can be used as early predictors for disease conversion.

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