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Plasma Lactate, Serum Uric Acid, C-Reactive Protein In Women With Pre-Eclampsia In Oredo Local Government Area, Benin City, South – South Nigeria – A Pilot Study

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Abstract
Background: *Preeclampsia is a pregnancy specific disease, associated with significant maternal and perinatal morbidity and mortality. Incidence in Nigeria ranges from 2 to 16.7% across urban to rural areas. Elevated levels of serum uric acid and C reactive protein have been reported in preeclampsia and said to be useful in early detection of the disease. The need for biomarkers for early detection and appropriate intervention in management of the disease, to ensure favorable maternal and foetal outcome is important.*
Aim/Objective: *To determine plasma lactate, serum uric acid and C reactive protein levels in women with preeclampsia, with the aim of assessing their usefulness in early detection of the disease and their use as a biomarker in monitoring severity of the disease.*
Material and methods: *This was a cross sectional study carried out in the State Specialist Hospital, Benin City, Edo State, Nigeria in May 2018. A total of 40 participants (20 Normotensive pregnant women, 10 Preeclamptic women, 10 Normotensive non pregnant women) were included in the study. They were of similar age groups. The pregnant women had singleton pregnancies and in the second and third trimester of pregnancy. Plasma lactate, Serum uric acid was assayed by enzymatic methods. Serum C reactive protein was assayed using Enzyme linked immunosorbentassay method. Statistical analysis was done with SPSS version 21.*
Results: *Mean systolic blood pressure, mean diastolic blood pressure, mean arterial blood pressure and body mass index was significantly higher in the preeclamptic subjects (154.3 ±19.0mmHg, 98.6 ± 6.9mmHg, 117.1 ± 8.0mmHg, 36.9 ± 12.0 kg/m^2) respectively than in the normotensive pregnant Subjects (101.6 ± 12.6mmHg, 59.5 ± 10.3mmHg, 73.5 ± 9.8mmHg, 28.9 ± 4.0 kg/m^2) P<0.05*
Plasma lactate was higher in the preeclampic subjects (2.8 ± 1.0mmol/l) than in the normotensive pregnant subjects (2.6 ± 1.5 mmol/l). Difference was not statistically significant P>0.05. Plasma lactate showed a strong positive correlation with systolic blood pressure in preeclamptic subjects r = 0.745, P = 0.05.
Serum uric acid was significantly elevated in preeclamptic subjects (7.6 ± 2.8mg/dl) compared with normotensive pregnant subjects (3.6 ± 1.3mg/dl) and normotensive non pregnant (4.2 ± 1.0mg/dl)P<0.05.
Serum C reactive protein was non significantly higher in preeclamptic subjects (7.4 ± 2.9 mg/l) compared with normotensive pregnant subjects (7.4 ± 2.2mg/l) p> 0.05, difference was significant when compared with normotensive non-pregnant subjects (3.0 ± 3.6mg/l) p<0.05.
Conclusion: *Serum uric acid may be a useful biomarker not only in early detection of preeclampsia, but in determining severity of disease. Plasma lactate may also be useful as a marker of severity of preeclampsia and provide a guide on when to institute delivery intervention. The role of C reactive protein in preeclampsia needs to be further elucidated*
Keywords: *Preeclampsia, Lactate, Uric acid, C Reactive Protein*

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I. Introduction

Gestational hypertension, preeclampsia and eclampsia contribute significantly to still births, maternal and neonatal morbidity and mortality[1]. Preeclampsia develops in 7% of all pregnancies. It is characterized by high blood pressure equal to or above 140/90 mmHg and proteinuria after 20 weeks of pregnancy. About 50,000 mothers die due to pregnancy induced hypertension per year all over the world[2]. It is responsible for 25% of all foetal growth retardation and 15% preterm birth in developed countries[2].

The incidence of preeclampsia in primipara is approximately 3-8%. Incidence is reported to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%)[4,5]. Itsprevalance in Nigeria ranges from 2 to 16.79[6,7,8].

The pathophysiology of preeclampsia is heterogenous, complex and poorly understood involving both maternal and placental factors[9,10]. Abnormalities in the development of placental vasculature is considered to be

a primary cause of the placental hypoxia and ischaemia, which then leads to release of numerous bioactive factors in the maternal circulation causing wide spread endothelial dysfunction[10,11] and culminating in hypertension, proteinunia and other manifestations of the disease affecting the liver, renal, haematologic systems[11,12].

Excessive cellular activity associated with the process of placenta ischaemia, has been reported to lead to overproduction of uric acid which serves as a marker of the disease[13,14,15] with abnormal levels seen much earlier than the detection of proteinuria[13].

CRP is a sensitive marker of systemic inflammation and is primarily synthesized in hepatocytes in response to infection and tissue injury[16,17] which is stimulated by the release of pro inflammatory cytokines. The value of CRP levels reflects the severity of endothelial cell injury which is one of the factors responsible for development or initiating preeclampsia.

Lactate is a product of lactose dehydrogenase activity, which converts pyruvate to lactate. The major stimulant for LDH and lactase are pH and hypoxia[18]. Hypoxia when encountered in preeclampsia, increases glycolytic rate, thereby increasing the activity of LDH which catalyzes the reversible reaction of pyruvate to lactate [18,19].

In this study, we aim to determine plasma lactate, serum uric acid, serum C Reactive in Preeclampsia and the roles they may play as biomarkers in detection of the disease and determining severity of the disease.

II. Materials and Methods

A total of 40 subjects were included in the study. 20 were normotensive pregnant women, 10 women with preeclampsia and 10 normotensive non-pregnant women, all in the same age group. The pregnant women (normotensive and preeclamptic) were recruited consecutively from the antenatal clinic and maternity ward of the State Specialist Hospital, Benin City. They all had singleton pregnancies and were in the 2nd and 3rd trimester of pregnancy. They were included after obtaining informed consent. The study was approved by the ethical committee of the Hospital. Relevant data including age, Gestational age, past medical history was obtained.
Those with Preeclampsia were selected using the following;

Inclusion Criteria

- New onset of Hypertension after 20 weeks of gestation with blood pressure ≥ 140/90mmHg or rise in blood pressure systolic > 30 mmHg and diastolic > 15 mmHg above booking blood pressure; in at least two occasions.
- Proteinuria >300 mg per day detected by dipsticks.

Exclusion Criteria

- Pregnant women in labour.
- Pregnant women with Diabetes, Nephritis and any other systemic disease were excluded.

General physical examination was carried out for all subjects. Blood pressure was measured in a sitting position using a sphygmomanometer, height was measured with a stadiometer and weight with a weighing scale. Body mass index was calculated

Sample Collection

6mls of venous blood was collected from the ante cubital vein under aseptic conditions, and dispensed into lithium heparin sample bottles and plain sample bottles. Samples were subsequently centrifuged at 3000 rpm and separated into plain bottles, and kept in an ultradfrizer at -80^0 until analysis. Plasma uric acid and lactate was measured by enzymatic methods. Serum C Reactive protein was measured determined by Enzyme Linked Immunosorbent Assay.

StatisticalAnalysis

It was done using SPSS version 21. Difference between means of variables was determined using the student "t" test. Correlation between variables was determined using pearson's correlation. Level of significance was set at $p \leq 0.05$.

III. Results

A total of 40 subjects were studied. Mean age of the subjects were 29.0 ± 3.6 years, 30.5 ± 3.7 years, 27.7 ± 5.2 years in the normotensive non-pregnant, normotensive pregnant and preeclamptic subjects respectively (table 1).

Mean systolic Blood pressure was 105.0 ± 5.8mmHg, 101.6 ± 12.6mmHg, 154.3 ± 19.0mmHg in the normotensive non-pregnant, normotensive pregnant, preeclamptic subjects respectively and Mean Diastolic blood pressure was 65.0 ± 5.8mmHg, 59.5 ± 10.3mmHg, 98.6 ± 6.9mmHg in the normotensive non-pregnant, normotensive pregnant, preeclamptic subjects respectively. Difference was statistically significant between groups in both systolic blood pressure $p < 0.001$, and diastolic blood pressure $p < 0.001$ (table 1).

Mean Arterial blood pressure was 78.3 ± 4.3, 73.5 ± 9.8, 117.1 ± 8.0 in the normotensive non-pregnant, normotensive pregnant, pre-eclamptic subjects respectively. Difference was statistically significant. P<0.001.
Plasma lactate was 1.8 ± 0.3mmol/l 2.6 ± 1.5mmol/l, 2.8mmol/l in the normotensive non-pregnant, normotensive pregnant and pre-eclamptic subjects respectively. Difference across groups was not statistically significant p = 0.145 (table 1).
Plasma uric acid was 4.2 ± 1.0 mg/dl, 3.6 ± 1.3mg/dl, 7.6 ± 2.8mg/dl in the normotensive non-pregnant, normotensive pregnant, pre-eclamptic subjects respectively. Difference across groups was statistically p =0.015 (table 1).
Mean serum C Reactive protein levels was 3.0 ± 3.6mg/l, 7.4 ± 2.2mg/l, 7.4 ±2.9 mg/l in the normotensive non-pregnant, normotensive pregnant, pre-eclamptic subjects respectively. Difference across groups was statistically significant p = 0.005 (table 1).
Figure 1 shows the means of plasma, lactate, serum uric acid, C reactive protein in the various groups.
There was a statistically difference between mean serum uric acid in the preeclamptic subjects (7.2±2.8mg/dl,) and the normotensive pregnant subjects (3.6±1.3mg/dl) p= 0.007 (Table 2).
No statistically significant difference in plasma lactate between preeclamptic subjects (2.8±1.0mmo/l) and normotensive pregnant subjects (2.6±1.5mmol/l) p=0.686. (Table 2)
No statistically significant difference in serum C reactive protein between preeclamptic subjects (7.4±2.9 mg/l) and normotensive pregnant subjects (7.4±2.2mg/l) p=0.992 (Table 2)
Systolic Blood pressure showed a strong positive correlation with lactate in the pre-eclamptic subjects r= 0.745, p =0.05 (table 3)

IV. Discussion

Preeclampsia is a common cause of morbidity and mortality in developing countries, Nigeria inclusive. Some authors[20,21] have reported prevalence of preeclampsia in their population of study. The need to control and prevent the development of this disease is very vital in reducing maternal mortality, morbidity and poor foetal outcomes. Identification of biomarkers to detect the development of the disease and also monitor progress of pregnancy, to ensure good maternal and foetal outcome is of utmost importance.

Mean age of the subjects with preeclampsia was similar to that reported by KooffrehME[2] and coauthors in their study on women with preeclampsia in calabar Nigeria. Mean Body Mass Index in preeclamptic subjects was significantly higher than in nomotensive pregnant subjects and normotensive non-pregnant controls. Obesity may be a risk factor in development of preeclampsia.

Mean systolic blood pressure, diastolic blood pressure and mean anterial pressure were all significantly elevated in the subjects with preeclampsia, compared with the normotensive pregnant and normotensive non-pregnant subjects. Several studies have reported similar findings [6,22,23] Elevated systolic, diastolic and mean arterial blood pressure above the cut off values remains an important criteria in diagnosis of preeclampsia.

Plasma lactate was non significantly higher in the preeclamptic subjects than in the normotensive pregnant and normotensive non-pregnant subjects. Kay HH[24] reported that under hypoxic conditions, Lactate Dehydrogenase A(LDHA), mRNA is increased in primary trophoblast cells and JEG3 cells. The HIF – 1α protein expression is higher in hypoxia treated JEG3 cells than controls. LDHA iso enzyme activity and its protein expression are increased most significantly at 24 hour of culture under hypoxia. Lactate secretion from JEG3 cells under hypoxia is increased, as is the lactate levels in plasma from preeclampsia patients, and concluded that their findings support the role of hypoxia in inducing HIF – 1α activity in trophoblasts and increasing lactate dehydrogenase transcription as well as activity. Higher levels of lactate are produced and secreted which may contribute to the higher lactate levels in plasma of preeclamptic subjects. In our study, plasma lactate correlated strongly and significantly with systolic blood pressure in the preeclamptic subjects, and no statistically significant correlation in the normotensive pregnant and normotensive non-pregnant subjects. This finding supports the theory that plasma lactate levels maybe a good indicator of hypoxia in preeclampsia and serial measurements may predict worsening disease, and poor maternal and foetal outcomes. Can plasma lactate levels be used in monitoring foetal wellbeing in preeclampsia, and serial measurements determine when to intervene and deliver baby to prevent intrauterine death? These are areas for further research study

Plasma uric acid was significantly elevated in the preeclamptic subjects compared with normotensive pregnant subjects and normotensive non pregnant subjects. Comparison of plasma uric acid in normotensive pregnant subjects with preeclamptic subjects still showed a statistically significant difference. Several authors have reported similar findings Enaruna ON and Colleagues[13] in their study reported elevated uric acid levels in preeclamptic women in Benin City, Nigeria, Zhao J and co-authors[25] also reported elevated uric acid levels in preeclamptic women in a chineese population. Several studies[2,26,27] have reported positive correlation between serum uric acid levels and severity of preeclampsia. Vazquez Rodriguez JG and coauthors[28] reported that it's the first biomarker of clinical chemistry considered as an early evidence of disease, and its not only a criterion for establishing the correct diagnosis and the differential with other hypertensive states but an indication of

termination of pregnancy. With the findings in our study, serum uric acid levels, prove to be a cheap and useful biomarker that can be used to detect and assess severity of preeclampsia and a guide as to when to institute delivery intervention. C-reactive protein levels were elevated in both the preeclamptic subjects and the normotensive pregnant subjects. Difference was not statiscally significant. Difference between means of C reactive protein of preeclamptic subjects and normotensive non pregnant subjects was however statistically significant. Ghazavi and co-authors[2], Stefanovic M and co-authors[26], Babah O.A[29] and co-authors, all reported significantly elevated C reactive protein levels in preeclamptic women and reported that levels correlate with severity of disease. The observation in our study of higher C reactive protein levels in the preeclamptic subjects compared with normotensive pregnant subjects which was not statistically significant, may be due to other factors, which was not explored in this study, also sample size may be contributory. However there was significant difference in C reactive protein between nomortensive non pregnant subjects and preeclamptic subjects, highlighting the fact that elevated CRP levels may still play a role in pathogenesis of preeclampsia.

We found in this study: Elevated serum uric acid levels in preeclamptic subjects which was statistically significant, compared with normotensive pregnant subjects, a significant and strong positive correlation of plasma lactate with systolic blood pressure in the preeclamptic subjects, and elevated C reactive protein levels with a statistically significant difference in the preeclamptic subjectswhen compared with non-pregnant normotensive women we therefore conclude;

V. Conclusion

Serum uric acid is an important and useful biomarker in detecting preeclampsia and monitoring severity of disease for appropriate intervention. Serial plasma lactate estimation may also be useful in monitoring severity of disease in pre-eclampsia, and as a guide in determining when to institute delivery intervention. Role of C reactive protein in preeclampsia needs to be further elucidated.

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TABLE 1: **Dermographic characteristics, plasma lactate,serum uric acid and c reactive protein in preeclamptic, normotensive pregnant, normotensive non pregnant subjects.**

	Non Pregnant (n=10) mean±SD	Normotensive Pregnant (n=20) mean±SD	Pre-eclampsia (n=10) mean±SD	P Value
Age (years)	29.0 ± 3.6	30.5 ± 3.7	27.7 ± 5.2	0.294
Gestational age (weeks)		25.5±7	28.5±5.8	0.135
Systolic Blood Pressure(mmHg)	105.0 ± 5.8	101.6 ± 12.6	154.3 ± 19.0	< 0.001
Diastolic Blood Pressure (mmHg)	65.0 ± 5.8	59.5 ± 10.3	98.6 ± 6.9	< 0.001
Mean Arterial Pressure (mmHg)	78.3 ± 4.3	73.5 ± 9.8	117.1 ± 8.0	< 0.001
Body mass index (kg/m^2)	23.1 ± 2.6	28.9 ± 4.0	36.9 ± 12.0	0.005
Lactate (mmol/l)	1.8 ± 0.3	2.6 ± 1.5	2.8 ± 1.0	0.145
Uric acid (mg/dl)	4.2 ± 1.0	3.6 ± 1.3	7.6 ± 2.8	0.015
CRP (mg/l)	3.0 ± 3.6	7.4 ± 2.2	7.4 ± 2.9	0.005

Table 2: Demographic characteristics, plasma lactate, serum uric acid and C reactive protein in preeclamptic and normotensive pregnant subjects

	Normotensive Pregnant (n=10) mean±SD	Pre-eclampsia (n=20) mean±SD	P Value
Age (years)	30.5 ± 3.7	27.7 ± 5.2	0.130
Gestational age (weeks)	25.5±7	32.7±5.8	0.135
Systolic Blood Pressure (mmHg)	101.6 ± 12.6	154.3 ± 19.0	< 0.001
Diastolic Blood Pressure (mmHg)	59.5 ± 10.3	98.6 ± 6.9	< 0.001
Mean Arterial Pressure (mmHg)	73.5 ± 9.8	117.1 ± 8.0	< 0.001
Body mass index (kg/m^2)	23.1 ± 2.6	36.9 ± 12.0	0.010
Lactate (mmol/l)	2.6 ± 1.5	2.8 ± 1.0	0.686
Uric acid (mg/dl)	3.6 ± 1.3	7.6 ± 2.8	0.007
CRP (mg/l)	7.4 ± 2.2	7.4 ± 2.9	0.992

Table 3: Correlation between Systolic Blood Pressure and Plasma Lactate, Uric acid, C Reactive Protein in preeclamptic subjects

	R	P value
Plasma Lactate	0.745	0.055
Serum uric acid	0.478	0.416
Semen C Reactive Protein	0.465	0.293

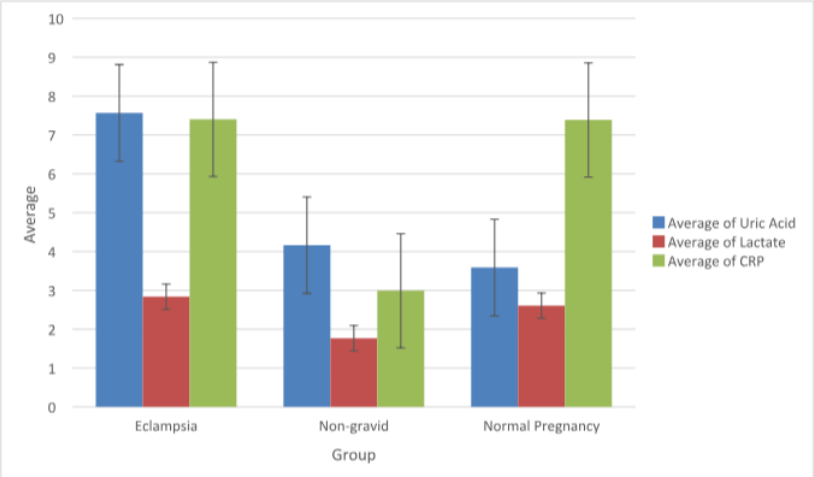

FIGURE 1

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