Haemorheologic And Biochemical Parameters Of Pre-Eclamptic Patients In University Of Calabar Teaching Hospital, Calabar, Nigeria

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Abstract: *Pre-eclampsia refers to pregnancy-induced hypertension, a condition characterized by diffuse maternal endothelial dysfunction and a systemic inflammatory response with possible haemorheological changes. This study assessed haemorheologic and biochemical parameters of thirty pre-eclamptic patients admitted in University of Calabar Teaching Hospital and compared same with those of thirty normal pregnant as well as thirty apparently healthy non-pregnant controls aged 18-45 years. Weight, height and blood pressure of subjects were measured using standard instruments while body mass index was calculated. Erythrocyte sedimentation rate, relative plasma viscosity and fibrinogen concentration were used to assess haemorheology while biochemical parameters included protein in urine, total protein, albumin, globulin and uric acid concentrations. All tests were performed using standard techniques. The systolic and diastolic blood pressures, body mass index, erythrocyte sedimentation rate, relative plasma viscosity, fibrinogen concentration, total protein, albumin, globulin and uric acid levels of the pre-eclamptic patients were significantly higher ($p<0.05$) than values obtained for normal pregnant and non-pregnant controls. Blood pressure correlated positively ($r=0.071$; $r=0.362$) with uric acid concentration and a directly proportional relationship was expressed between levels of protein in urine and uric acid concentration of pre-eclamptic patients. Fibrinogen concentration was significantly higher ($p<0.05$) in the third versus second trimesters for normal pregnant subjects. Gestational age had no significant effect on the measured parameters among pre-eclamptic patients. Altogether, significant changes in haemorheologic and biochemical parameters existed in pre-eclamptic condition with increased risk of developing thrombosis and other complications of hypercoagulation.*
Key words: *Pre-eclampsia, haemorheology, hypercoagulation*

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I. Introduction

Pre-eclampsia refers to pregnancy-induced hypertension characterized by large amounts of protein in urine. It is diagnosed when the systolic blood pressure is greater than or equal to 140mmHg and the diastolic blood pressure is greater than or equal to 90mmHg observed in two separate readings taken at least six hours apart. The other defining feature is the presence of up to 300mg of protein in a 24-hour urine sample (proteinuria)[1,2,3]. High blood pressure in pregnancy accounts for 10% of ill-health induced by pregnancy which affects nearly twenty million women worldwide each year[4]. The incidence of pre-eclampsia has been reported to be seven times higher in developing countries with a prevalence of 1.2% recorded in University of Calabar Teaching Hospital[5,6,7]. Pre-eclampsia mostly occurs in pregnant teens and in women over forty years and first-time pregnancies and is often characterized by excess salt and water retention in the kidneys, development of edema and hypertension in the mother and weight gain. In addition, there is vascular endothelium impairment with occurrence of arterial spasm in the brain, kidneys and liver[8,9]. This medical condition and its advanced stage (eclampsia) can result in rare but serious complications including stroke, presence of water in the lungs, heart failure, bleeding from the liver, reversible blindness and postpartum haemorrhage. Another associated complication is that of sudden detachment of placenta from the uterus (placental abruptio) which could result in stillbirth[10].

Pre-eclampsia is characterized by diffuse maternal endothelial dysfunction and a systemic inflammatory response which may significantly influence haemorheological variables. Haemorheology studies the flow properties of cellular and plasma components of blood, and these relate to the packed cell volume (PCV), plasma viscosity (PV), red cell aggregation and deformability. Moreover, plasma viscosity is largely

determined by the amount of proteins (especially fibrinogen) present in plasma. Already established is the fact that pregnancy on its own induces hypercoagulability(propensity to develop thrombosis) which is a physiologically adaptive mechanism to prevent postpartum bleeding. Indeed, increased relative plasma viscosity, plasma proteins and fibrinogen concentration as well as decreased packed cell volume and whole blood viscosity has been reported in normal pregnancy[11,12,13]. However, when pregnancy is combined with an additional underlying hypercoagulable state, the risk of developing thrombosis or embolism may become substantial[14]. Despite the need for closer investigation of this condition however, paucity of scientific data on biomedical variables associated with pre-eclampsia has been a challenge in our population. Thus this study set out to assess haemorheologic and protein variables of pregnant women with pre-eclampsia in Calabar in order to provide information that will aid management of pregnant women generally and those with pre-eclampsia specifically.

II. Materials and Methods

This study was sited at the University of Calabar Teaching Hospital (UCTH), a tertiary hospital located in Calabar, Nigeria. A cross-sectional study design was used without follow-up. Approval for the study was given by the health research ethics committee of UCTH and informed consent was obtained from all participants prior to sampling. A total of ninety (90) subjects aged 18 years and above were enrolled. Test subjects consisted of thirty (30) pregnant women with pre-eclampsia admitted in the antenatal ward while controls were thirty (30) apparently healthy pregnant women without any complications attending antenatal clinic as well as thirty (30) apparently healthy non-pregnant women selected from staff of UCTH. Pregnant women with any disease condition and subjects who did not give their consent were excluded. A structured questionnaire was completed by each participant prior to measurement of blood pressure and collection of blood sample. Erythrocyte sedimentation rate (ESR) was measured by Westergren technique[15] while relative plasma viscosity (RPV) was determined by the method of Reid and Ugwu[16]. Fibrinogen concentration (FIB) was determined by Clauss technique[17] using kit purchased from Giesse Diagnostics, Italy. Total protein (TP) in serum was determined by Biuret method using kit purchased from Randox laboratories, United Kingdom. Albumin (ALB) was measured by Bromocresol Green method while uric acid was by Uricase technique using kits purchased from BIOLABO REAGENTS, France; globulin concentration (GLOB) was calculated by subtracting albumin from total protein concentration. One-way analysis of variance (ANOVA), Tukey HSD post hoc, student's t –test and Pearson's correlation were used to analyze the data obtained on statistical package for social sciences version 20. Significance was set at a P-value <0.05. Results are expressed in figures and as mean ± standard deviation in tables.

## III. Results

In this study, some haemorheologic and biochemical parameters of 30 pre-eclampsia patients and their pregnant and non-pregnant controls were investigated. As presented in table 1, the systolic and diastolic blood pressures as well as the body mass index were significantly higher (p<0.05) for pre-eclamptic patients when compared to their controls. Similarly, the erythrocyte sedimentation rate, relative plasma viscosity and fibrinogen concentration of the pre-eclamptic patients were significantly higher (p<0.05) than values obtained for normal pregnant and non-pregnant controls. The total protein, albumin and globulin of the test subjects were observed to be significantly higher (p<0.05) versus normal pregnant subjects but similar to non-pregnant levels. Pre-eclamptic patients had a significantly higher (p<0.05) uric acid concentration (0.30±0.06 mmol/L) when compared to both control groups. Figures 1a and 1b shows that blood pressure correlates (r=0.071; r=0.362) positively with uric acid concentration while figure 2 expresses a directly proportional relationship between levels of protein in urine and uric acid concentration of pre-eclamptic patients. Table 2 shows the haemorheologic and biochemical parameters of pre-eclamptic patients and normal pregnant controls based on gestational age. Of the thirty women in each group, fifteen were in the second trimester and fifteen in the third trimester; no subject was found to be in the first trimester. The fibrinogen concentration of pre-eclamptic patients in the second trimester was not significantly different from those in the third trimester however; normal pregnant subjects in the third trimester had a significantly higher (p<0.05) fibrinogen concentration (202.54±32.31mg/dl) versus the second trimester (166.41±47.02mg/dl). There were no significant differences for ESR, RPV, TP, ALB, GLOB and uric acid concentration between the second and third trimesters for both pre-eclamptic patients and their normal pregnant control.

TABLE 1. Haemorheologic and biochemical parameters of pre-eclamptic patients and control subjects

PARAMETERS	PRE-ECLAMPTIC PATIENTS (n=30)	NORMAL PREGNANT CONTROL (n=30)	NON-PREGNANT CONTROL (n=30)	P-VALUE
SBP (mmHg)	156.67±20.73[b]	114.33±8.17	116.33±6.15	0.001
DBP (mmHg)	95.77±6.72[c]	72.33±9.71	72.33±8.58	0.001
BMI (Kg/m^2)	36.17±5.20[b]	30.74±5.74	26.69±3.95	0.001
ESR (mm/hr)	45±21[c]	30±20	19±11	0.001
RPV	1.93±0.19[c]	1.71±0.23	1.56±0.22	0.001
FIB (mg/dl)	364.60±82.78[c]	182.07±44.54[b]	132.23±29.97	0.001
TP (g/L)	75.27±8.46[a]	58.93±5.34[b]	71.83±5.23	0.001
ALB (g/L)	42.77±5.05[a]	37.60±5.12	40.23±3.93	0.001
GLOB (g/L)	32.50±8.95[a]	21.33±6.80[b]	31.47±5.29	0.001
URIC ACID (mmol/L)	0.30±0.06[c]	0.20±0.05	0.23±0.04	0.001

Post Hoc: a=Different from normal pregnant control   b=Different from non pregnant controls
c=Different from normal and non pregnant controls

$y = 23.68x + 149.5$
$R^2 = 0.005$ r=0.071
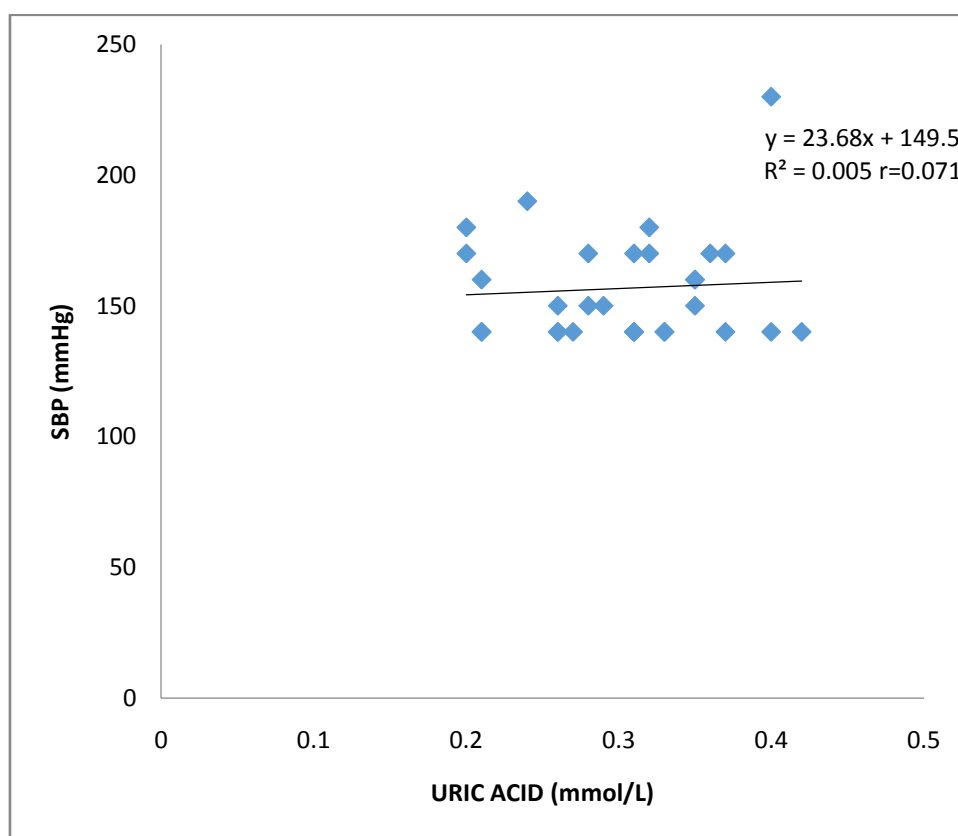
Fig. 1a: Correlation between systolic blood pressure (SBP) and uric acid concentration of pre-eclamptic patients
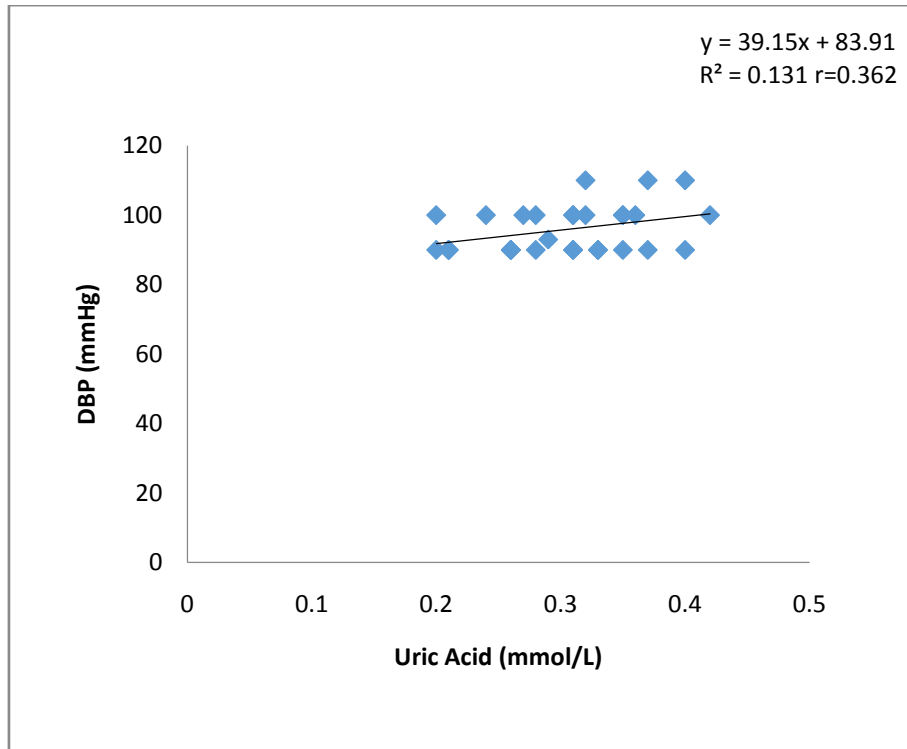
Fig. 1b: Correlation between diastolic blood pressure (DBP) and uric acid concentration of pre-eclamptic patients
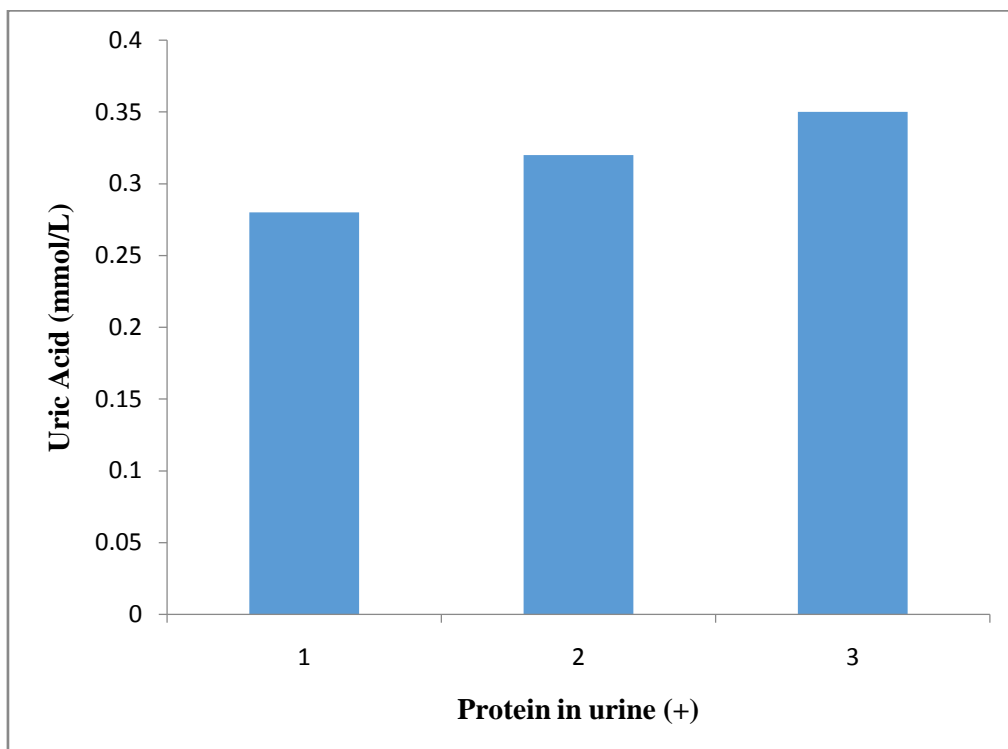

Fig. 2: Appearance of protein in urine and uric acid concentration of pre-eclamptic patients

Table 2. Haemorheologic and biochemical parameters of pre-eclamptic patients and normal pregnant controls based on gestational age

PARAMETER	PRE-ECLAMPTIC N=30	PATIENTS	NORMAL PREGNANT CONTROL N=30	
	SECOND TRIMESTER n=15	THIRD TRIMESTER n=15	SECOND TRIMESTER n=15	THIRD TRIMESTER n=15
ESR (mmHg)	45±21	44±22	21±9	41±25
RPV	1.90±0.13	1.96±0.23	1.72±0.27	1.72±0.18
FIB (mg/dl)	387.07±82.52	342.13±79.39	166.41±47.02	202.54±32.31*
TP (g/L)	72.40±8.63	78.13±7.51	57.82±5.29	60.38±5.24
ALB (g/L)	42.40±5.59	43.13±4.61	38.35±5.46	36.62±4.65
GLOB (g/L)	30.00±8.86	35.00±8.61	19.47±6.48	23.77±6.67
URIC ACID (mmol/L)	0.30±0.07	0.31±0.06	0.20±0.05	0.19±0.04

*Significantly higher (P<0.05) in third trimester compared to second trimester

IV. Discussion

The haemorheologic and biochemical parameters of pre-eclamptic patients in addition to normal pregnant and non-pregnant controls were investigated in this study. The higher blood pressures observed in pre-eclamptic patients is expected since pre-eclampsia is a condition of pregnancy induced hypertension. Obesity is also associated with the development of pre-eclampsia[18] as confirmed by the increase in body mass index recorded in this study. Increases in erythrocyte sedimentation rate and relative plasma viscosity as well as fibrinogen as observed in pre-eclamptic patients indicates impaired rheology (flow) of blood. This could be attributed to insufficient blood supply to the placenta in pre-eclampsia which could result in the release of inflammatory cytokines such as tumor necrotic factor alpha and interleukin six. These cytokines are known to mediate widespread dysfunction of the maternal vascular endothelium[2]. Furthermore, pre-eclampsia is a state of pregnancy induced hypertension and proteinuria often characterized by impaired function of the vascular endothelium and haemorheology. Pre-eclampsia is believed to occur from an abnormal placenta, the removal of which ends the disease in most situations[19]. During normal pregnancy, the placenta vascularizes to allow for blood flow between the mother and child. Abnormal maturation of the placenta leads to poor placental perfusion. The placenta of women with pre-eclampsia is abnormal and characterized by poor trophoblastic invasion. It is thought that this results in oxidative stress, hypoxia, and the release of factors that promote endothelial dysfunction, inflammation, and other possible reactions hence the clinical manifestations of pre-eclampsia are associated with general endothelial dysfunction, including vasoconstriction and end-organ ischemia[20]. On its own, pregnancy induces a state of inflammation and is a factor of hypercoagulability[13] as a physiologically adaptive mechanism to prevent post-partum bleeding. However, when complicated with an additional underlying condition such as pre-eclampsia, the changes observed in normal pregnancy may be amplified with increased risk of developing thrombosis, disseminated intravascular coagulation (DIC) and subsequently postpartum haemorhage as earlier reported[14].

The total protein, albumin and globulin concentrations of patients with pre-eclampsia were significantly higher (p<0.05) than the normal pregnant as well as the non-pregnant control values. Protein metabolism has been known to be affected by pregnancy. It has been documented that one kilogram of extra protein is deposited during pregnancy with half going to the fetus and placenta and the other half going to uterine contractile proteins, breast glandular tissue, plasma protein and haemoglobin[21]. However, the change in the serum proteins measured in this research could be attributed to the complication of hypertension in pregnancy which amplifies the changes observed in normal pregnancy. Indeed, the excretion of up to 300mg of protein in a 24-hour urine sample (proteinuria) is an important diagnostic marker for pre-eclampsia[3]. Pre-eclampsia has been associated with increased capillary permeability secondary to endothelial damage which is partly responsible for the observed proteinuria[22]. It has been reported that albumin levels decrease during pregnancy due to an increase in plasma and interstitial volume as well as increase in albumin metabolism and that albumin is lower in women with pre-eclampsia than in healthy pregnant women also due to increased capillary permeability secondary to endothelial damage[23,24]. However, the findings of the present study deviate from these reports probably as a result of difference in methodology. Since globulin is derived from total protein and albumin, its values follow the same pattern. Pre-eclamptic patients had a uric acid level of 0.30±0.06mmol/L and this was significantly higher (p<0.05) than values obtained for control groups. Hyperuricaemia is a common finding in pre-eclamptic pregnancies[25]. Previously, hyperuricemia was associated with gout but is now been identified as a marker for a number of metabolic and hemodynamic abnormalities. Numerous reports have demonstrated a relationship between uric acid concentrations and severity of pre-eclampsia, however the clinical utility of hyperuricemia in the management of pre-eclampsia is controversial[26,27]. The findings of this work as shown in figures 1b and 2, highlights a strong positive

relationship between uric acid and diastolic blood pressure as well as proteinuria in pre-eclampsia hence this study strongly suggests that hyperuricemia may be a useful diagnostic marker for pre-eclampsia.

In this study, it was observed that both the pre-eclamptic patients and their normal pregnant controls were all in their second and third trimesters of pregnancy (Table 2), suggesting that women in the study area do not register for antenatal care in their first trimester. This is a cause for concern as early monitoring of pregnant women will improve the health of mother and child and prevent complications that may otherwise arise. The fibrinogen concentration of normal pregnant subjects increased significantly from second to third trimester. This may be due to increased liver production of coagulation factors mainly fibrinogen in pregnancy as a physiological adaptation to prevent postpartum bleeding. However, if not controlled, this could result to increased risk for developing blood clot and embolisms as a result of a hypercoagulable state and disseminated intravascular coagulation (DIC)[21]. Hypercoagulation results in consumption of platelets and clotting factors which could subsequently lead to post-partum hemorrhage (PPH). Other haemorheologic and biochemical parameters were not affected by gestational age.

V. Conclusion

It is concluded from this study that pre-eclampsia amplifies the haemorheological changes which occur in normal pregnancy with increased risk of developing thrombosis and other complications of hypercoagulation. It is therefore suggested that erythrocyte sedimentation rate, relative plasma viscosity, fibrinogen, total protein, albumin, globulin and uric acid should be included as routine tests for all pregnant women and pre-eclamptic patients in particular. Also awareness should be created in the populace by public health personnel to encourage early registration of pregnant women for antenatal care.

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