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Basavaraj V Savadi
Associate Professor,
Department of Biochemistry,
Basaveshwara Medical College
& Hospital, Chitradurga,
Karnataka, India

Gaurang K Anandpara
Associate Professor,
Department of Biochemistry,
Dr. M K Shah Medical College
and Research Institute,
Ahmedabad, Gujarat, India

BM Rashmi
Associate Professor,
Department of Community
Medicine, Basaveshwara
Medical College & Hospital,
Chitradurga, Karnataka, India

Bhagyajyoti Nalwarkar,
Postgraduate student,
Department of Obstetrics and
Gynecology, Vijayanagar
Institute of Medical Sciences,
Ballari, Karnataka, India

Association of lipoprotein (a) and high-sensitive C-reactive protein in preeclampsia

Basavaraj V Savadi, Gaurang K Anandpara, BM Rashmi and Bhagyajyoti Nalwarkar

Abstract

Background: Preeclampsia is a hypertensive disorder associated with substantial perinatal morbidity and mortality. Neonates born to hypertensive mothers are at increased risk of prematurity and foetal growth restriction. Timely prediction and accurate diagnosis are the key to limiting the morbidity and mortality caused by preeclampsia. Early identification of PE using inflammatory biomarkers could reduce PE related comorbidities.

Aim: To compare levels of inflammatory markers: hsCRP and Lipoprotein (a) levels in preeclamptic pregnant women, with the levels of inflammatory markers among women with normal pregnancy at a tertiary care teaching hospital

Material and Methods: This comparative cross-sectional study included 60 Preeclamptic women and 60 apparently healthy singleton pregnant women matched for gestational age and parity. Data were analyzed in SPSS V:16. To find an association between inflammatory markers and blood pressure levels, statistical tests like chi-square, independent student t-test were applied.

Results: LP(a) and hsCRP levels were significantly higher among the preeclamptic group compared to the normal pregnancy group and these levels had moderate positive correlation with SBP (r=0.650) and DBP (0.627) among preeclamptic women.

Conclusion: Increased levels of lipoprotein (a) and hsCRP are found in the present study, which is correlated with the progression of preeclampsia by causing endothelial dysfunction and inflammatory cascade. Also, the earliest detection of Lp(a) and hsCRP during pregnancy could help to detect preeclampsia and to prevent its further complications.

Keywords: Preeclampsia, lipoprotein (a), high sensitivity CRP, predictors of inflammation

Introduction

Hypertensive disorders are the commonest complications in pregnancy, occurring in about 10% of pregnancies globally [1]. Neonates born to hypertensive mothers are at increased risk of prematurity and foetal growth restriction [1]. Preeclampsia (PE) occurs in 5–14% of pregnancies and 20% of high-risk pregnancies [1-4]. PE is defined as blood pressure >140/90 mmHg after 20 weeks of pregnancy and either proteinuria ≥300mg/24h or protein: creatinine ratio ≥0.3 or one of the following: thrombocytopenia, elevated liver transaminases, pulmonary edema, new onset renal insufficiency, or cerebral or visual disturbances [2].

Unrecognized PE can lead to serious complications, including eclampsia [2-4]. Its burden is greatest in developing countries (15% maternal deaths) compared to 2% in the developed world. This difference is attributed to inadequate prenatal care in poor regions of the world, and subsequently missing timely detection of preeclampsia at early stages. Therefore, timely prediction and accurate diagnosis are key to limiting morbidity and mortality caused by PE [1-6]. As there is increasing scientific evidence of the role of inflammation in PE, it is hypothesized that the early identification of PE using appropriate inflammatory biomarkers could substantially reduce preeclampsia related comorbidities [5, 6]. Such studies on inflammatory markers in pre-eclampsia in Central Karnataka are scarce. Hence, the present study was conducted to compare the levels of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and Lipoprotein (a) [Lp(a)] levels in pregnant women diagnosed with mild or severe PE, with the levels of inflammatory markers among women with normal pregnancy at a tertiary care teaching hospital in Chitradurga.

Corresponding Author:
Gaurang K Anandpara
Associate Professor,
Department of Biochemistry,
Dr. M K Shah Medical College
and Research Institute,
Ahmedabad, Gujarat, India

Material and Methods

After obtaining institutional ethics committee clearance, this comparative cross-sectional study was conducted from September 2020 to February 2021, at a tertiary care teaching hospital in Chitradurga. A total of 60 diagnosed cases of preeclampsia along with 60 age, parity and gestational age matched singleton normal pregnant women attending an antenatal clinic or admitted and treated in obstetrics wards of the Basaveshwara Medical College Hospital, during the study period was selected by the simple random sampling method. They were included in the study after explaining the purpose of the study and obtaining their informed consent.

Preeclampsia was defined as blood pressure >140/90mmHg after 20 weeks of pregnancy and either proteinuria ≥300 mg/24h or protein: creatinine ratio ≥0.3 or one of the following: thrombocytopenia, elevated liver transaminases, pulmonary edema, new onset renal insufficiency, or cerebral or visual disturbances [2].

Exclusion criteria consisted of pregnancy with renal disease, multiple pregnancies, gestational trophoblastic disease, Pregnant women with chronic hypertension, diabetes, pregnancy with cardiovascular diseases, and patients with a history of acute or chronic liver diseases. Patients taking corticosteroids. Patients having chronic inflammatory disorders like rheumatoid arthritis, tuberculosis, osteoarthritis, inflammatory bowel disease, patients on drugs like diuretics, patients on magnesium or other metal containing medications.

Information was collected by interview technique, clinical examination and investigations, in a pre-formed semi-structured questionnaire that included participant's socio-demographic details, clinical history, natal history, anthropometric measurements of height and weight as per WHO guidelines [8]. Blood pressure was recorded in supine posture after a rest period of 10 minutes with the standard mercury sphygmomanometer, by a single observer. An average of two readings was noted [8].

Under aseptic precautions, 5 ml of venous blood sample was collected from the antecubital vein in a plain vacutainer for both study groups. This blood sample was allowed to clot and serum was separated by centrifugation at 5000 rpm for 5 minutes. The serum was used to estimate sodium, potassium, magnesium and calcium levels.

Under aseptic precautions, 5 ml of venous fasting blood sample was collected from an antecubital vein in plain vacutainer both from study groups. This blood sample was allowed to clot and serum was separated by centrifugation at 5000 rpm for 5 minutes. The serum was used to estimate lipoprotein (a) and hs-CRP levels. Analysis was done in the central laboratory of the hospital. lipoprotein (a) was measured by using Cobas-e411 auto-analyzer (Roche Diagnostics GmbH, Mannheim, Germany) which applied immunoturbidimetric method and hsCRP was measured by using VITROS 4600 - Dry Chemistry Analyzer which applied immune-turbidimetric assay

Statistical analysis

Data was compiled in an MS Office Excel spreadsheet and analyzed using SPSS V:16 (Statistical Package for Social Service). Qualitative data variables were expressed in frequency and percentages. Quantitative data variables are expressed in mean and standard deviation. Pearson's Chi-square test was used to find the association between categorical variables. Independent sample t-test was applied to find the significance of association between continuous variables such as systolic blood pressure (SBP), diastolic blood pressure (DBP), hsCRP, Lp (a), among the two study groups. The Bivariate Correlations procedure computes Pearson's correlation coefficient was applied to measure the linear association between continuous variables. Associations with a p-value of < 0.05 were considered to be statistically significant.

Results

The study included 60 pre-eclamptic patients (The preeclamptic group) and 60 singleton pregnant women with normal pregnancy (Normal singleton pregnancy group). The mean age among pre-eclamptic patients was 21.94±1.62 years and the comparative group was 22.35±1.71 years. The study groups were comparable with respect to age and parity (*p*>0.05). Incidence of pre-eclampsia was higher among primigravida (65%) when compared to multigravida women (35%). (Table 1)

Table 1: Characteristics of the study participants

Parameters	Pre-eclamptic group	Normal singleton pregnancy group
Age in years	21.94±1.62	23.8±2.6
Gravida		
Primigravida	39 (65%)	32 (53.3%)
Multigravida	21 (35%)	28 (46.7%)
Gestation age in weeks	32.91± 3.42	31.85 ± 2.94

Table 2: Comparison of weight, blood pressure, serum lipoprotein a and serum HS CRP levels among the 2 study groups.

Parameters	Pre-eclamptic group	Normal singleton pregnancy group	t Value	p Value
Weight in kg (Mean±SD)	51.92±2.01	50.58±1.93	-3.38	<0.001
SBP in mmHg (Mean±SD)	159.36±6.33	120.52±6.79	30.58	<0.001
DBP in mmHg (Mean±SD)	99.72±5.98	81.4±2.6	17.44	<0.001
Serum Lipoprotein (a) (mg/dl) Mean±SD	43.25±12.3	23.75±5.43	10.24	<0.001
Serum HS CRP (mg/dl) Mean±SD	7.54±2.44	5.8±3.0	3.008	<0.001

Data are shown as Mean±SD; Student's t-test applied to test the significance of the association

Table 2 shows that the average height of the pre-eclamptic group was 152.88±4.84 cms and of the normal pregnancy group was 151.18±3.86 cms. The difference in height was not found to be statistically significant. The average weight of the pre-eclamptic group was significantly greater (51.92± 2.01 kg) compared normal pregnancy group weight (50.58±1.93 kg). Whereas, there was no statistical difference in BMI between the two groups.

The average systolic and diastolic blood pressure level among the preeclamptic group was 150.36±6.33 mmHg, and 98.72±6.79 mmHg, respectively, which was significantly higher when compared to that of the normal singleton pregnancy group (120.52±6.79 mmHg and DBP was 80.0±4.63 mmHg, respectively). Accordingly, the average levels of serum lipoprotein a as well as serum HS CRP were significantly greater among the preeclamptic group (43.25±12.3 and 7.54±2.44 mg/dl respectively) when compared to the normal pregnancy group (23.75±5.43 and 5.8±3.0 mg/dl respectively). (Table 2)

Table 3: Correlation of serum lipoprotein (a) levels and blood pressure in preeclamptic group

Correlation of	with	'r' value	'p' value
Serum lipoprotein (a)	Systolic blood pressure (mm Hg)	0.650	<0.001
	Diastolic blood pressure (mm Hg)	0.627	<0.001
HS CRP level	Systolic blood pressure (mm Hg)	0.523	<0.001
	Diastolic blood pressure (mm Hg)	0.528	<0.001

r- Pearson correlation Co-efficient.

The correlation of serum lipoprotein (a) levels and HS CRP levels with systolic blood pressure and diastolic blood pressure is shown in table 3. Serum lipoprotein (a) had moderate positive correlation with SBP (r=0.650) and DBP (0.627). These associations were found to be statistically significant.

Serum HS CRP also had a moderate positive correlation with SBP (r=0.523) and DBP (0.528). These associations were found to be statistically significant.
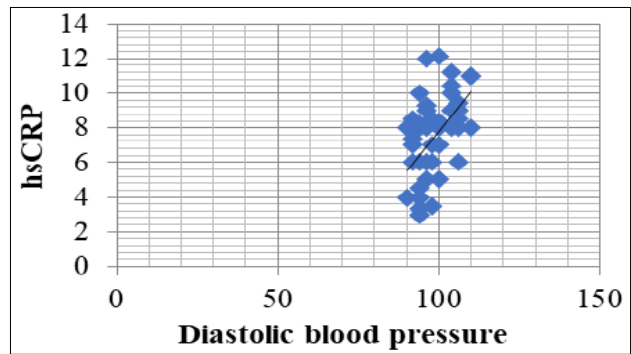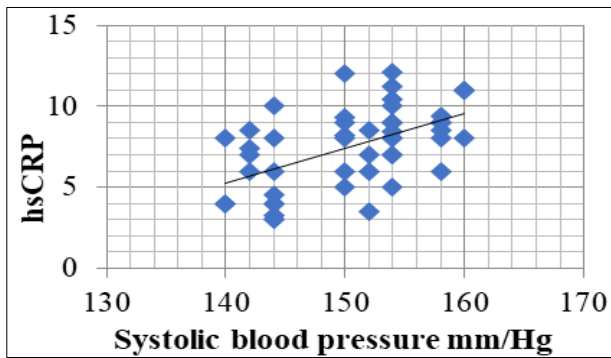

Fig 1: Scatterplot of serum HS CRP levels, according to systolic and diastolic blood pressure among preeclamptic study group
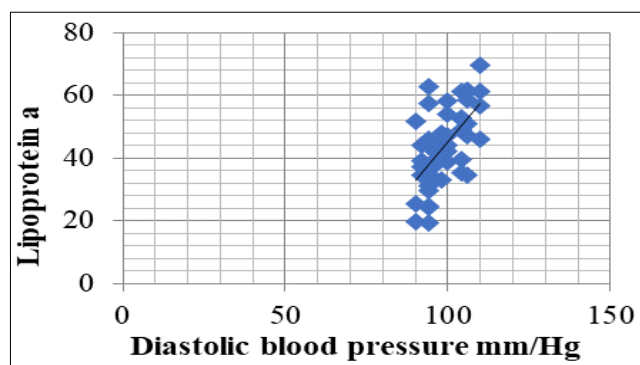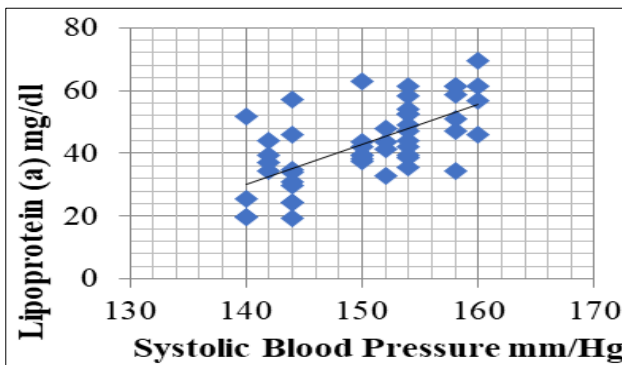

Fig 2: Scatterplot of serum lipoprotein (a) levels, according to systolic and diastolic blood pressure among preeclamptic study group

Discussion

Preeclampsia is a pregnancy specific hypertensive disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks of gestation and can present as late as 4-6 weeks postpartum [2]. The age of preeclamptic group was 21.94±1.62 years and the normal pregnancy group was 23.8±2.6years. Preeclampsia was found in higher percentage among primigravida compared to multigravida, whereas this association was not significant. These findings are similar to studies conducted by Sayyed AAK *et al*., and Prerna B *et al* [9, 10].

The average levels of weight, average levels of systolic and diastolic blood pressure levels were significantly higher among the preeclamptic group compared to the normal pregnancy group. (Table 2) These results are comparable with the studies conducted elsewhere [11-13].

Patho-physiologically, the hallmark of preeclampsia includes increased vasoconstriction resulting in maternal hypertension and reduced uteroplacental blood flow, disturbed vascular endothelial integrity with increased vascular permeability, and activation of the coagulation cascade [5, 7, 13, 14]. Inflammatory cells are activated in preeclampsia and

localized to the site of vascular injury and associated with higher levels of pro-inflammatory molecules, cytokines and adhesion molecules [5, 7, 13, 14].

In the present study, the average lipoprotein (a) levels were significantly higher among preeclamptic group (43.25±12.3 mg/dl) compared to normal pregnancy group 23.75±5.43 mg/dl). (Table 2, Figure 2). Endothelial cell dysfunction is a key feature of the pathogenesis of pre-eclampsia. Although, the cause of endothelial cell injury is multifactorial, poor placental perfusion plays a major role. In pre-eclampsia, characteristic pathological lesions in the placenta are fibrin deposits, acute atherosis and thrombosis. The combination of direct effect of oestrogen on lipid synthesis in the liver, as well as a state of relative insulin resistance in pregnancy results in hyperlipidemias state, leading to increased coagulation and vasoconstriction. The similarity between the lesions of pre-eclampsia and atherosclerosis, together with the antifibrinolytic properties of Lp(a) has led to speculations of a common pathophysiological pathway [4]. The findings of Lp (a) in the present study are comparable with the studies conducted elsewhere [10, 12].

In the present study, the average hsCRP levels were significantly among preeclamptic group (7.54±2.44 mg/dl) compared to normal pregnancy group (5.8±3.0 mg/dl). (Table 2, Figure 1) Similar results are found in studies conducted by Bej P *et al* and Vasava SN *et al* [12, 13]. As there is increasing evidence that activation of inflammation is a major contributor in the pathogenesis of PE, the biochemical markers of inflammation are sensitive in predicting preeclampsia. During normal pregnancy, the innate immune system is activated, and maternal inflammatory response is stimulated. In PE, the systemic maternal inflammatory response is enhanced, and it is characterized with more generalized intravascular inflammatory reaction. Intravascular leukocytes and the clotting and complement systems are involved in the pathogenesis of PE [6]. hsCRP is one of the markers of systemic inflammation and tissue damage and its levels are found to be higher in women with PE. The hepatic synthesis of hs-CRP increases in response to inflammatory cytokines such as IL-10 and IL-6 which are responsible for inflammatory reactions and maternal endothelial activation in pre-eclampsia [9, 10]. As there is evidence that there is an association between first-trimester hsCRP levels and subsequent preeclampsia which supports the hypothesis that systemic inflammation is involved in the pathogenesis of preeclampsia, this biomarker has gained significance as it is easily available and is a cost-effective test as compared to other markers of inflammation [4, 9, 10, 12, 13].

Conclusion
Increased levels of lipoprotein (a) and hsCRP are found in the present study, which are correlated with the progression of preeclampsia by causing endothelial dysfunction and inflammatory cascade. Also, the earliest detection of Lp(a) and hsCRP during pregnancy could help to detect preeclampsia and to prevent its further complications, which would go a long way in preventing the adverse unfavourable outcomes due to preeclampsia. Prospective studies on lipoprotein (a) and hsCRP are needed to find their predictive value in preeclampsia.

Increased levels of lipoprotein (a) and hsCRP are found in the present study, which are correlated with the progression of preeclampsia by causing endothelial dysfunction and inflammatory cascade. Also, the earliest detection of LP (a)

and hsCRP during pregnancy could help to detect preeclampsia and to prevent its further complications, which would go a long way in preventing the adverse unfavourable outcomes due to preeclampsia. Prospective studies on lipoprotein (a) and hsCRP are needed to find their predictive value in preeclampsia.

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